

Vitamin B₁₂ Deficiency Anemia

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- A 50 years old morbidly obese female with diabetes mellitus, underwent a stomach surgery procedure to reduce the capacity of the stomach to be able to reduce weight. 3 years later she developed a macrocytic type of anemia. Her medications included metformin for diabetes. She had a history of dyspepsia. Serum folic acid was normal

Vitamin B₁₂

- 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 B₁₂

Pharmacokinetics:

1. Vitamin B₁₂, in physiologic amounts is absorbed after it complexes with the intrinsic factor (a glycoprotein secreted by the parietal cells of the gastric mucosa).
2. The intrinsic factor-vitamin B₁₂ complex is absorbed in the terminal ileum **by a highly specific receptor-mediated endocytosis.**

Vitamin B₁₂

- 3. Daily absorption ~ 1-5 µg.
- 4. Vitamin B₁₂ 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 B₁₂

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 B₁₂ due to:

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

Vitamin B₁₂

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 B₁₂

- 4. Atrophic gastritis (from *Helicobacter pylori*)**
- 5. Lack of gastric HCl (cobalamin is NOT released from protein).**
- 6. Drugs: proton pump inhibitors and other gastric acid lowering drugs, and metformin.**

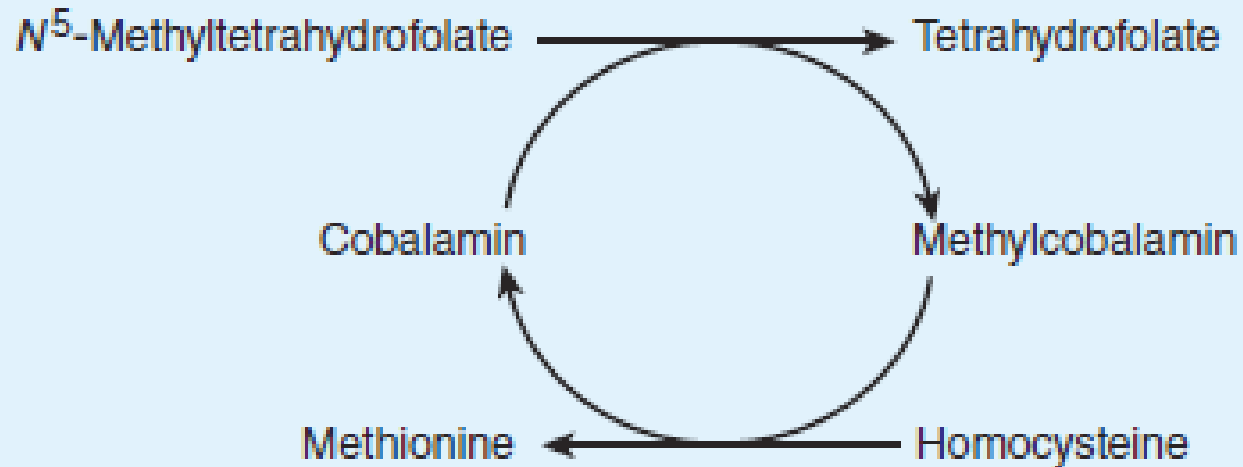
Vitamin B₁₂

Pharmacodynamics:

Vitamin B₁₂ 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 B₁₂ deficiency, **methylmalonyl-CoA accumulates.**

A. Methyl transfer



B. Isomerization of L-Methylmalonyl-CoA

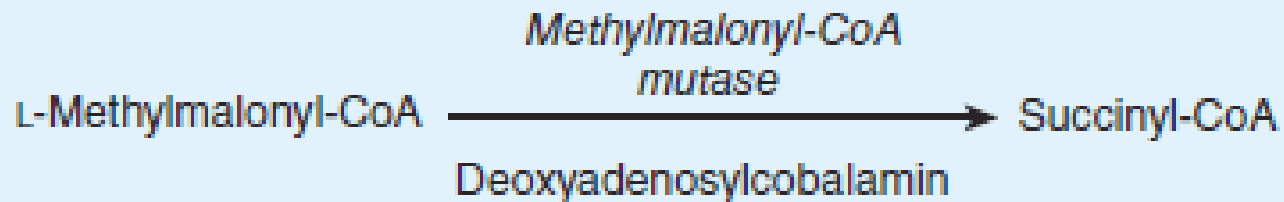


FIGURE 33-2 Enzymatic reactions that use vitamin B₁₂.

Vitamin B₁₂

- 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 B₁₂ deficiency, folate cofactors become deficient leading to defects in several biochemical reactions involved in the transfer of one-carbon groups.

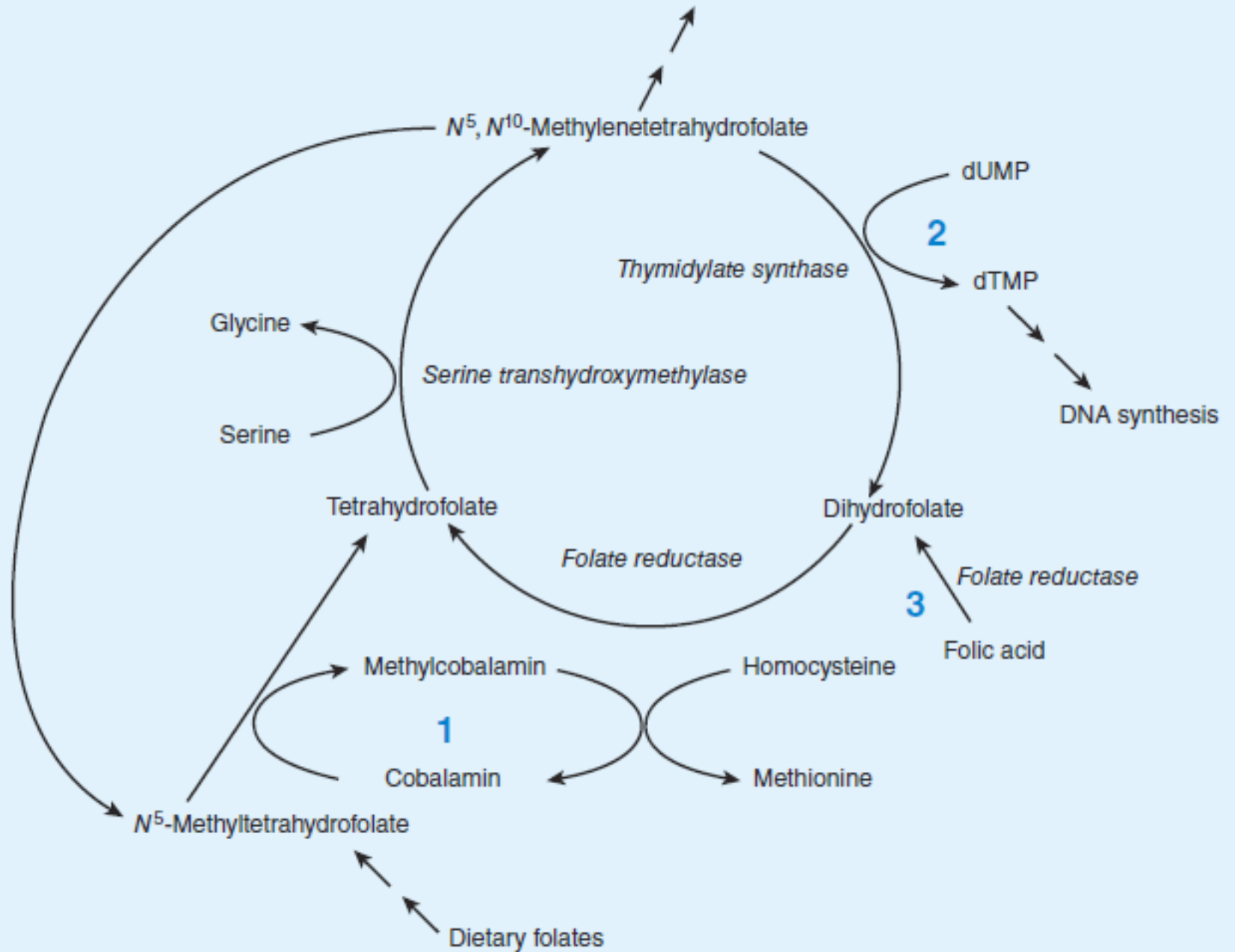


FIGURE 33-3 Enzymatic reactions that use folates. **Section 1** shows the vitamin B₁₂-dependent reaction that allows most dietary folates to enter the tetrahydrofolate cofactor pool and becomes the "folate trap" in vitamin B₁₂ deficiency. **Section 2** shows the deoxythymidine monophosphate (dTMP) cycle.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

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- 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 B₁₂

- This is where vitamin B₁₂ and folic acid metabolism are linked, and explains why the megaloblastic anemia of Vitamin B₁₂ deficiency can be partially corrected by large doses of folic acid, which is converted to dihydrofolate and then to THF by folate reductases.

Vitamin B₁₂

Causes of neurological manifestations of Vitamin B₁₂ deficiency:

- 1. Impaired Methionine Synthase Activity: A deficiency decreases the production of methionine and S-adenosylmethionine (SAM), which is vital for the synthesis and maintenance of the myelin sheath protecting nerve fibers.**

Vitamin B₁₂

- 2. Accumulation of Methylmalonic Acid (MMA) and Homocysteine: When B12 is low, MMA and homocysteine levels rise, leading to toxic, abnormal myelination, oxidative stress, and neural overstimulation.**
- 3. Upregulation of Inflammatory Cytokines: The deficiency triggers an increase in neurotoxic tumor necrosis factor-alpha (TNF-alpha) and a decrease in protective neurotrophic factors.**

Vitamin B₁₂

- Whatever the cause, administration of folic acid for Vitamin B₁₂ deficient individuals will **NOT correct neurological manifestations, but** will largely correct the anemia.

Vitamin B₁₂

Clinical Pharmacology:

1. Treatment of pernicious anemia
 2. Treatment of neurological manifestations of Vitamin B₁₂ deficiency.
- Used as parenteral injection of cyanocobalamin or hydroxocobolamin, both to replenish stores and maintenance, usually for life.

Vitamin B₁₂

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