Pharmacology of the Hematopoietic System

Prof. Dr. Özlem Uğur
Dept. Medical Pharmacology

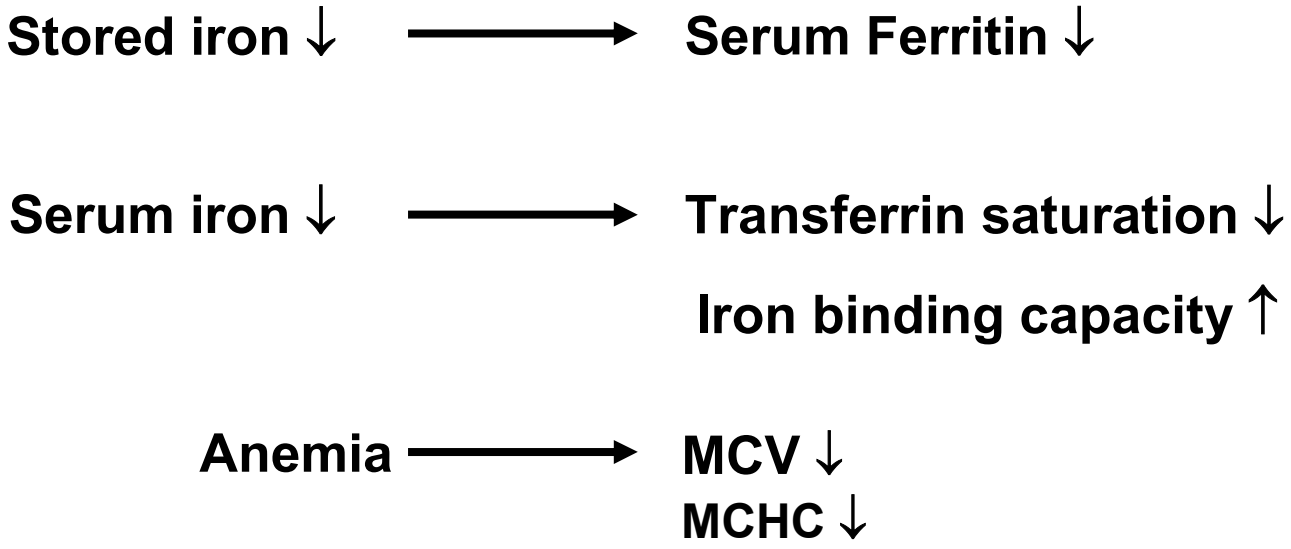
- Hematopoiesis is the production of erythrocytes, leucocytes and platelets from undifferentiated stem cells. Constant supply of iron, vitamin B12 and folic acid is necessary for normal hematopoiesis. Inadequate supply of either one of these nutrients results in deficiency of functional blood cells, especially erythrocytes. Thus, in the case of iron, vitamin B12 or folic acid deficiency, anemia is the most common and generally the first clinical finding.

Agents Used in Anemias

Iron

Source	Various
Requirement	0.5-1 mg/day
Absorption	duodenum, proximal jejunum
Distribution	transferrin
Storage	ferritin, hemocyiderine (liver, spleen, bone marrow)
Elimination	1 mg/day

Laboratory Findings of Iron Deficiency



Treatment

Iron deficiency anemia is generally treated with oral iron preparations that containvarious salts of ferrous iron. Dosing should be done so as to deliver 200 - 400 mg/day elementary iron

Ferrous Sulphate
Ferrous Gluconate
Ferrous fumarate

Oral treatment is generally efficient and sufficient. In patients who can not absorb or tolerate oral preparations, IV ferric dextran may be used.

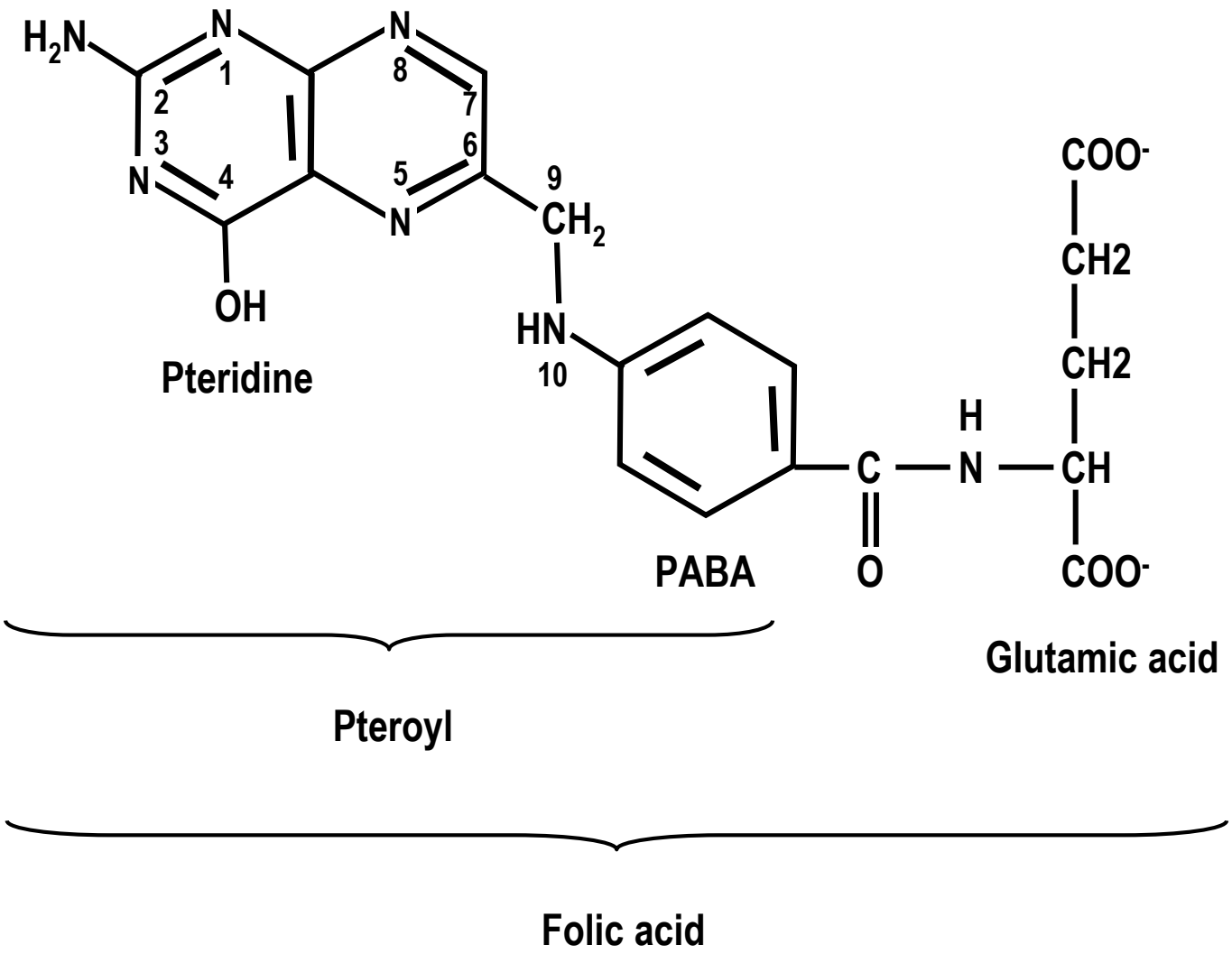
Indications of the Correct Diagnosis and Treatment

Reticulocytosis	→	3 - 4 days
Increase in haemoglobin levels	→	2 - 4 weeks
Return of haemoglobin to the normal levels	→	1 - 3 months
Total duration of treatment	→	3 - 6 months

Folic Acid

Source	giblets, green vegetables
Requirement	50 - 200 µg / day
Absorption	Proximal jejunum
Elimination	With feces and urine
Storage	5 - 20 mg (liver)

Folic acid is composed of a pteridine, p-aminobenzoic acid and glutamic acid. It donates one-carbon groups in de-novo synthesis of nucleic acids.



Laboratory Findings of Folic Acid Deficiency

Serum and erythrocyte folic acid levels ↓

Megaloblastic Anemia ⟶ MCV ↑

Treatment of Folic Acid Deficiency Anemia

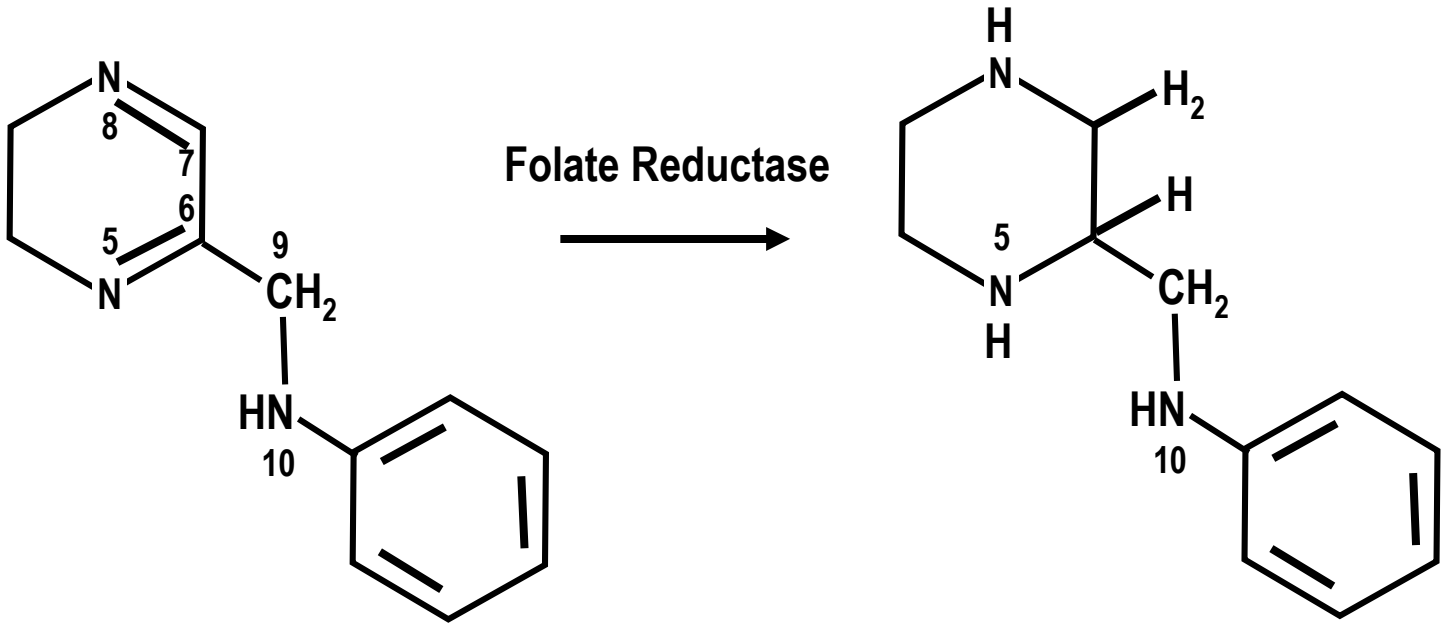
Anemia can be treated effectively by oral 1 mg/day folic acid.

Deficiency is usually due to inadequate dietary intake.
Therapy should be continued until the underlying cause is corrected.

Vitamin B12

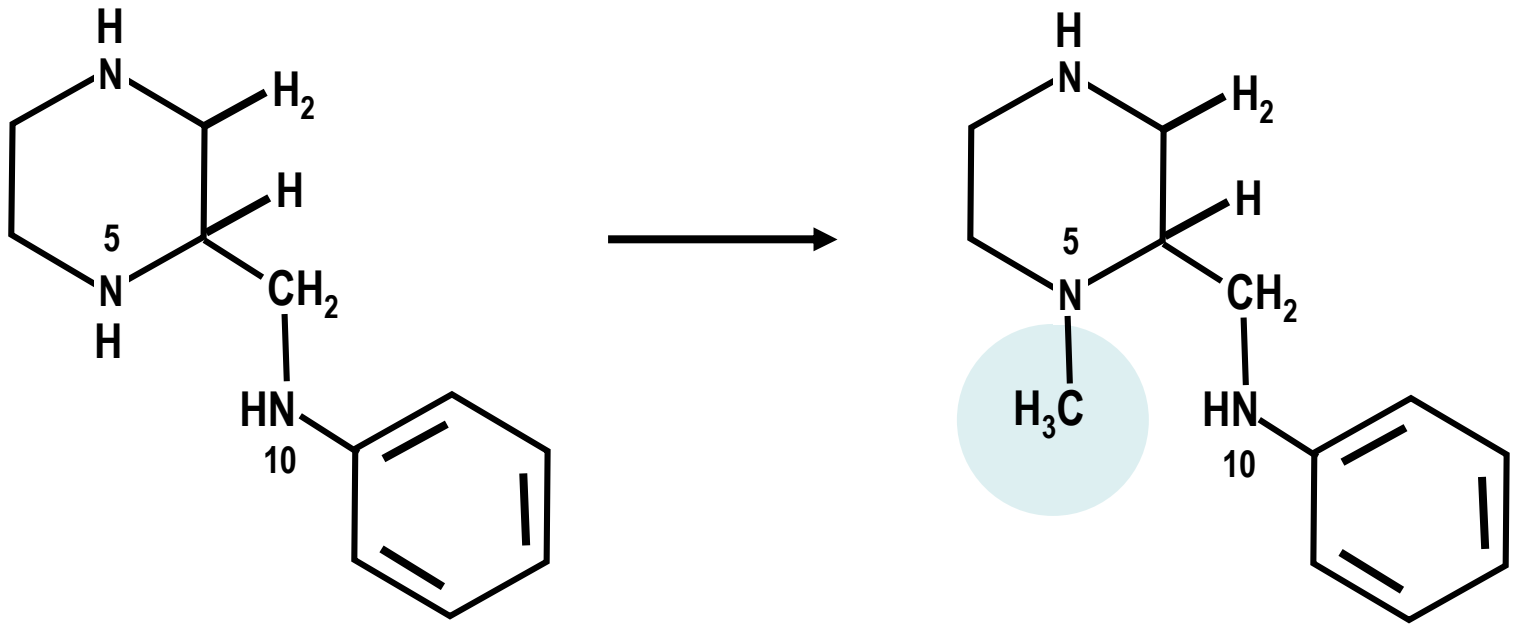
Source	Meat, milk products
Requirement	2 µg / day
Absorption	Distal ileum
Distribution	Transcobalamin II
Elimination	Trace amounts with feces and urine
Storage	3-5 mg (liver)

Folic acid has to be reduced to tetrahydrofolate before it can participate in the one-carbon-group transfer reactions.



Folic acid **Tetrahydrofolic acid**

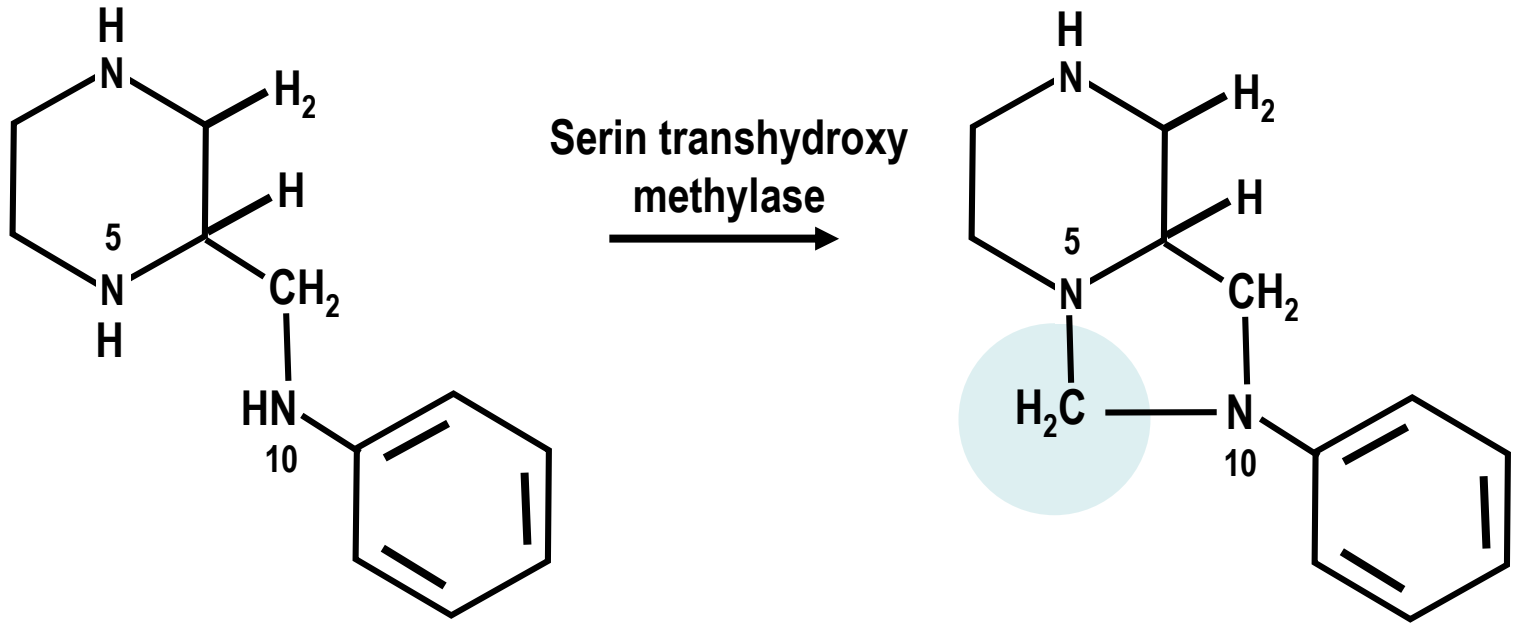
Dietary and storage folate is largely in the form of N^5-Methyl-H_4folate.
This form has to be converted to H_4folate, the precursor of the folate cofactors.



H_4folate

N^5-Methyl-H_4folate

H_4folate is then converted by various reactions to folate cofactors such as N_5,N_{10}-Methylene-H_4folate



H_4folate

N^5,N^{10}-Methylene-H_4folate

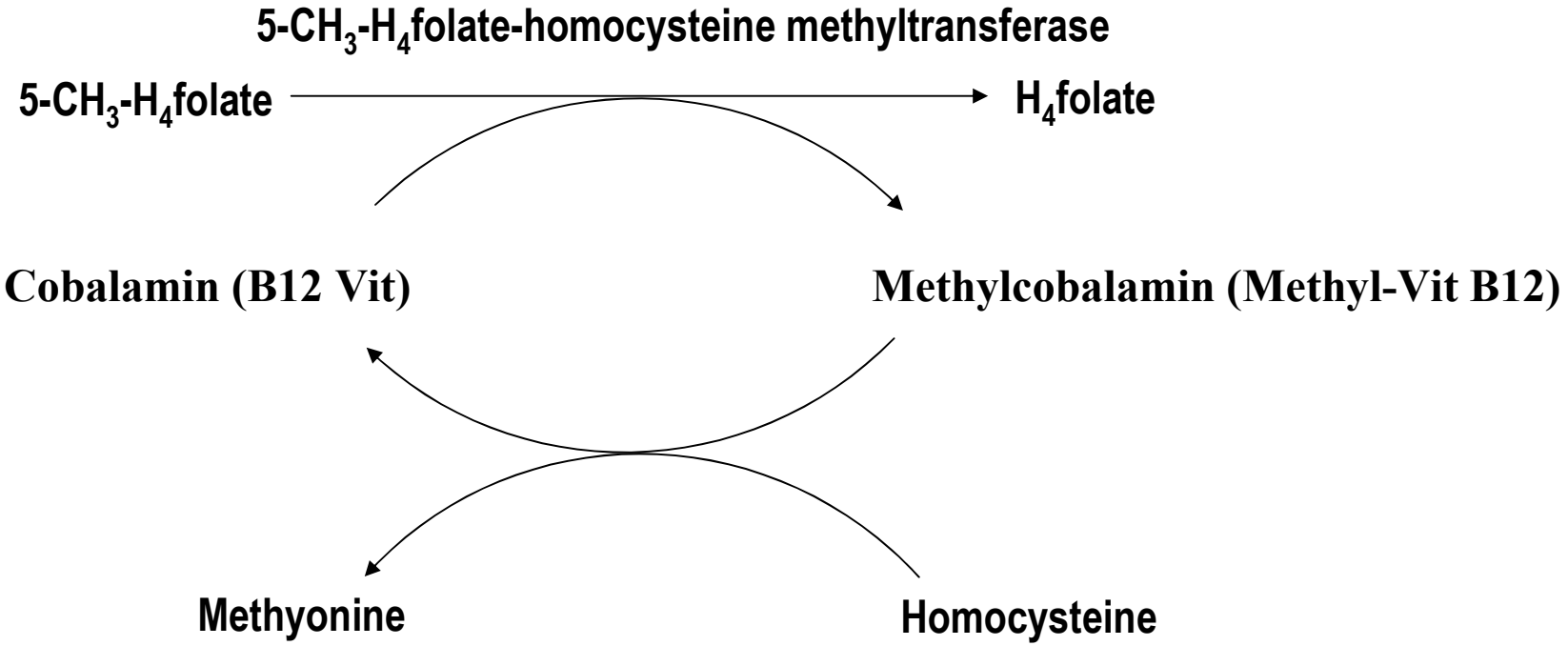
Other folate cofactors

N^5,N^{10}-Methenyl-H_4folate

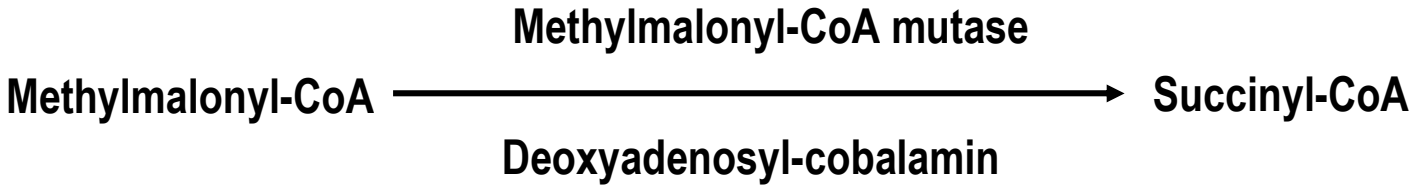
N^{10}-Formyl-H_4folate

N^5-Formyl-H_4folate

Vitamin B12 functions as a cofactor in the reaction by which N^5-Methyl-H_4folate is converted to H_4folate. Vitamin B12 deficiency leads to accumulation of body folate in the form of unusable N^5-Methyl-H_4folate.



Vitamin B12 also participates in the isomerisation of Methylmalonyl-CoA to Succinyl-CoA.
This reaction also can not take place in vitamin B12 deficiency.



Laboratory Findings of B12 Vit. Deficiency

Serum vitamin B12 levels ↓

Megaloblastic Anemia ⟶ MCV ↑

Mild or moderate leucopenia and thrombocytopenia

Progressive and irreversible neurologic abnormalities

Treatment of Vit. B12 Deficiency Anemia

In almost all cases, Vit. B12 deficiency is due to the malabsorbtion of the vitamin and in most cases, the underlying cause can not be cured. Thus:

Most patients need a life-long parenteral Vit. B12 treatment.

Recombinant Hematopoietic Growth Factors

Erytropoietin (rhuEPO, epoetin alfa)
Anemia due to chronic renal insufficiency

G-CSF (filgrastim) and G-MCSF (sargromastim)
Neutropenia, stem cell or bone marrow transplantation

Interleukin-11 (IL-11, oprelvekin)
Thrombocytopenia

Romiplostim ve eltrombopag
Thrombocytopenia