Drugs Used in Blood Disorders

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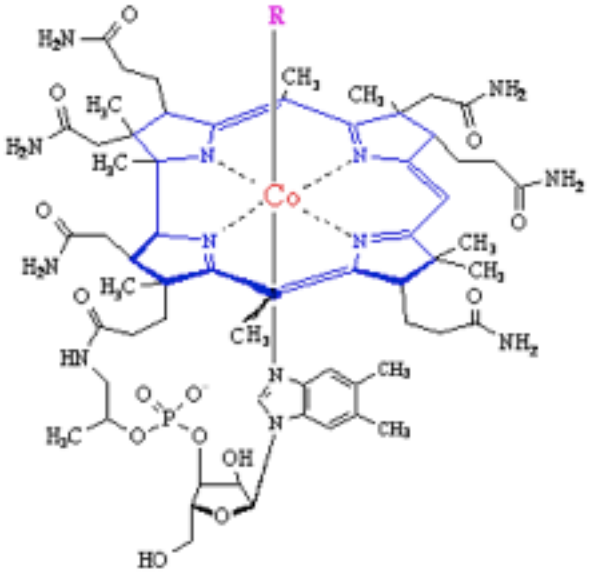
Vitamin B_{12}

- Its deficiency leads to anemia, gastrointestinal symptoms and neurological abnormalities.
- It consists of a porphyrin-like ring with a central cobalt atom attached to the nucleotide.



Active forms are:

1. Deoxyadenosylcobalamin
2. Methylcobalamin

Vitamin B_{12}

Pharmacokinetics:

1. Vitamin B_{12}, in physiologic amounts is absorbed only after it complexes with the intrinsic factor (a glycoprotein secreted by the parietal cells of the gastric mucosa).
2. The intrinsic factor-vitamin B_{12} complex is absorbed in the terminal ileum by a highly specific receptor-mediated endocytosis.

Vitamin B_{12}

3. Daily absorption ~ 1-5 µg.
4. Vitamin B_{12} is stored mainly in the liver with an average normal storage pool of 3-5 mg.
5. Daily requirements are ~ 2 µg.

How long would it take for the storage pool to be depleted and symptoms of deficiency to appear?

Vitamin B_{12}

6. Only trace amounts are lost in urine and stool.
7. Once absorbed it is transported in the body bound to a plasma glycoprotein, transcobalamin II.

Causes of deficiency:

Malabsorption of Vitamin B_{12} due to:

1. Lack of intrinsic factor.
2. Loss or malfunction of the terminal ileum.

Vitamin B_{12}

3. Strict vegetarians (long-term):

- The vitamin is NOT synthesized by animals or plants.
- The ultimate source is microbial synthesis
- Mainly present in meat (liver), eggs and dairy products.
- It has to be released from these sources before absorption.

Vitamin B_{12}

4. Atrophic gastritis (from *Helicobacter pylori)*

5. Lack of gastric HCl (cobalamin is NOT released from protein).

6. Drugs: proton pump inhibitors and metformin.

Vitamin B_{12}

Pharmacodynamics:

Vitamin B_{12} is involved in 2 essential enzymatic reactions in humans:

1. **Deoxyadenosylcobalamin is responsible for the isomerization of methylmalonyl-CoA to succinyl-CoA by the enzyme methylmalonyl-CoA mutase.**

- **In Vitamin B_{12} deficiency, methylmalonyl-CoA accumulates.**

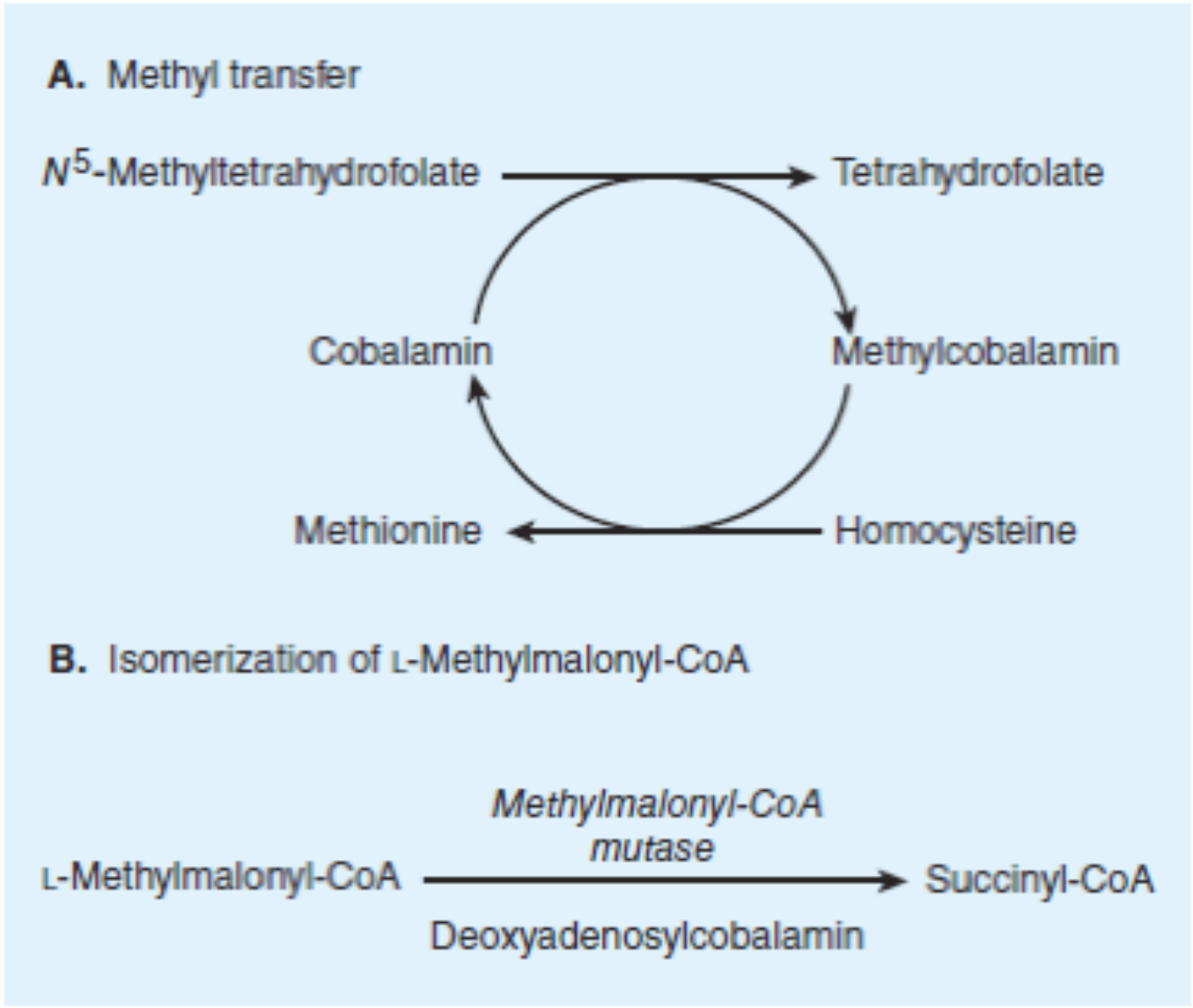


FIGURE 33–2 Enzymatic reactions that use vitamin B_{12}.

Vitamin B_{12}

2. **Methylcobalamine is involved in the transfer of a methyl group from N^5-methyltetrahydrofolate to homocysteine to form methionine and tetrahydrofolate (THF).**

- **THF is the precursor of many folate cofactors.**
- **In Vitamin B_{12} deficiency, folate cofactors become deficient leading to defects in several biochemical reactions involved in the transfer of one-carbon groups.**

Vitamin B_{12}

- In particular, depletion of THF prevents the synthesis of dTMP and purines required for DNA synthesis in rapidly dividing cells.
- The accumulation of folate as N^5-methyltetrahydrofolate and the associated depletion of THF has been referred to as the "methylfolate trap".

Vitamin B_{12}

- This is where vitamin B_{12} and folic acid metabolism are linked, and explains why the megaloblastic anemia of Vitamin B_{12} deficiency can be partially corrected by large doses of folic acid, which is converted to dihydrofolate and then to THF by folate reductases.

Vitamin B_{12}

- Evidence implicates disruption of the methionine synthesis pathway as a cause of neurological manifestations of Vitamin B_{12} deficiency in contrast to accumulation of methylmalonyl-CoA.
- Whatever the cause, administration of folic acid for Vitamin B_{12} deficient individuals will NOT correct neurological manifestations, but will largely correct the anemia.

Vitamin B_{12}

Clinical Pharmacology:

1. Treatment of pernicious anemia
2. Treatment of neurological manifestations of Vitamin B_{12} deficiency.

- Used as parenteral injection of cyanocobalamin or hydroxocobolamin, both to replenish stores and maintenance, usually for life.

Vitamin B_{12}

- **Hydroxocobalamin is preferred because it is more highly protein-bound and remain longer in the circulation.**

Folic Acid

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

The consequences of folate deficiency include:

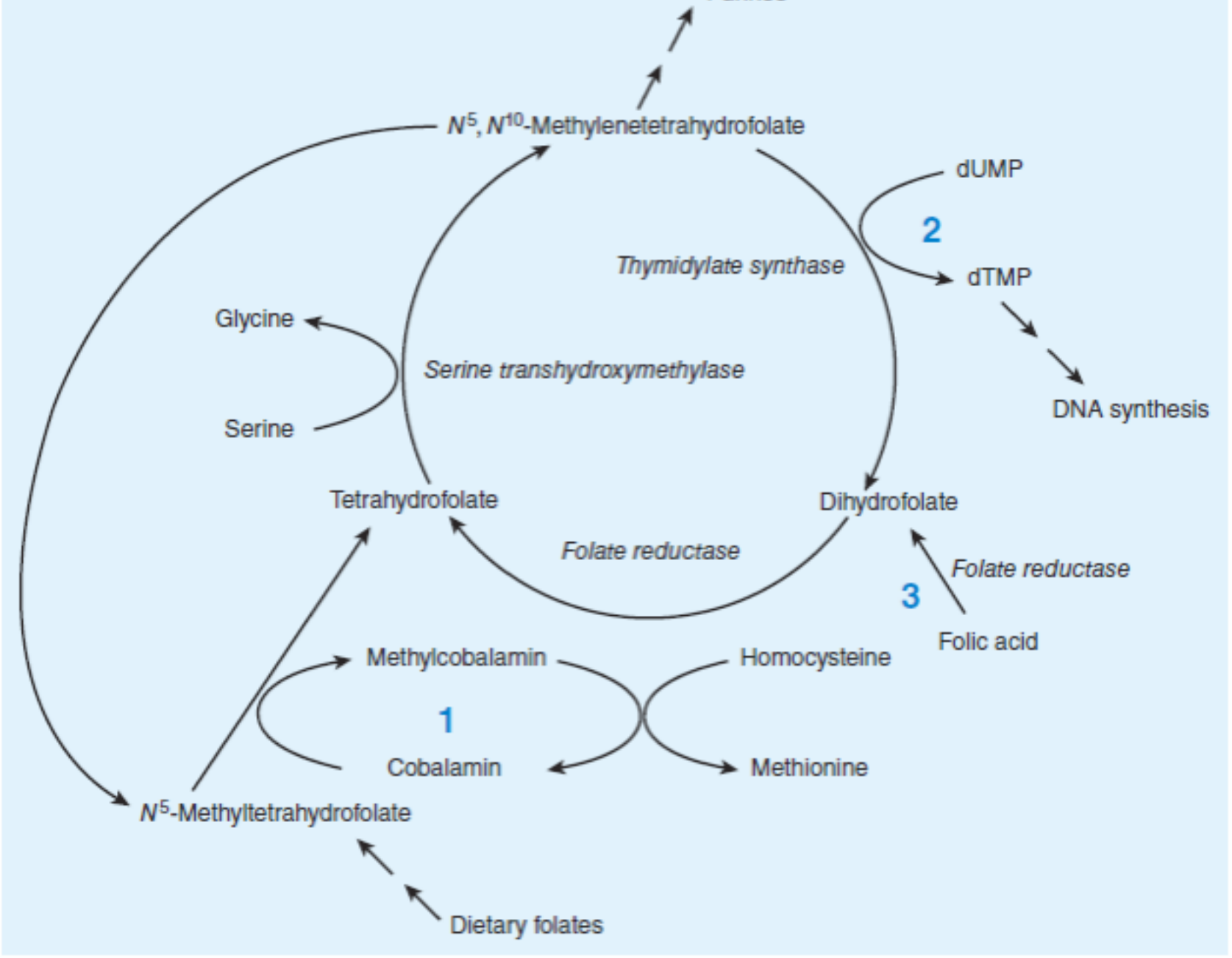
1. Megaloblastic anemia.
2. Congenital malformations – neural tube defects, such as spina bifida and anencephaly,
3. Occlusive vascular disease due to homocysteine accumulation.

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 possessing one-carbon.**
- **The folate cofactors are inter-convertable and serve the donation of one-carbon units at various level of oxidation.**



URE 33–3 Enzymatic reactions that use folates. **Section 1** shows the vitamin B_{12}–dependent reaction that allows most dietary fol
nter the tetrahydrofolate cofactor pool and becomes the "folate trap" in vitamin B_{12} deficiency. **Section 2** shows the deoxythymidine

Folic Acid

Pharmacokinetics:

- Food rich in folic acid include yeast, liver, kidney & green vegetables.

1. Usual daily absorption from diet ~ 50-100 µg, depending on metabolic requirements.
2. Pregnant women may absorb up to 300-400 µg.

Folic Acid

3. Normal tissue storage in liver and other tissues ~ 5-20 mg.
- If folic acid absorption stops, megaloblastic anemia develops in 1-6 months.
4. Folic acid is absorbed in the proximal jejunum.

Folic acid

Clinical pharmacology:

1. Megaloblastic anemia. Vitamin B_{12} 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 dihdrofolate reductase

B. Long-term phenytoin therapy impair folate absorption

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

- 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.

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.