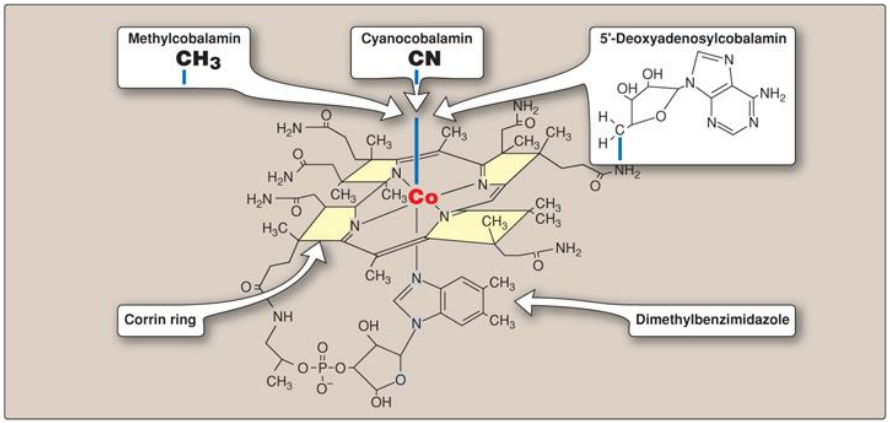
Vitamins

B_6 and B_{12}



Neuropsychiatry Block

Dr. Usman Ghani

Biochemistry

Objectives

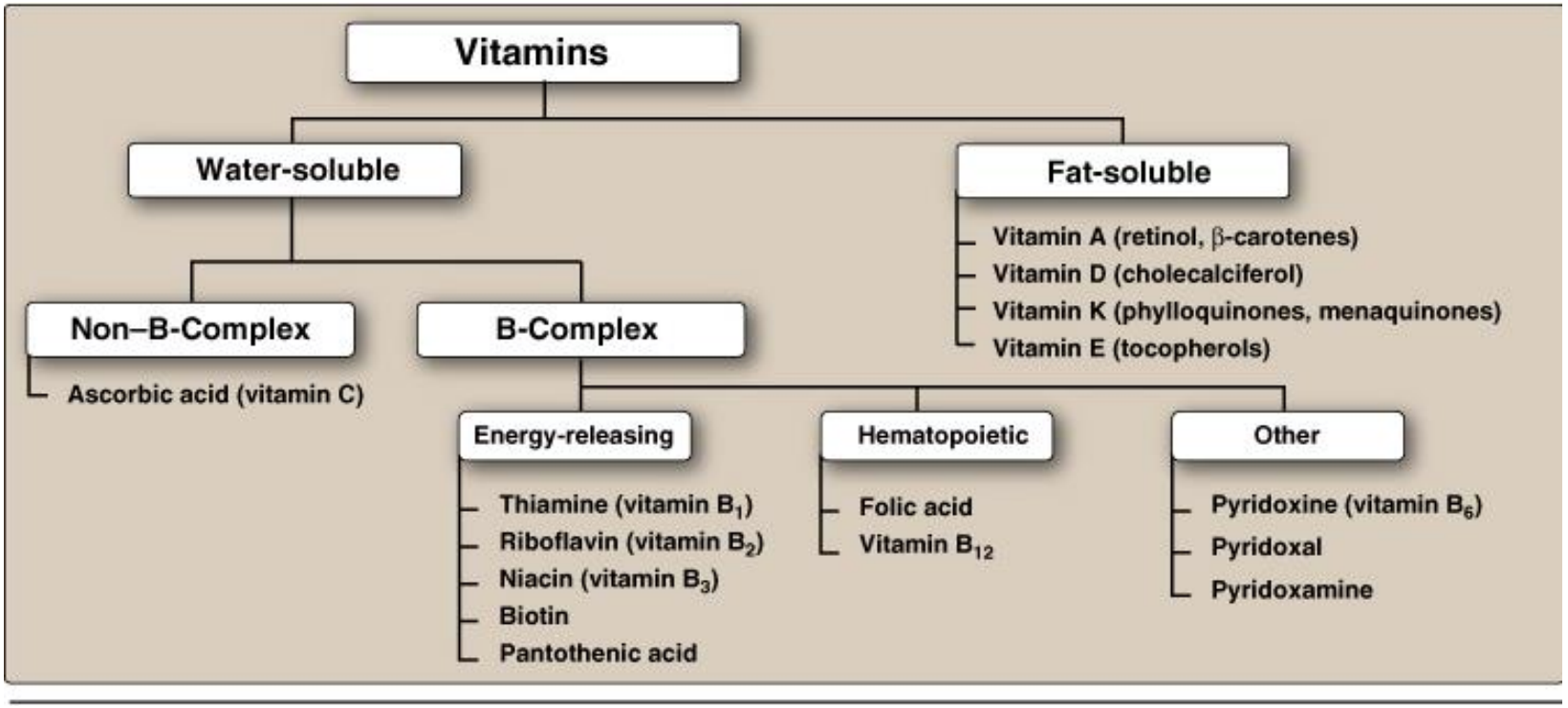
By the end of this lecture the Second Year students will be able to:

- Understand the types and functions of vitamins B_6 and B_{12}
- Recognize the role of these vitamins in maintaining the myelin sheath of nerves and their function
- Discuss the consequences of vitamin B_6 and B_{12} deficiency that can lead to nerve degeneration and irreversible neurological damage

Overview

- Types and functions of vitamins B_6 and B_{12}
- Disorders due to Vitamins B_6 and B_{12} deficiency
- Vitamin B_{12} deficiency and folate trap
- Demyelination, neuropathy and neuropsychiatric symptoms of vitamin B_{12} deficiency

Classification of Vitamins



Water-Soluble Vitamins

- **B vitamins**
  - **Thiamin (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_7), cobalamin (B_{12}), folate**

- **Not significantly stored in the body**
- **Must be supplied regularly in the diet**
- **Excess excreted**

Vitamin B Complex

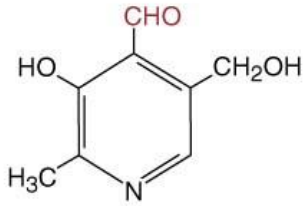
- **Present in small quantities in different types of food**
- **Important for growth and good health**
- **Help in various biochemical processes in cell**
- **Function as coenzymes**

Vitamin B_6

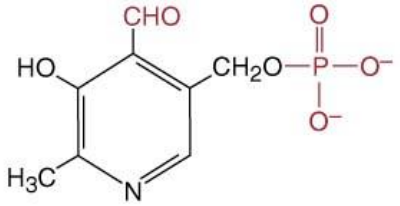
- **Three forms**
  - **Pyridoxine**
  - **Pyridoxal**
  - **Pyridoxamine**
- **Active form**
  - **All 3 are converted to pyridoxal phosphate (PLP)**

Pyridoxine

Pyridoxamine



Pyridoxal



Pyridoxal phosphate

Figure 28.11. Structures of vitamin B_6.

Functions of Vitamin B_6

- **As coenzyme for**
  - **Transamination**
  - **Deamination**
  - **Decarboxylation**
  - **Condensation reactions**

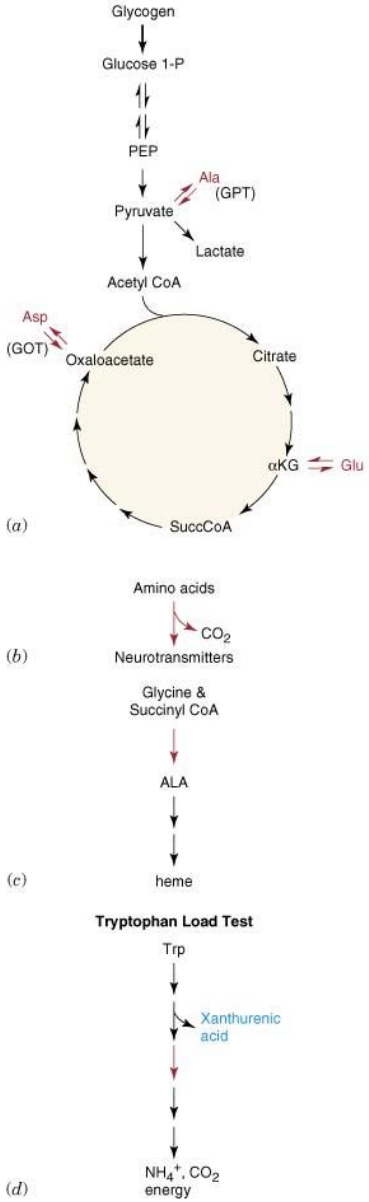
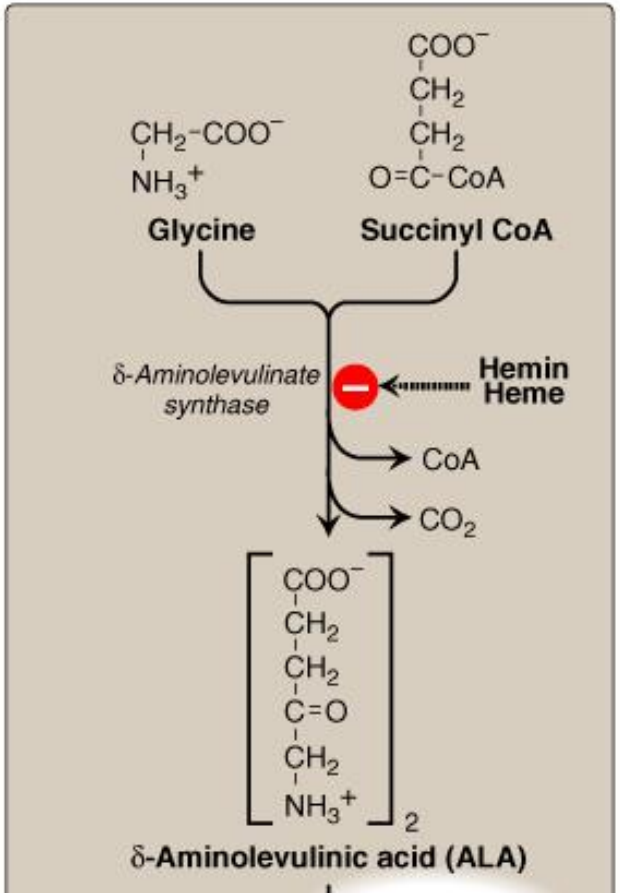


Figure 28.12. Some important metabolic roles of pyridoxal phosphate.

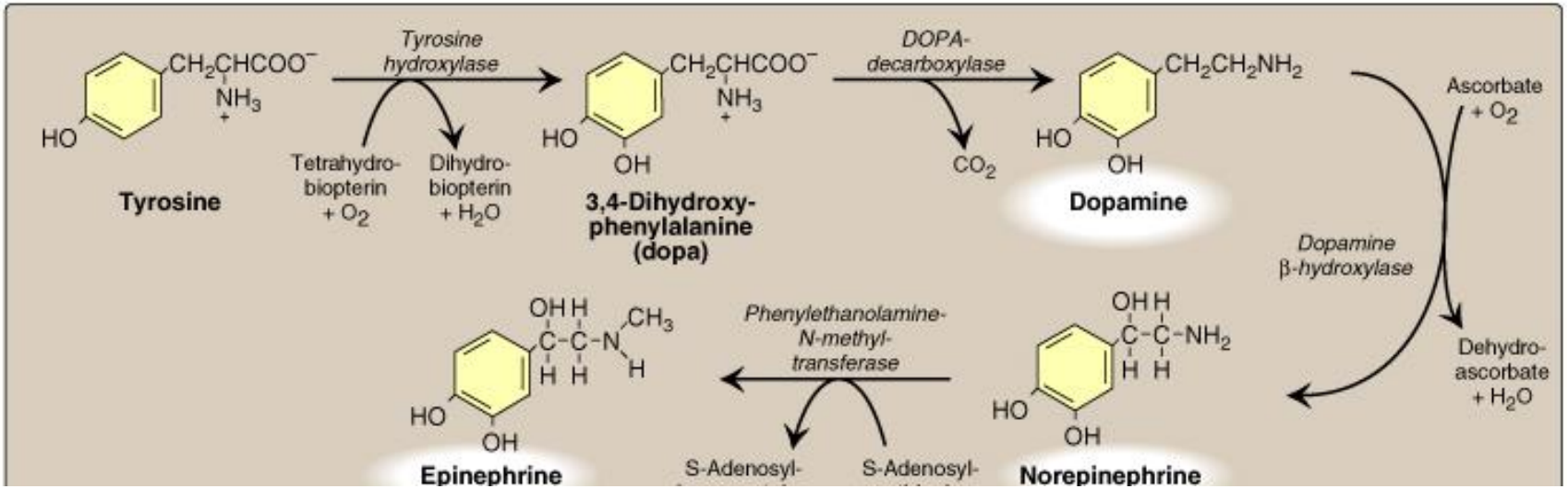
Condensation Reaction

Formation of ALA by ALA synthase,
The regulatory step in hemoglobin synthesis



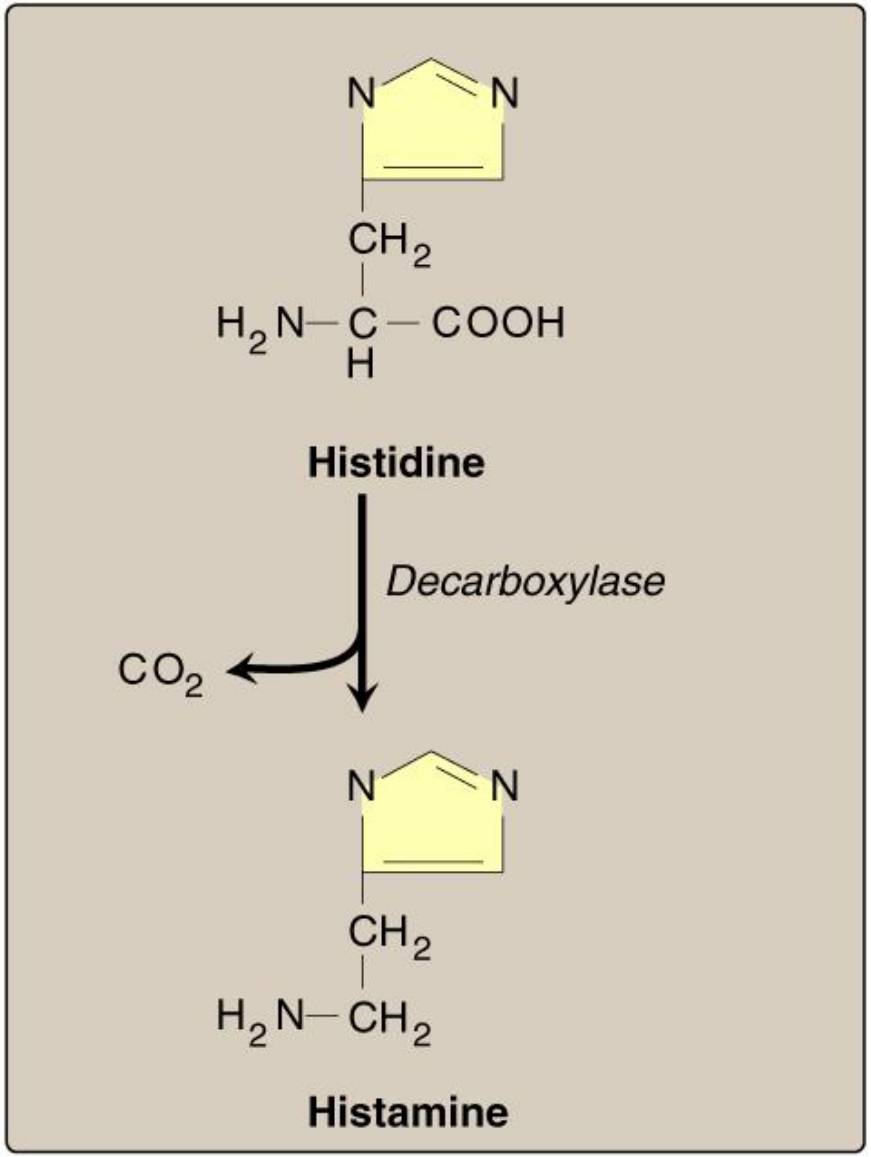
Decarboxylation Reaction:

Formation of Chatecholamines: Dopamine, norepinephrine and epinephrine



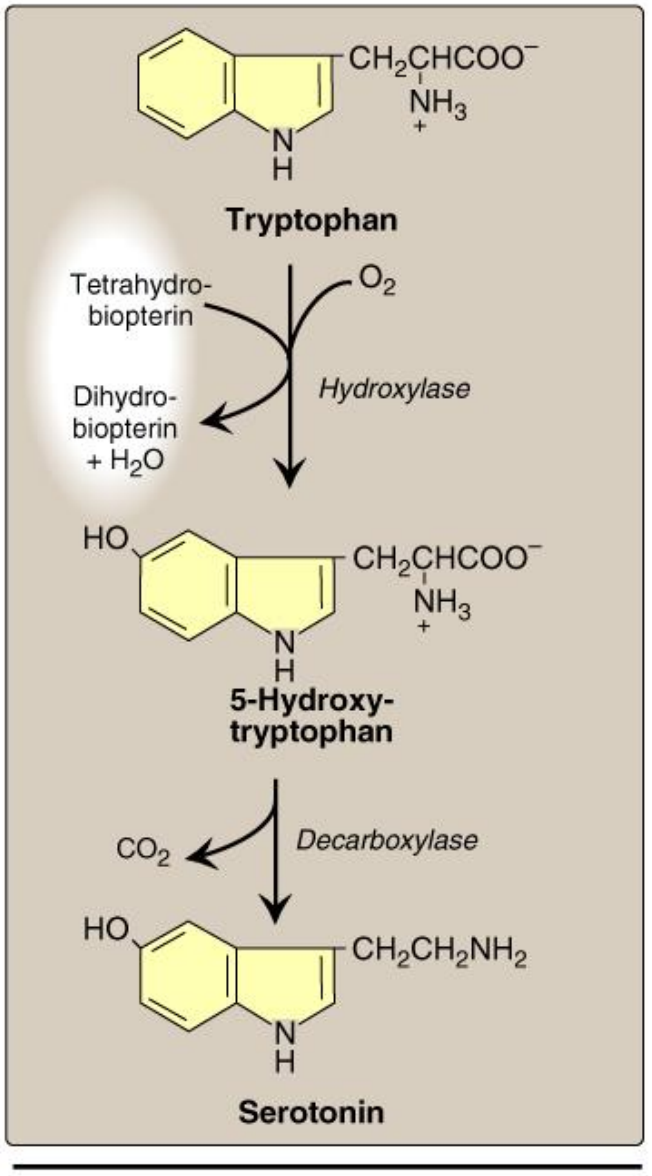
Decarboxylation Reaction:

Formation of histamine

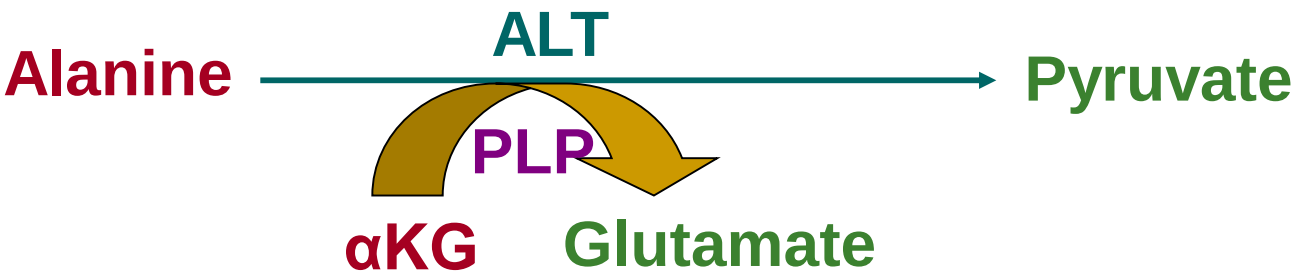


Decarboxylation Reaction:

Formation of Serotonin



Transamination Reaction



Disorders of Vitamin B_6 Deficiency

- **Dietary deficiency is rare, but it is observed in:**
  - **Newborn infants fed on formulas low in B_6**
  - **Women on oral contraceptives**
  - **Alcoholics**
- **Isoniazid treatment for tuberculosis can lead to vitamin B_6 deficiency by forming inactive derivative with PLP**

Disorders of Vitamin B_6 Deficiency

- **Deficiency leads to poor activity of PLP-dependent enzymes causing:**
  - **Deficient amino acid metabolism**
  - **Deficient lipid metabolism**
  - **Deficient neurotransmitter synthesis:**
    - **Serotonin, epinephrine, norepinephrine and gamma-aminobutyric acid (GABA)**

Disorders of Vitamin B_6 Deficiency

- **PLP is involved in the synthesis of sphingolipids**
- **Its deficiency leads to demyelination of nerves and consequent peripheral neuritis**

Disorders of Vitamin B_6 Deficiency

- **Mild deficiency leads to:**
  - **Irritability**
  - **Nervousness**
  - **Depression**

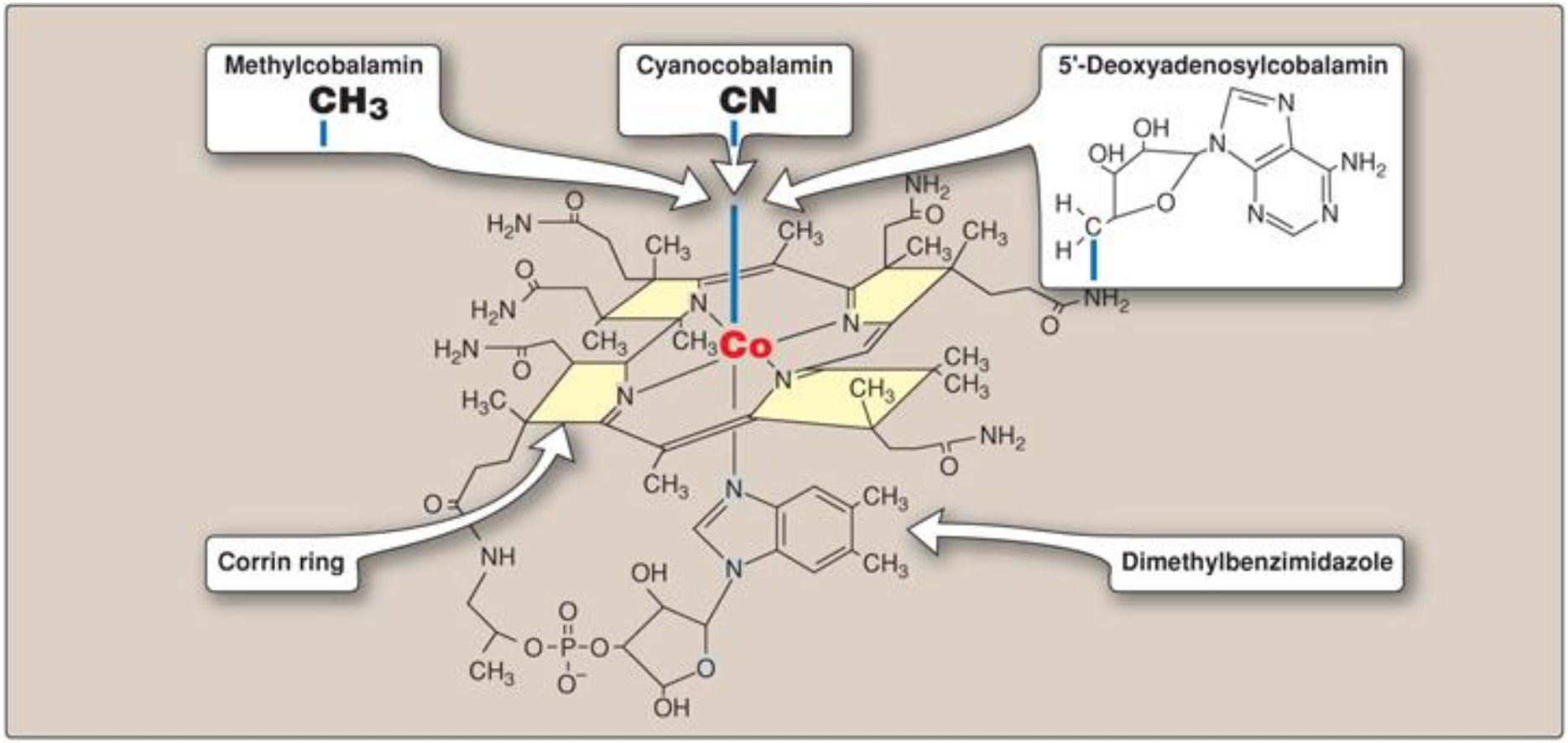
- **Severe deficiency leads to:**
  - **Peripheral neuropathy**
  - **Convulsions**

Forms of Vitamin B_{12}

- Cyanocobalamin
- Hydroxycobalamin
- Adenosylcobalamin (major storage form in the liver)
- Methylcobalamin (mostly found in blood circulation)

Coenzyme forms of B_{12}

- Adenosylcobalamin and Methylcobalamin
  - Coenzymes for metabolic reactions
- Body can convert other cobalamins into active coenzymes



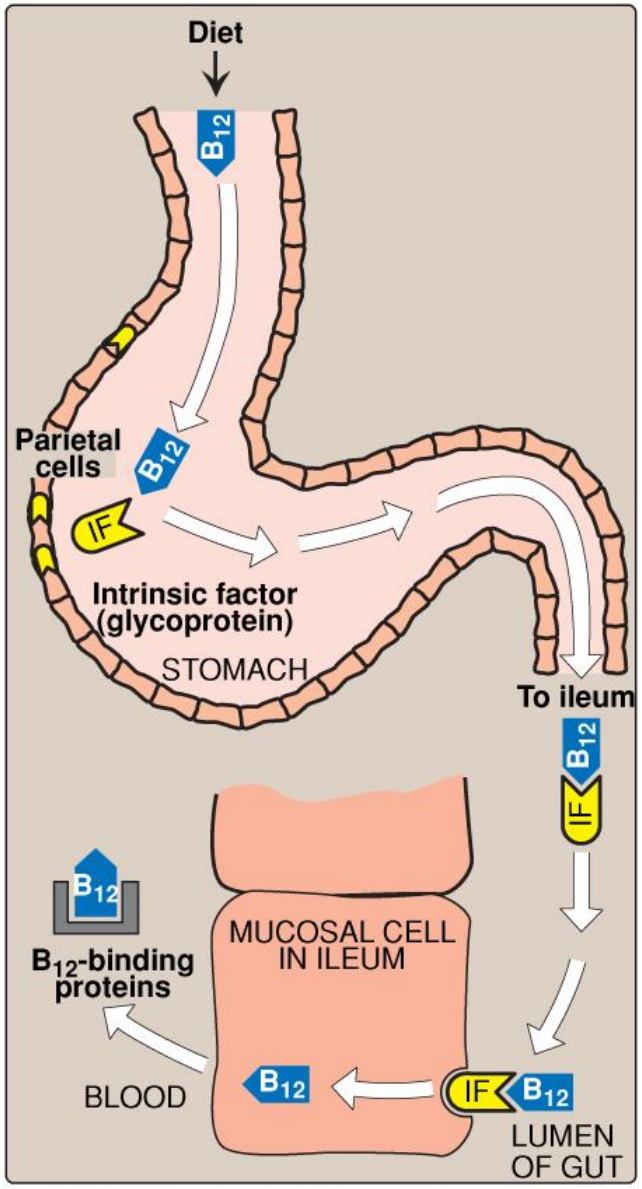
Vitamin B_{12}

(Cobalamin)

- Mainly found in animal liver
- Bound to protein as
  - Methylcobalamin or
  - 5’-deoxyadenosylcobalamin

Vitamin B_{12}

- Essential for normal nervous system function and red blood cell maturation
- Not synthesized in the body and must be supplied in the diet
- Binds to intrinsic factor and absorbed by the ileum
- Intrinsic factor is a protein secreted by cells in the stomach



Vitamin B_{12} Storage

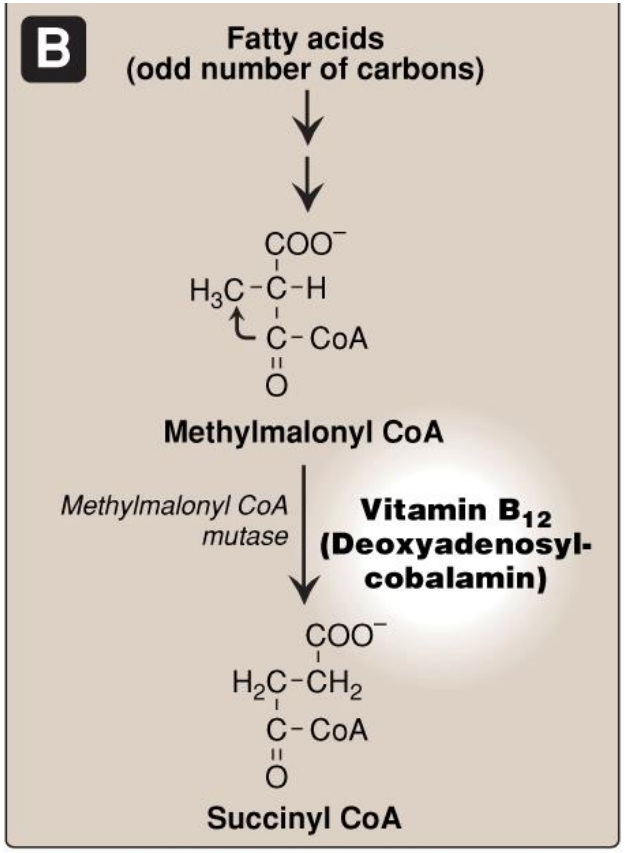
- Liver stores vitamin B_{12} (4-5 mg)
- Other B vitamins are not stored in the body
- Vitamin B_{12} deficiency is observed in patients with IF deficiency due to autoimmunity or by partial or total gastrectomy
  - Clinical deficiency symptoms develop in several years

Functions of Vitamin B_{12}

Two reactions require B_{12}

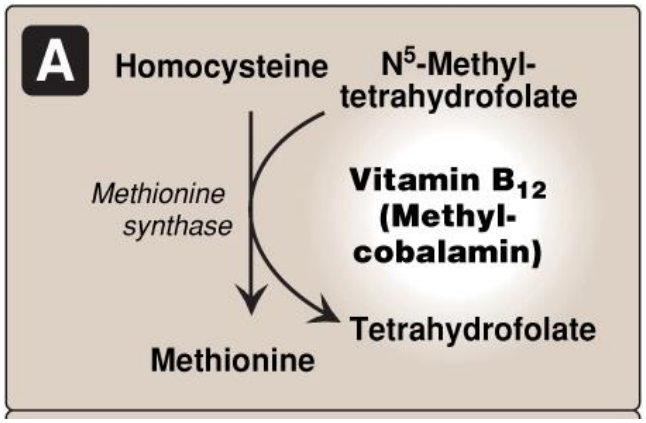
1. Conversion of methylmalonyl-CoA to succinyl-CoA

- The enzyme in this pathway, methyl-malonyl-CoA mutase, requires B_{12}



Functions of Vitamin B_{12}

2. Conversion of homocysteine to methionine



- Methionine synthase requires B_{12} in converting homocysteine to methionine

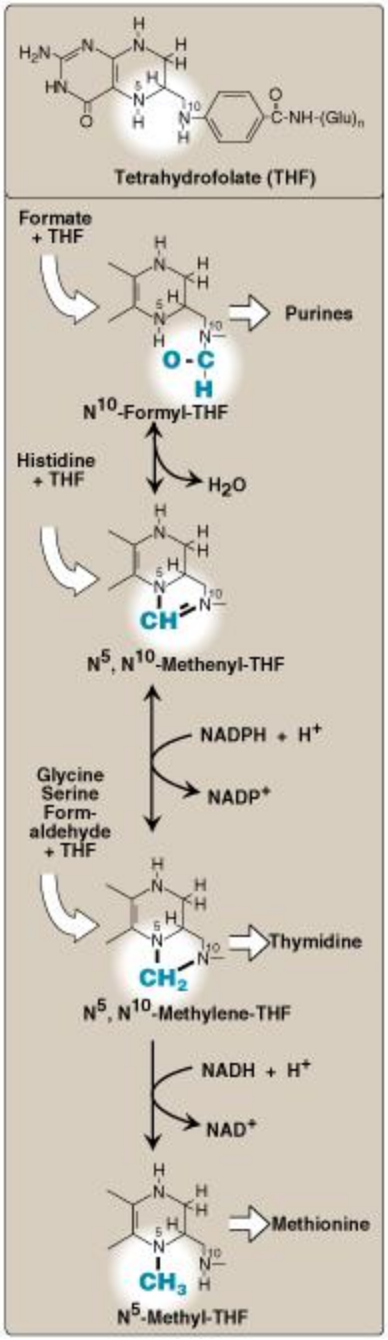
B_{12} Deficiency and Folate Trap

- Homocysteine re-methylation reaction is the only pathway where N^5-methyl TH4 can be returned back to tetrahydrofolate pool
- Hence folate is trapped as

  N^5-methyltetrahydrofolate (folate trap)
- This leads to folate deficiency and deficiency of other TH4 derivatives (N^5-N^{10} methylene TH4 and N^{10} formyl TH4) required for purine and pyrimidine syntheses

TH4: Tetrahydrofolate

Interconversion between TH4 carrier of "one-carbon units"



Disorders of Vitamin B_{12} Deficiency

Pernicious anemia

- Megaloblastic anemia
- Vitamin B_{12} deficiency is mainly due to the deficiency of intrinsic factor

Disorders of Vitamin B_{12} Deficiency

Demyelination

- Myelin sheath of nerves is chemically unstable and damaged

Neuropathy

- Peripheral nerve damage

Disorders of Vitamin B_{12} Deficiency

Causes of neuropathy

- Deficiency of vitamin B_{12} leads to accumulation of methylmalonyl CoA
- High levels of methylomalonyl CoA are used instead of malonyl CoA for fatty acid synthesis
- Myelin synthesized with these abnormal fatty acids is unstable and degraded causing neuropathy

Neuropsychiatric symptoms of Vitamin B_{12} Deficiency

Neurological symptoms

- Paraesthesia (abnormal sensation) of hands and feet
- Reduced perception of vibration and position
- Absence of reflexes
- Unsteady gait and balance (ataxia)

Neuropsychiatric symptoms of Vitamin B_{12} Deficiency

Psychiatric symptoms

- Confusion and memory loss
- Depression
- Unstable mood

Take home message

- Vitamins B_6 and B_{12} are essential in maintaining the nerve function and the central nervous system
- Various neurological symptoms have been associated with their deficiency

References

- Lippincott's Biochemistry. 5th Edition, pp 375-376, 378, Lippincott Williams & Wilkins, New York, USA