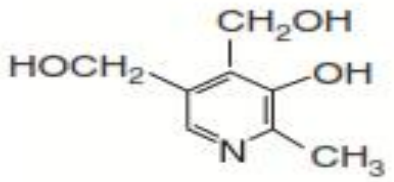
B-COMPLEX VITAMINS

PYRIDOXINE (Vitamin B_6)

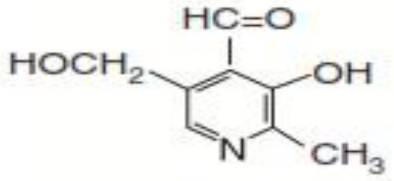
Chemistry

- 2-methyl, 3-OH, 4-5-dihydroxymethylpyridine
- Pyridoxine (pyridoxol) , pyridoxal (an aldehyde), pyridoxamine (an amine)
- All 3 exhibit vit.B6 activity

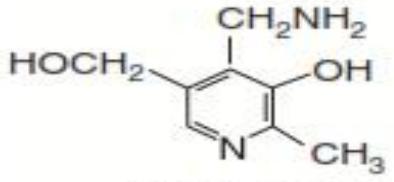


Pyridoxine

Vitamers: One of two or more related chemical substances that fulfill the same specific vitamin function



Pyridoxal



Pyridoxamine

- Biologically active - phosphorylated derivatives

1.Pyridoxal-PO4

2.Pyridoxamine-PO4

Phosphorylation occurs in brain, liver & other tissues (dehydrogenase, pyridoxal kinase, ATP, Zn^{++})

- 6 compounds have vit.B6 activity: pyridoxine, pyridoxal, pyridoxamine & their 5-phosphates

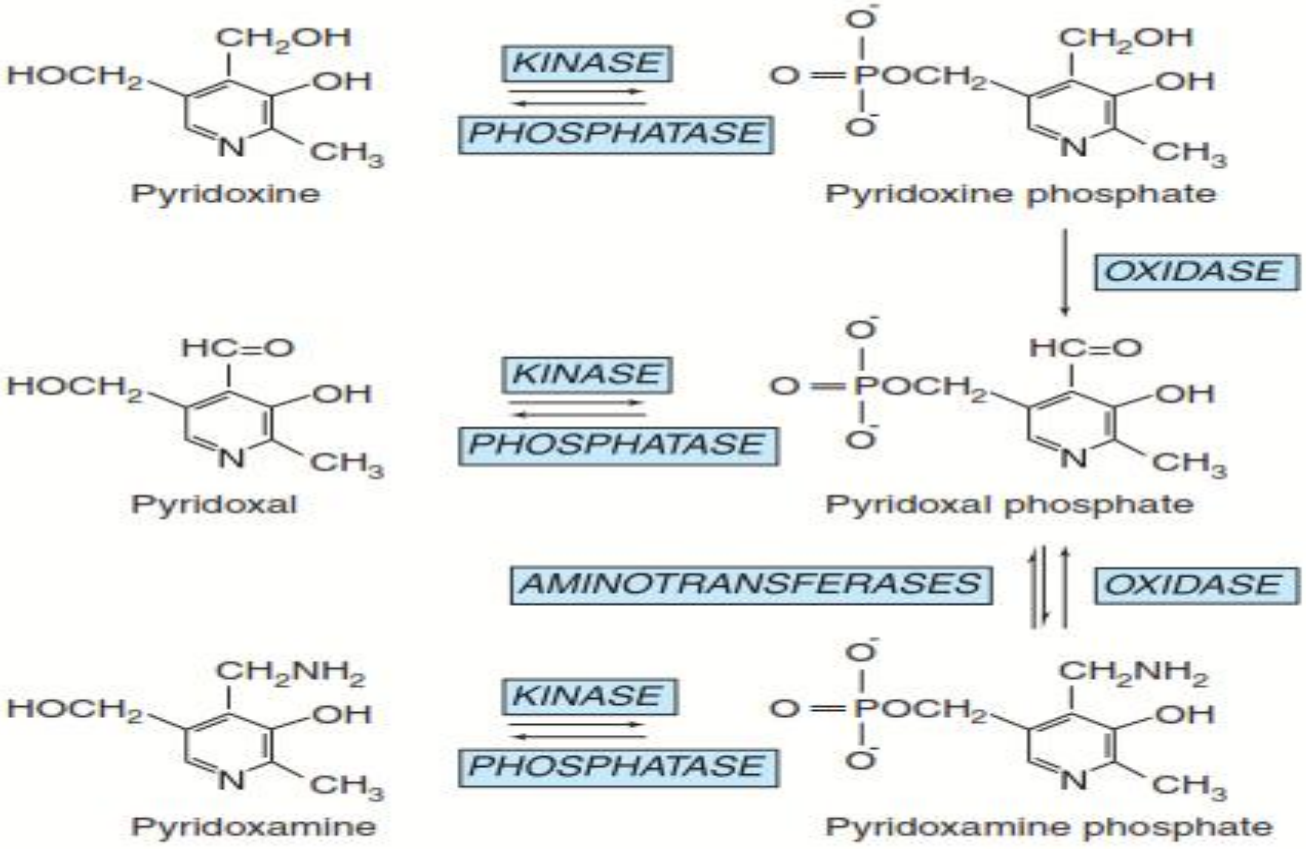


Figure 45–12. Interconversion of the vitamin B_6 vitamers.

Biosynthesis/RDA

- Plants & microbes can synthesize
- HUMAN: cannot synthesize, intestinal bacteria can

- RDA: Adults 2 mg
  Children 0.3-0.4 mg

Requirement relate to dietary protein intake, as it is coenzyme in amino acid metabolism

Occurrence & Sources

- Widely distributed in animals & plants
- Animal sources: liver, kidney, fish
- Plants sources: Germinating parts of seeds, rice, cereal grains, yeast

Metabolism

- Absorption: absorbed in small intestine

- Excretion:

1. As pyridoxal & pyridoxamine (0.5-0.7mg/day)
2. As 4-pyridoxic acid (inactive form, 3 mg/day)

Amino acids & glycogen metabolism

Active coenzyme - pyridoxal 5'-phosphate

Approximately 80% of the body's total vitamin B_6 is present as pyridoxal phosphate in muscle, mostly associated with glycogen phosphorylase

This is not available in B deficiency but is released in starvation, when glycogen reserves become depleted, and is then available, especially in liver and kidney, to meet increased requirement for gluconeogenesis from amino acids.

Gluconeogenesis

Pyridoxal phosphate can catalyze transamination reactions

Reaction essential for the providing amino acids as a substrate for gluconeogenesis

Vitamin B_6 - coenzyme of glycogen phosphorylase, the enzyme necessary for glycogenolysis to occur

Metabolic Role

- **As coenzyme (amino acid metabolism)**

- Transaminases: transamination reactions
- Decarboxylases: decarboxylation reactions
- Deaminases: deamination reactions

- As coenzyme (lipid metabolism)

- In arachidonic acid biosyn. From linoleic acid
- In sphingomyelin biosyn. From serine

- **In aminoacetone biosyn. From acetyl CoA & Gly**
- **In CoA-SH biosyn. From pantothenic acid**

- Transaminases

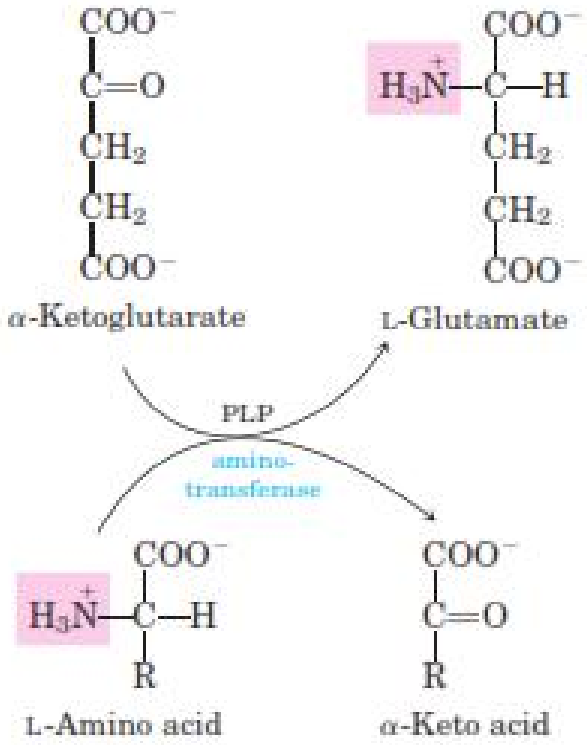


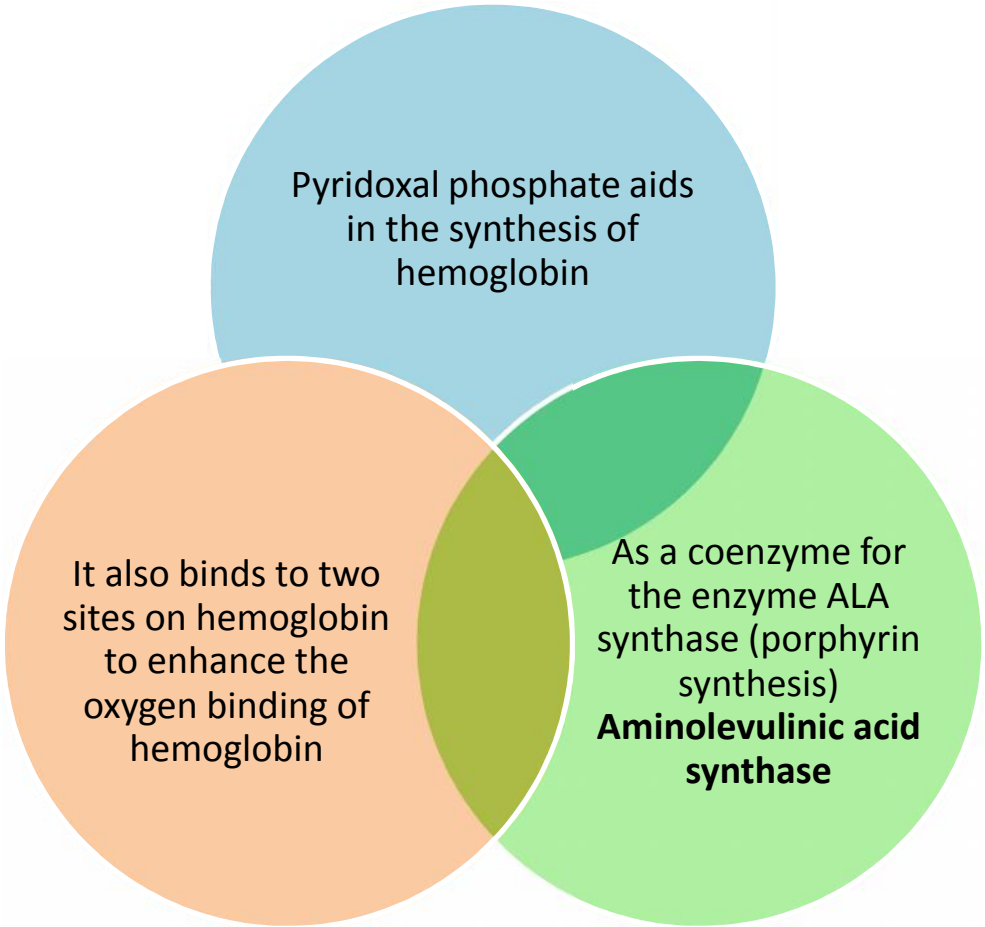
FIGURE 18–4 Enzyme-catalyzed transaminations. In many aminotransferase reactions, α-ketoglutarate is the amino group acceptor. All aminotransferases have pyridoxal phosphate (PLP) as cofactor. Although the reaction is shown here in the direction of transfer of the amino group to α-ketoglutarate, it is readily reversible.

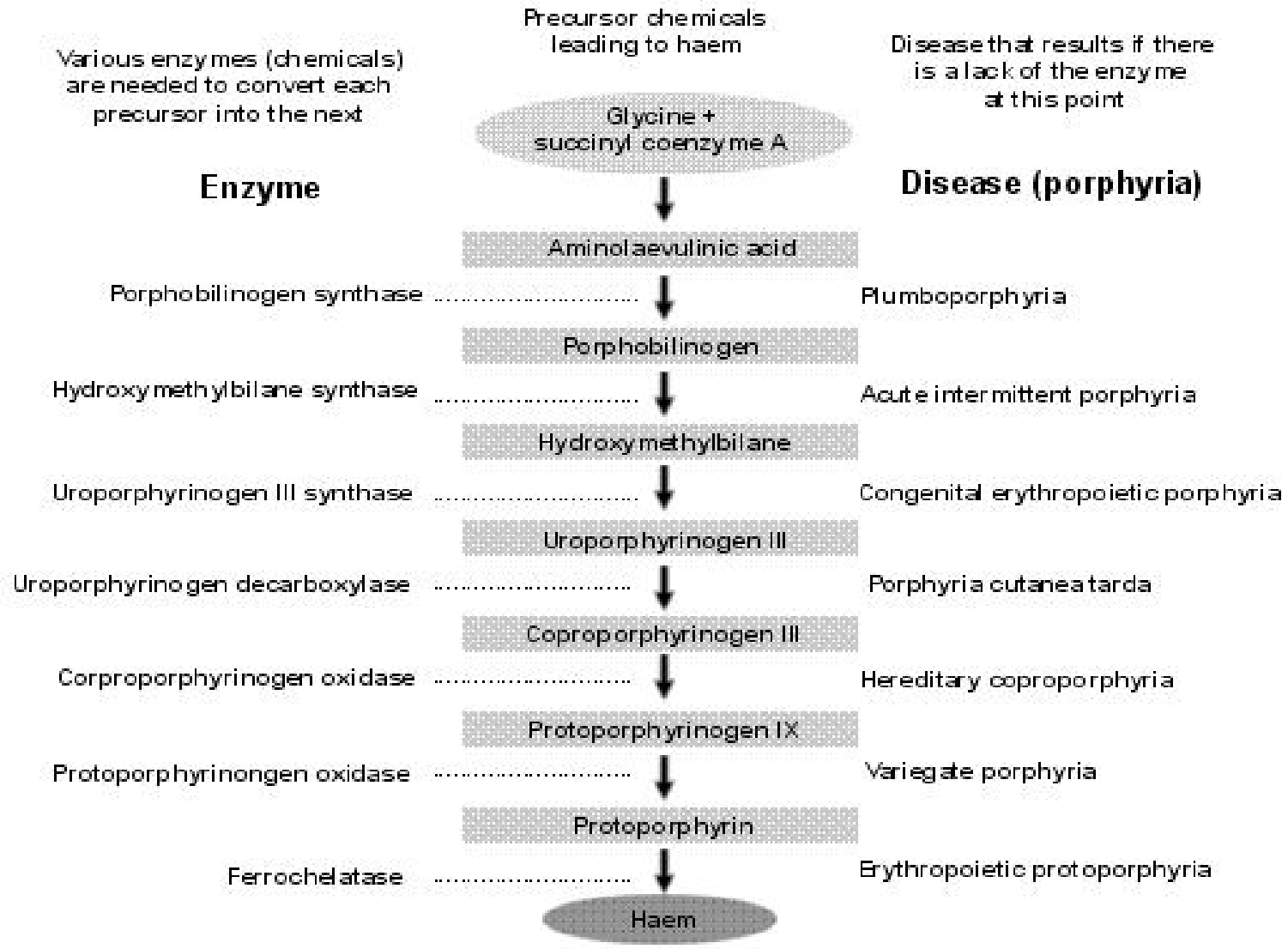
Amino acid Metabolism

Reaction type	Example
Transamination	Oxaloacetate + glutamate ⇄ aspartate + α-ketoglutarate
Deamination	Serine → pyruvate + NH_3
Decarboxylation	Histidine → histamine + CO_2
Condensation	Glycine + succinyl CoA → δ-aminolevulinic acid

- Coenzyme for kynureninase
- Levels of kynurenine, 3-OH-kynurenine increases
- Xanthurenic acid formation occurs, excreted in urine
- Coenzyme for transulfuration reactions
- Coenzyme for inter-conversion of glycine and serine
- Coenzyme for sphingomyelin synthesis
- Coenzyme for Fatty acid chain elongation
- Coenzyme for muscle phosphorylase
- Coenzyme for aminoacetone synthetase
- Promotes K^+ transport into the cell

Hemoglobin synthesis and function





The pathway of chemicals leading up to Haem

Haem is needed to make haemoglobin in red blood cells. Blocks at points in this pathway of chemicals result in a build up of various precursor chemicals which cause the different porphyrias.

Neurotransmitter synthesis

- Pyridoxal-P-dependent enzymes play role in transmitters (serotonin, dopamine, epinephrine, norepinephrine, gamma-aminobutyric acid GABA).

- Serine racemase, which synthesizes the neuromodulator D-serine from L-serine, is also a pyridoxal phosphate-dependent enzyme

Neuromodulator A chemical agent that is released by a neurosecretory cell and acts on other neurons in a local region of the central nervous system by modulating their response to neurotransmitters.

Histamine synthesis

- Pyridoxal phosphate is involved
- **Histamine** - an organic N compound involved in local immune response & regulate physiological function in the gut
- As a neurotransmitter
- Involved in the inflammatory response

(The immune response is how your body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful)

Gene Expression

- Pyridoxal phosphate - implicated in increasing or decreasing the expression of certain genes
- Increased intracellular levels of the vitamin will lead to a decrease in the transcription of some hormones
- Vitamin B_6 deficiency will lead to the increased expression of albumin mRNA
- Pyridoxal phosphate will influence gene expression of glycoproteins

- Vit. B_6 important in steroid hormone action where it removes the hormone-receptor complex from DNA binding, terminating the action of the hormones

- In vitamin B_6 deficiency, this results in increased sensitivity to the actions of low concentrations of estrogens, androgens, cortisol & vitamin D

High intake may lower the risk of Parkinson's disease, by protecting brain cells from damage caused by free radicals

Vitamin B_6 Deficiency Is Rare

- Clinical deficiency disease is rare
- Evidence - a significant proportion of the population have marginal vitamin B_6 status
- Moderate deficiency results in abnormalities of Trp & Met metabolism
- Increased sensitivity to steroid hormone action may be important in the development of **hormone-dependent cancer** of the breast, uterus, prostate (it terminates H action by affecting receptors)
- Vitamin B_6 status may affect the prognosis

Clinical manifestations – B_6 Deficiency

- Epileptiform convulsions

Less glutamic acid decarboxylase activity (Pyridoxal-P coenzyme), less GABA in brain, So convulsions

- Pyridoxine induced anaemia

Heme syn. Affects, Fe not utilized, microcytic anaemia

Epilepsy (from the Ancient Greek meaning "to seize, possess, or afflict")

- A group of long-term neurological disorders characterized by epileptic seizures
- Seizures are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking
- In epilepsy, seizures tend to recur, and have no immediate underlying cause,

contraction of the body caused by violent, involuntary muscular contractions

a violent disturbance

an outburst of great, uncontrollable laughter

- **Isoniazid (isonicotinic acid hydrazide), a drug frequently used to** treat tuberculosis, can induce a deficiency by forming an inactive derivative with pyridoxal phosphate

- Dietary supplementation with B6 is, thus, an adjunct to isoniazide treatment
- Otherwise, dietary deficiencies in pyridoxine are rare but have been observed in born infants fed formulas low in vitamin in women taking oral contraceptives, and in alcoholics

Excessive Vitamin B_6 Causes Sensory Neuropathy

- Development of sensory neuropathy reported in patients taking 2–7 g of pyridoxine per day for a variety of reasons
- Other reports suggest that intakes in excess of 200 mg/d are associated with neurologic damage
- Substantial improvement, but not complete recovery, occurs when the vitamin is discontinued.

Sensory neuropathy is a type of peripheral neuropathy that involves damage to sensory nerves. These are the nerves that relay information about sensory experiences such as a light touch or the pain of a minor injury.

- Neurologic symptoms have been observed at intakes of greater than 2 g/day.
- Substantial improvement, but not complete recovery, occurs when the vitamin is discontinued.

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- Chatterjee, M. N. and R. Shinde. 2007. Textbook of Medical Biochemistry. 7th ed (Indian edition). Jaypee Brothers, Medical Publishers (P) Ltd, New Delhi, India.
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