Folic acid

Folic acid is obtained from the Latin word folium, meaning leaf.

It serves as a carrier of one-carbon (C1) units during several biosynthetic processes. Additionally, two other co-factors are known to be involved in the addition of the C1 unit to a metabolic precursor, including:

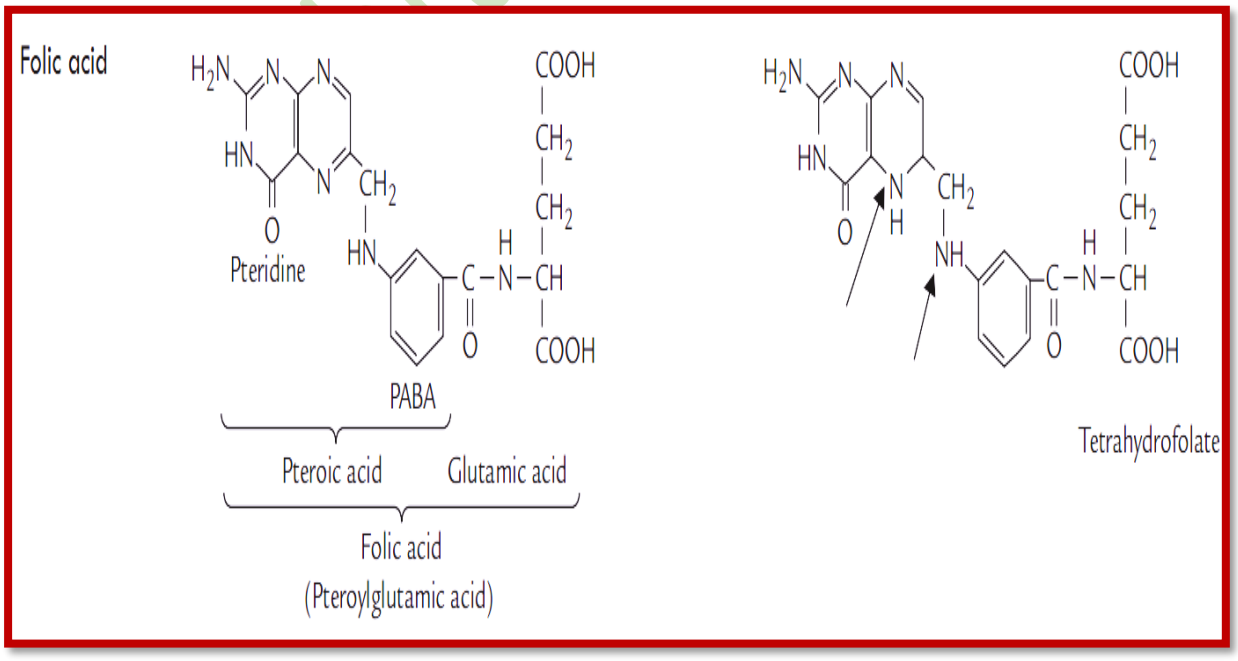
1- biotin in carboxylation reactions
2- S-adenosylmethionine (SAM) as a methylating agent.

However, folic acid is more versatile than either of these two because it can transfer the C1 units in several oxidation states.

Structure of Folic acid

Folic acid consists of three components:

A **pteridine ring** linked in sequence to **para-aminobenzoic acid** (PABA) and a **glutamate residue** (Table 18.2). Up to five additional glutamate residues are connected to the first glutamate to form a polyglutamyl tail.



Synthesis of folic acid

Pteridine and para-aminobenzoic acid are linked covalently to form pteroic acid. Pteroic acid is attached to a glutamate residue to form folic acid (Fig. 18.8). A polyglutamyl tail is built by the addition of more glutamyl residues, which gives the molecule multiple negative charges, preventing it from crossing membranes by passive diffusion. Thus, the role of **polyglutamylation** serves to isolate folate in the cells in which it is required.

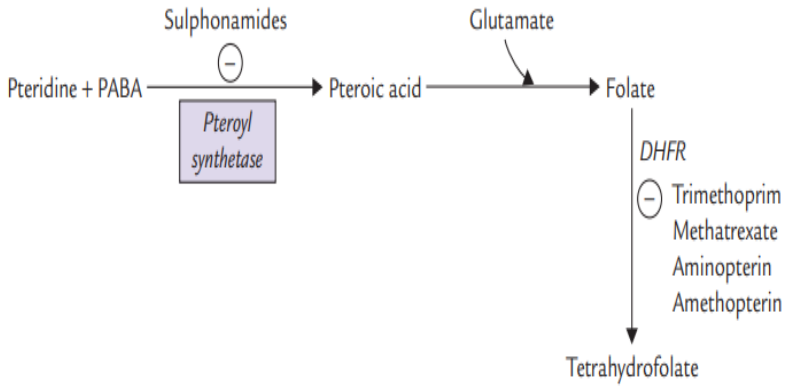


Fig. 18.8. Tetrahydrofolate synthesis and action of antifolates. Sulphonamides and trimethoprim are pharmacological inhibitors in bacteria. Methatrexate, aminopterin and amethopterin inhibit the *DHFR* reaction (PABA = para-amino benzoic acid).

Activation of folic acid

Folate in the human organism must be doubly reduced to become an active coenzyme tetrahydrofolate (THF). The reduction reaction is a stepwise process:

1- Folate is converted to dihydrofolate, and
2- then to tetrahydrofolate (THF). A single NADPH-dependent enzyme, dihydrofolate reductase (DHFR), catalyzes both steps.

$$\text{Folate} \xrightarrow{DHFR} \text{Dihydrofolate} \xrightarrow{DHFR} \text{Tetrahydrofolate}$$

Folate antagonists:

The dihydrofolate reductase (DHFR) reaction is inhibited by the antitumor agents (e.g., methotrexate and aminopterin), which competitively inhibit the DHFR. This blocks the synthesis of tetrahydrofolate (THF).

Because THF is required for DNA biosynthesis, and tumor cells have a very high level of DNA biosynthetic activity. Therefore, a decrease in THF level will inhibit tumor growth.

Mammals cannot synthesize folic acid, so it must be obtained from the diet or produced by intestinal microorganisms. Many microorganisms can synthesize their folate when **para-aminobenzoic acid** (PABA) is present in the medium. Therefore, the PABA analogs (e.g., sulphonamides) can inhibit the formation of folate.

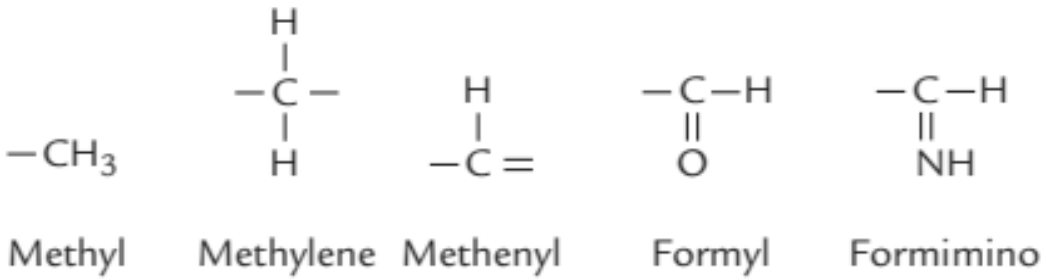


Fig. 18.9. The one-carbon groups transferred by THF.

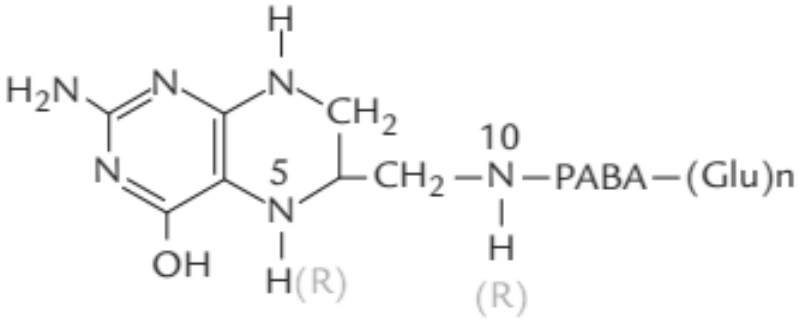


Fig. 18.10. The one-carbon units bound two N^5 and N^{10} of tetrahydrofolate.

Absorption and Distribution of folic acid

Folic acid is absorbed in the jejunum. In the intestinal lumen.

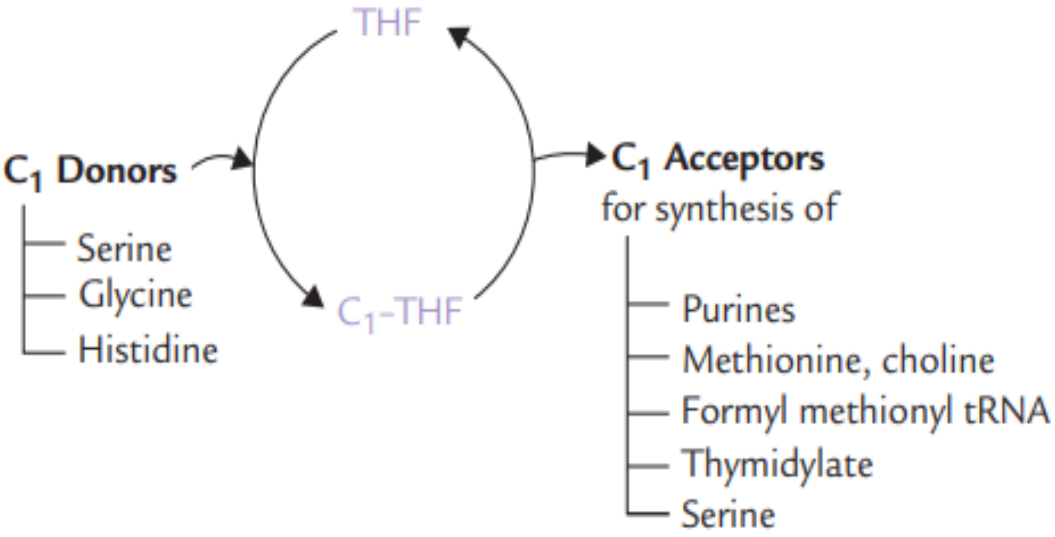
Before absorption, all of the glutamyl residues are removed by hydrolysis, except one of them remains in the folic acid. Following absorption, folic acid is transported in the blood by globulins.

The primary circulating form is methyl-tetrahydrofolate, and the normal range o is 5–15 ng/mL. When it arrives in the liver, the methyl derivatives are taken up by hepatocytes, where various coenzyme forms are produced.

Folic acid is not stored in tissues.

Coenzyme Functions

Tetrahydrofolate serves as a carrier of one-carbon units at different oxidation levels (Fig. 18.9). These C1 units are bound to one or both of the two nitrogens in the molecule, N5 and N10 (Fig. 18.10). THF receives the C1 units from various donor molecules during catabolic reactions and can transfer them to specific acceptors for the synthesis of multiple compounds. The role of THF is thus vital in those reactions that **require either the addition or removal of C1 units of various oxidation states**.



1- Donors of C1 units:

THF acquires C1 units from various donors during the following reactions:

Once bound to THF, the C1 unit can be enzymatically oxidized or reduced. Thus, various oxidation states are interconvertible, such as: (Fig. 18.11)

(a) Conversion of serine to glycine by serine hydroxymethyltransferase.

$$\text{THF} + \text{Serine} \rightleftharpoons N^5\ N^{10}\ \text{Methylene THF} + \text{Glycine} + H_2O$$

(b) Histidine breakdown, where a C1 unit from FIGLU is transferred to THF (Fig. 13.13)

$$\text{FIGLU} + \text{THF} \rightarrow N^5\text{-Formimino THF} + \text{glutamate}$$

2- Acceptors of C1 units:

Some important one-carbon addition reactions in which C1 unit is transferred to an acceptor are as here.

(a) Synthesis of purine nucleotides:

(b) Conversion of homocysteine to methionine: The methyl group required for the synthesis of methionine from homocysteine is provided by methyl THF.

(c) Synthesis of serine: The hydroxymethyl group required for glycine to serine conversion is provided by N5, N10 Methylene THF.

(d) Synthesis of choline: Serine to choline conversion requires methyl group from N5, N10 methylene THF.

NOTE: Folic acid is involved in addition of one-carbon units to several metabolic precursors. It is more versatile than biotin (in carboxylation reactions) and S-adenoxylmethionine (methylating agent) as a carrier of one-carbon units.

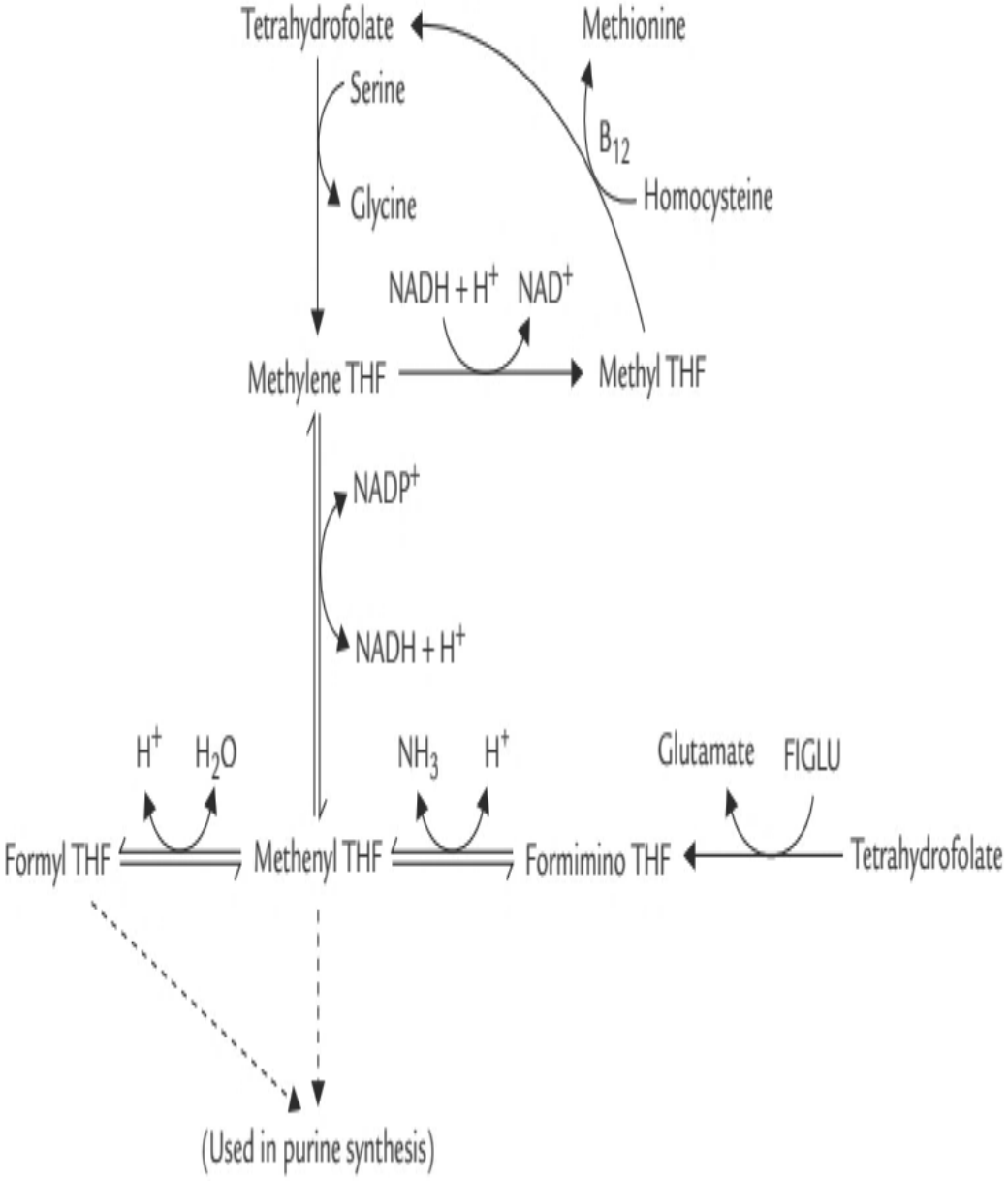


Fig. 18.11. Tetrahydrofolate as carrier of one-carbon units (FIGLU = formiminoglutamate).

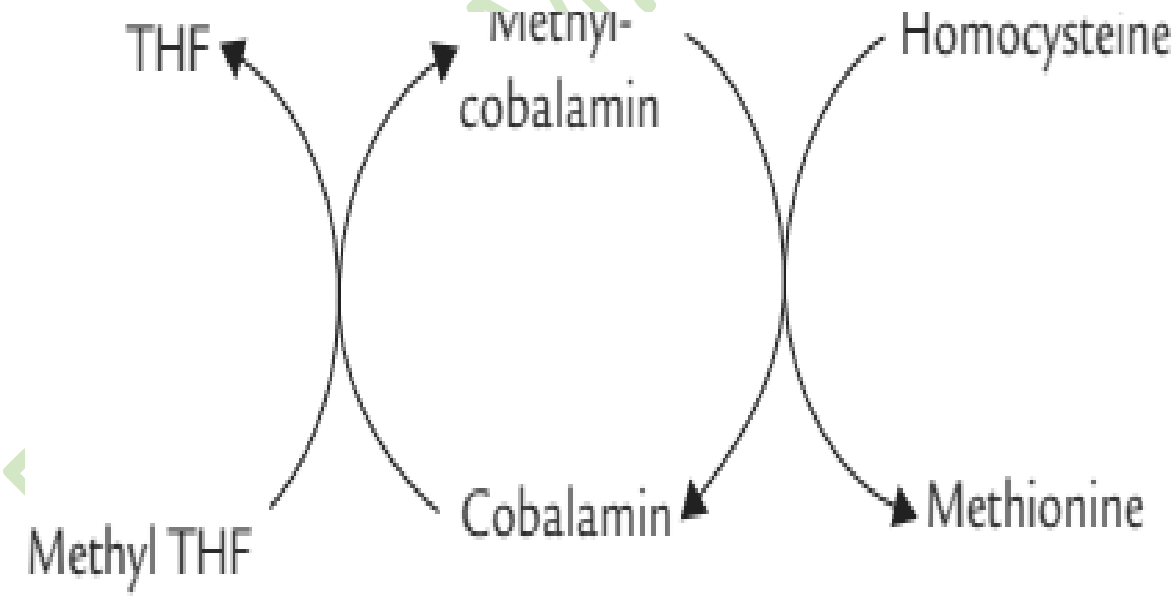
Causes and Effects of Folate Deficiency

Deficiency of this vitamin is widespread due to dietary deficiency and impaired intestinal absorption. Also, chronic alcoholism is a known cause.

DNA synthesis indirectly requires folic acid because of its role in the synthesis of purines and thymidylate synthesis. Hence, folic acid is needed in DNA replication and cell division.

Folate Trap Hypothesis

A deficiency of cobalamin leads to functional folate deficiency through the following mechanism. During the metabolism of one-carbon units, a small amount of methylene tetrahydrofolate is reduced irreversibly to methyl-tetrahydrofolate (Fig. 18.11). Since it cannot be used for the synthesis of purines or thymine, methyl-THF has to be converted back to one of the other coenzyme forms. The only reaction of methyl-THF is the methylation of homocysteine to methionine, which regenerates free THF. This reaction requires cobalamin; therefore, methyl THF tends to accumulate in cases of cobalamin deficiency.



Accumulation of methyl THF leads to the depletion of the other coenzyme forms that are needed for nucleotide synthesis. Thus, the folate trap hypothesis explains the

anemia of cobalamin deficiency, but it cannot for the neurological manifestations of pernicious anemia.

Assessment of folate status

Measurement of the serum or red blood cell folate concentration is the method of choice, and several simple and **reliable radio ligand-binding assays** have been developed.

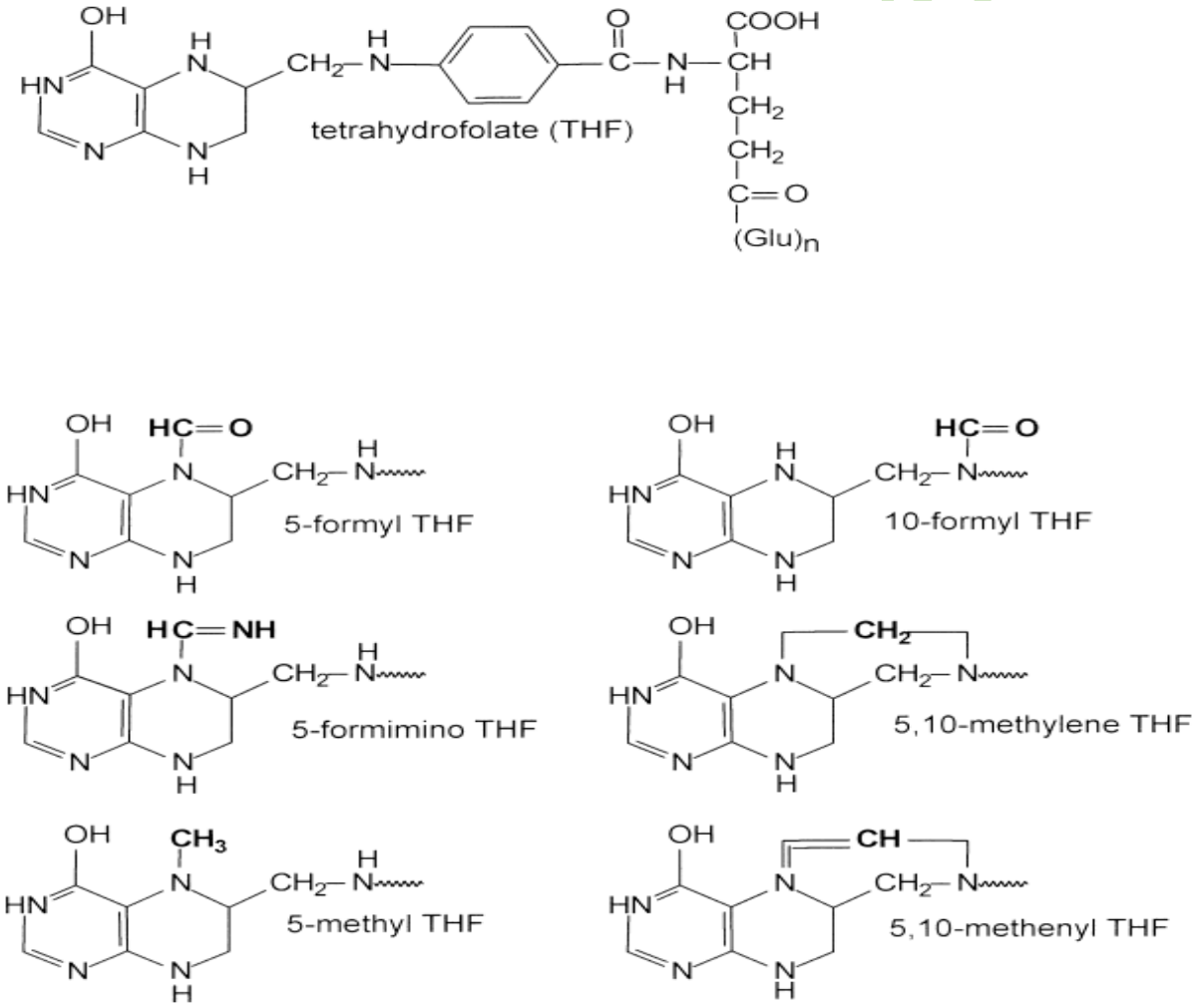


Figure 11.19 Folic acid and the various one-carbon substituted folates