

Folic Acid Deficiency Anemia

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Folic Acid

- Reduced forms of folic acid are required for the synthesis of amino acids, purines and DNA.

The consequences of folate deficiency include:

1. Megaloblastic anemia.
2. Congenital malformations – neural tube defects, such as spina bifida and anencephaly,
3. Occlusive vascular disease due to homocysteine accumulation.

Folic Acid

- Folic acid (pteroylglutamic acid) can exist in the form of monoglutamate, triglutamate and polyglutamate.
- It undergoes reduction by folate reductase to dihydrofolate and tetrahydrofolate.

Folic Acid

- **Tetrahydrofolate can be transformed to folate cofactors.**
- **The folate cofactors are inter-convertable and serve the donation of one-carbon units at various level of oxidation.**

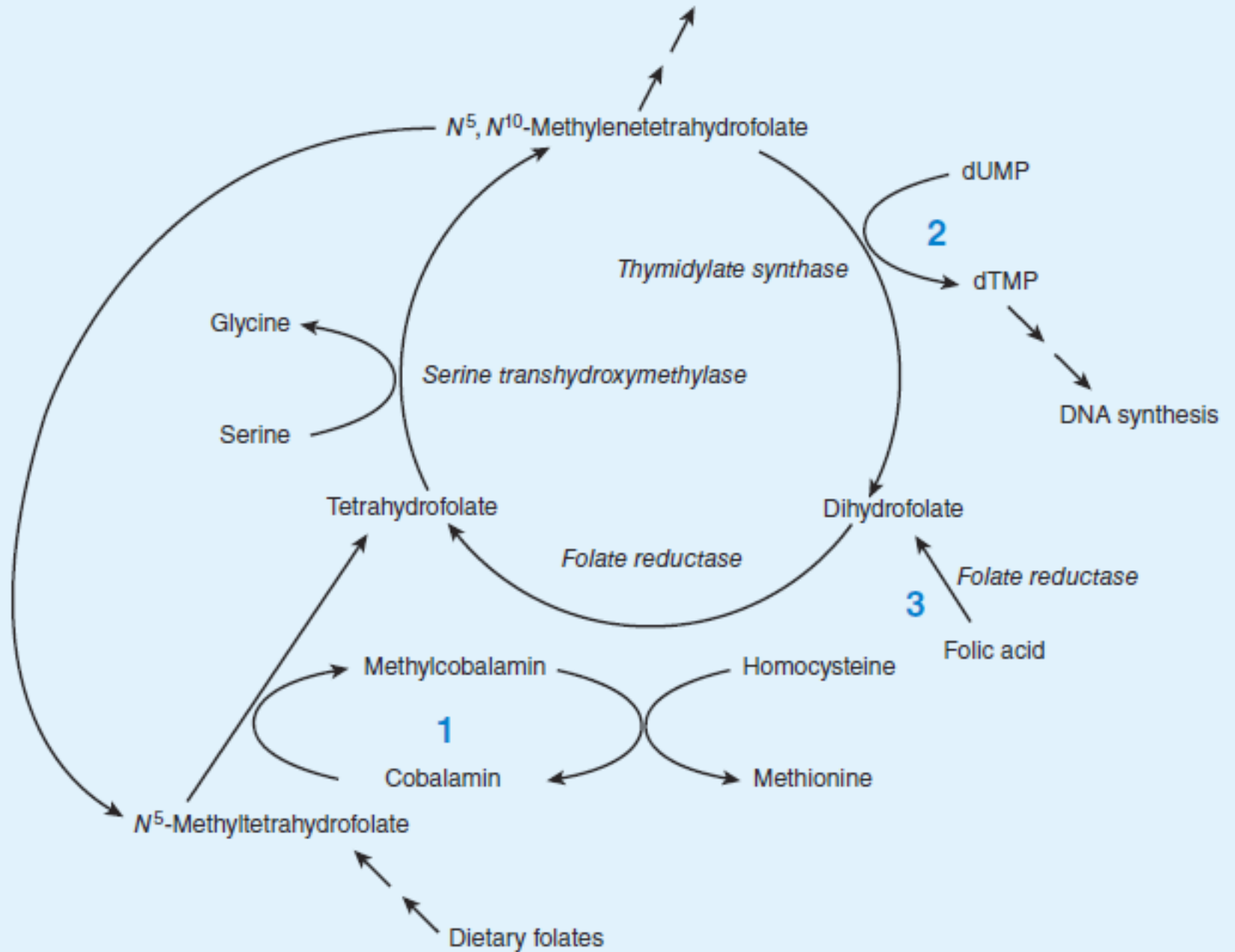


FIGURE 33-3 Enzymatic reactions that use folates. **Section 1** shows the vitamin B₁₂-dependent reaction that allows most dietary folates to enter the tetrahydrofolate cofactor pool and becomes the "folate trap" in vitamin B₁₂ deficiency. **Section 2** shows the deoxythymidine monophosphate (dTMP) cycle. **Section 3** shows the pathway by which folic acid enters the tetrahydrofolate cofactor pool. Double arrows

Folic Acid

Pharmacokinetics:

- Food rich in folic acid include yeast, liver, kidney & green vegetables.
1. Folic acid is absorbed in the proximal jejunum.
 2. Usual daily absorption from diet ~ 50-100 µg, depending on metabolic requirements.
 3. Pregnant women may absorb up to 300-400 µg daily.

Folic Acid

- 4. Normal tissue storage in liver and other tissues
~ 5-20 mg.**
- 5. If folic acid absorption stops, megaloblastic
anemia develops in 1-6 months.**

Folic Acid

Daily Requirements:

- Infants (0–6 months): 65 µg / day
- Infants (7–12 months): 80 µg / day
- Children (1–3 years): 150 µg / day
- Children (4–8 years): 200 µg / day
- Children (9–13 years): 300 µg / day
- Teens (14+ years) and Adults: 400 µg / day
- Pregnant Women: 600 µg / day
- Breastfeeding / Lactating Women: 500 µg / day

Folic acid

Clinical pharmacology:

- 1. Megaloblastic anemia. Vitamin B₁₂ deficiency must first be excluded. Why?**
- 2. Prevention of folic acid deficiency in high risk groups such as pregnancy, alcohol dependence, hemolytic anemia, ...**
 - Usually used orally until the cause is removed and stores are replenished.**

Folic acid

Causes of deficiency:

- 1. Inadequate dietary intake.**
- 2. Liver disease and alcohol dependence because of diminished stores and poor diet.**
- 3. Increased requirements: pregnancy, hemolysis**
- 4. Malabsorption syndromes.**
- 5. Renal dialysis.**

Folic acid

6. Drugs:

- A. Methotrexate, trimethoprim, pyrimethamine inhibit dihydrofolate reductase**
- B. Long-term phenytoin therapy impair folate absorption**

Hematopoietic Growth Factors

Hematopoietic Growth Factors

- **The hematopoietic growth factors are glycoprotein hormones that regulate the proliferation and differentiation of hematopoietic progenitor cells in the bone marrow.**

Erythropoietin

- Formed by the kidney in response to tissue hypoxia (severe anemia).
- Recombinant human Erythropoietin is available for use (**epoetin alpha**).

Pharmacodynamics:

1. It stimulates erythroid **proliferation** and **differentiation** by interacting with specific receptors on red cell progenitors.
2. It induces release of reticulocytes from bone marrow.

Erythropoietin

3. It corrects the anemia (**provided that bone marrow response is not impaired** by iron deficiency, primary bone marrow disorders, or bone marrow suppression from drugs or chronic diseases).
4. Normally, an inverse relationship exists between the hematocrit and erythropoietin level. **This is NOT true in anemia of chronic renal failure.**

Erythropoietin

Clinical Pharmacology:

- **Used for anemia of chronic renal failure, NOT other types of anemia where endogenous erythropoietin is usually high.**
- **Iron and folate supplementation may be required in cases of inadequate response.**

Erythropoietin

Adverse Effects:

1. Most common are those associated with rapid rise of hemoglobin and hematocrit: hypertension and thromboembolic complications.
 - Hemoglobin levels should not be increased > 11 g/dL because of risk of serious cardiovascular events, thromboembolic events, stroke, and mortality.
2. Infrequent and mild allergic reactions.

Myeloid Growth Factors

Myeloid Growth Factors

- Granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF).
- Recombinant human G-CSF (rHuG-CSF):
Filgrastim
- Recombinant human GM-CSF (rHuGM-CSF):
Sargramostim

Myeloid Growth Factors

Pharmacodynamics:

- They stimulate **proliferation** and **differentiation** by interacting with specific receptors found on myeloid progenitor cells.

1. G-CSF stimulates proliferation and differentiation of progenitors committed to the **neutrophil lineage**. It also activates the phagocytic activity of mature neutrophils and prolongs their survival in the circulation.

Myeloid Growth Factors

2. GM-CSF has broader biologic actions than G-CSF.

- It is a multipotential hematopoietic growth factor that stimulates proliferation and differentiation of **early and late granulocytic, erythroid and megakaryocyte progenitors.**

Myeloid Growth Factors

Clinical Pharmacology:

1. Cancer Chemotherapy-Induced Neutropenia.

- **G-CSF and GM-CSF accelerate the rate of neutrophil recovery and reduces the duration of neutropenia after dose-intensive myelosuppressive chemotherapy.**

Myeloid Growth Factors

Adverse effects:

- 1. Bone pain.**
- 2. Fever, arthralgias, myalgias.**
- 3. Capillary leak syndrome characterized by peripheral edema, and pleural or pericardial effusions.**
- 4. Allergic reactions.**
- 5. Splenic rupture.**

Megakaryocyte Growth Factors

- Thrombopoietin and interleukin-11 (IL-11) are endogenous regulators of platelet production.
- Thrombopoietin agonists: **Romiplostim** and **Eltrombopag**.
- Recombinant form of IL-11: **Oprelvekin**.

Megakaryocyte Growth Factors

Eltrombopag:

- It is an orally active small nonpeptide thrombopoietin agonist used for therapy of patients with **chronic immune thrombocytopenia** who have had an inadequate response to other therapies (steroids, immunoglobulins, or splenectomy).

Megakaryocyte Growth Factors

- It is also used for treatment of **thrombocytopenia in patients with hepatitis C** to allow initiation of interferon therapy.

Romiplostim:

- It is used for therapy of patients with **chronic immune thrombocytopenia**.

Megakaryocyte Growth Factors

Adverse effects:

Eltrombopag:

- 1. Hepatotoxicity.**
- 2. Portal vein thrombosis.**

Megakaryocyte Growth Factors

Romiplostim:

- 1. Portal vein thrombosis.**
- 2. In patients with myelodysplastic syndromes, it increases the blast count and risk of progression to acute myeloid leukemia.**
- 3. Bone marrow fibrosis.**
- 4. Rebound thrombocytopenia after stopping the drug administration.**

Megakaryocyte Growth Factors

Oprelvekin:

- 1. Fatigue,**
- 2. Transient atrial arrhythmias.**
- 3. Anemia (due to hemodilution).**
- 4. Dyspnea (due to fluid accumulation in the lungs).**
- 5. Hypokalemia (due to diuretic therapy for fluid retention).**