II. WATER SOLUBLE VITAMINS

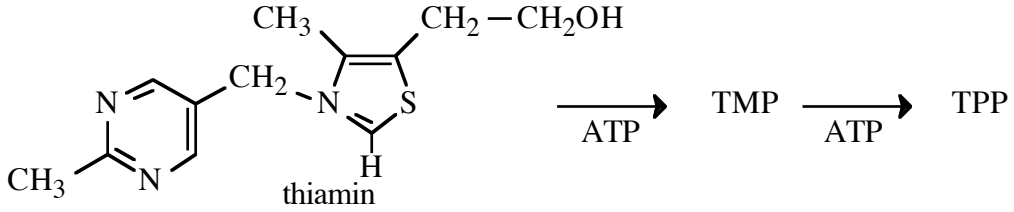
A. Generalities

1. Metabolism and storage -- only B_{12} and folate are appreciably stored.

2. Toxicity -- only niacin and pyridoxine are at all toxic (in high conc.)

B. Thiamin -- (Vitamin B_1)

1. Structure



2. Function

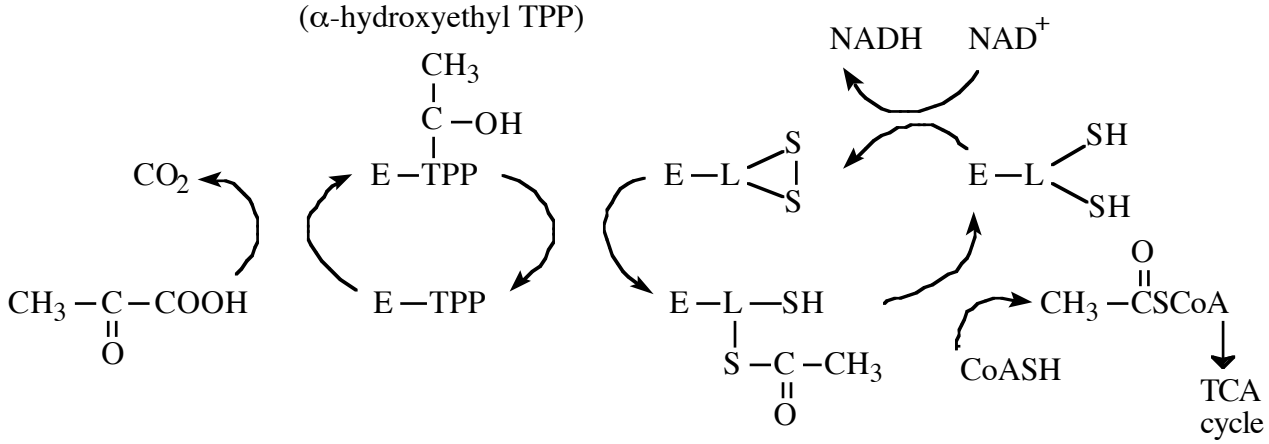
a. Oxidative decarboxylation of α-keto acids

e.g. $CH_3—C(=O)—CO_2H \xrightarrow[\text{lipoic acid, NAD}^+\text{, CoASH, pyruvate dehydrogenase complex}]{\text{TPP}} CH_3—C(=O)—SCoA + CO_2 + NADH$ (mitochondria)

e.g. α -ketoglutaric acid $\xrightarrow[\text{NAD}^+\text{, CoASH, lipoic acid, α-ketoglutarate dehydrogenase complex}]{\text{TPP}}$ succinyl CoA + CO_2

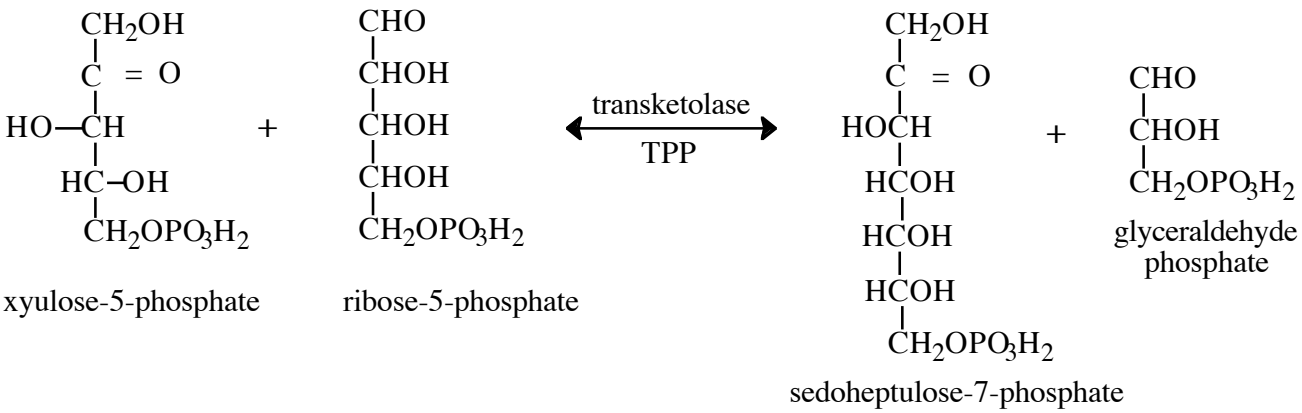
The decarboxylation is accomplished by a mitochondrial enzyme complex as shown below. L = lipoic acid, E - enzyme, TPP = thiamin pyrophosphate.

Pyruvate dehydrogenase complex in detail



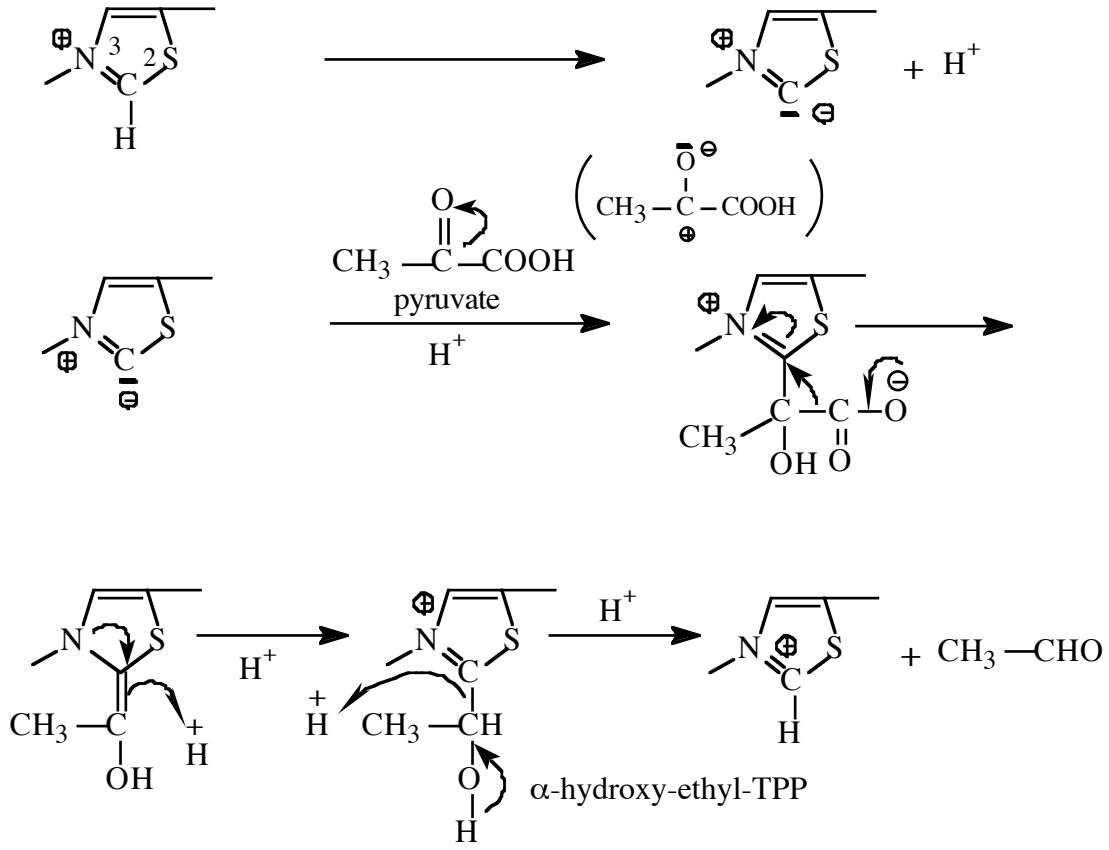
b. Transfer of α-ketols (pentose phosphate pathway) -- 10% of carbohydrate metabolized this way. This pathway provides pentoses for RNA and DNA synthesis and NADPH for the biosynthesis of fatty acids and other endogenous reactions.

e.g.



c. Non-coenzyme function – TTP involved in the control of chloride channels in brain and elsewhere in nerve impulse conduction

3. **<u>Mechanism</u>** -- formation of adduct with C_2 of thiazole ring.



4. **<u>Deficiency</u>** -- thiamin needs are proportional to caloric intake and is essential for carbohydrate metabolism. Usually consider requirement as 0.5 mg/1000 calories plus 0.3 mg during pregnancy and lactation. Studies show laboratory evidence of thiamin deficiency (transketolase assay) in 20-30% of elderly patients and 40-50% of chronic alcoholics. <2% of healthy controls showed evidence of deficiency.

a. Early signs of deficiency -- anorexia, nausea, vomiting, fatigue, weight loss, nystagmus, tachycardia.

b. Late signs of deficiency: Beriberi
cardiac -- increased heart size, edema
cerebral -- depression, irritability, memory loss, lethargy
GI tract -- vomiting, nausea, weight loss
neurological – weakness, polyneuritis, convulsions

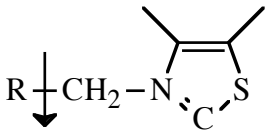
Signs and symptoms vary with age of patient, rapidity of onset, and severity of deficiency.

c. Thiamin and the alcoholic
1. intake low and alcohol blocks conversion of thiamin → TPP
2. ↓ absorption - ↓ active transport
3. ↓ storage
4. increased fluid intake and urine flow causes thiamin washout
4. involved in fetal alcohol syndrome

d. Wernicke-Korsakoff syndrome -- seen in some alcoholics; neurological disorder resulting in impaired mental functioning → institutionalization for a significant number of patients.
Symptoms: confusion, memory loss, confabulation, psychotic behavior; maybe irreversible in part

e. Factors → B_1 deficiency
1. ↑ carbohydrate intake -- TPN, alcoholics
2. ↓ absorption -- ulcerative colitis, etc., alcoholism
3. ↓ intake -- poor diet, geriatrics, breast fed infant from B_1 deficient mother, etc.
4. alcoholism.

5. **<u>Source</u>** -- present in most tissues (as TPP) and plants (as thiamin); rich sources include: lean meat, especially pork, cereal grains, eggs, yeast, nuts. Thiaminase – in some fish (raw) and shellfish (raw) and ferns. This enzyme can hydrolyze thiamin.



In the milling or processing of rice and flour, the thiamin is lost. Today in the USA, most white flour, rice and pastas are "enriched" to bring thiamin levels to near original levels. "Enriched" products also have added riboflavin, niacin, iron, and folic acid.

6. **Stability** -- labile at pH > 4 and when heated (especially at alkaline pH values) prolonged cooking ↓ levels especially at pH > 4.

7. **Diagnosis of deficiency state**

a. ↑ pyruvate and lactate in plasma
b. transketolase activity in RBC -- most important technique.

8. **Uses**

a. deficiency states -- for alcoholics
b. thiamin responsive inborn errors of metabolism -- see below
c. mosquito repellant -- efficacy? -- for dogs, for humans 50 mg QID 2d before and during exposure is recommended.
d. acute alcoholism: give 100 mg IM or IV stat. This is a common practice.
e. Alzheimer's disease—little evidence for benefit (huge doses used)

9. **Thiamin responsive inborn errors of metabolism**:

Disease	Defect
Wernicke - Korsakoff	Transketolase
Maple Syrup urine disease	Failure to decarboxylate branched chain amino acids
Thiamin responsive megaloblastic anemia	?
Hyperalanemia	Pyruvate dehydrogenase
Hyperpyruvate acidurea	Pyruvate dehydrogenase

10. **Requirement** -- 0.5 mg/1000 cal. DV = 1.5 mg. Minimum intake should be at least 1 mg.

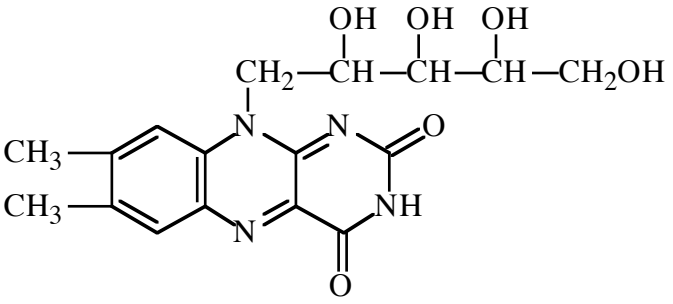
11. **Toxicity** -- nontoxic on oral administration; No UL value. Anaphylactic reactions have been observed in patients receiving repetitive parenteral doses.

12. Patient Counseling/ patient use issues

a. Needed to drive carbohydrates to energy
b. Rarely needed as a single supplement. Use a multivitamin to get needed thiamin.
c. **Special benefit in alcoholics a higher doses**
d. **Benefit in high doses in rare thiamin-responsive inborn errors of metabolism**
e. **Uncertain benefit as a mosquito repellant**
f. **Nontoxic**

C. Riboflavin (Vitamin B_2)

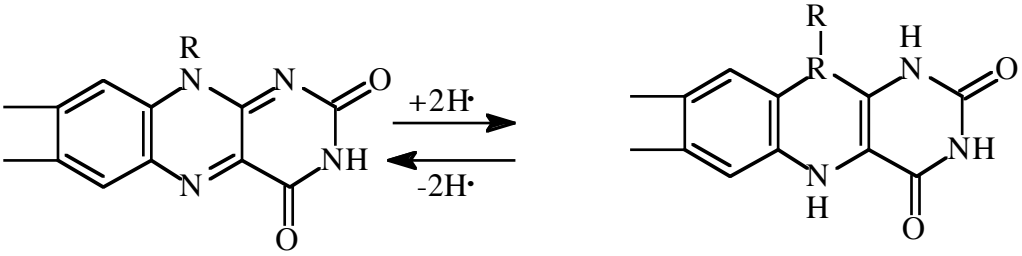
1. Structure



FMN = riboflavin monophosphate
FAD = flavin adenine dianucleotide
} riboflavin coenzymes

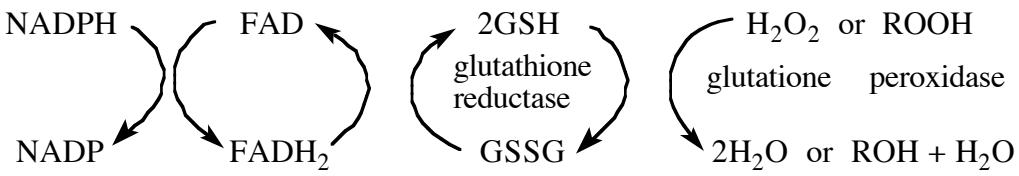
riboflavin $\xrightarrow[\text{ATP}\ \text{ADP}]{\text{gut mucosa}}$ FMN $\xrightarrow[\text{ATP}\ \text{ADP}]{\text{liver}}$ FAD

2. Function -- redox, tissue respiration, H transfer as flavin containing enzyme



oxidized – yellow reduced – colorless

Examples of enzymes having flavin groups:
succinate dehydrogenase (-succinate → fumerate in TCA cycle)
fatty acid acyl CoA dehydrogenase (β-oxidation of lipids)
glutathione reductase – important in antioxidant activities



The following are important flavoproteins (containing FMN). Cytochrome C reductase (electron transport); $NADP^+$ -- cytochrome C reductase; cytochrome P-450 reductase (drug metabolism), flavin monooxygenase (drug metabolism).

3. Deficiency state –

a. not usually seen in isolation but occurs in combination with other B vitamin deficiencies.
b. Fatigue, cheilosis, glossitis, vascularization of cornea, dermatitis
c. Vegans and teenagers may be low in B2 if dairy intake is low.
d. Low B_2 intake may be a risk factor for cataract development.
e. Alcoholics are at risk due to low intake and low absorption

4. Source

milk, meats, leafy vegetables, eggs, yeast; "enriched" products.

5. Stability

usually > 30% destroyed by cooking
labile to light
more stable in acid than alkali in absence of light.

6. Use

- Deficiency states. Is a component of most multivitamin mixtures.
- New--May help in migraine headache prevention
- New—high intake associated with lower risk for cataracts and a 3mg supplement reduced risk

7. Requirements

DV = 1.7 mg
"Average" U.S. diet contains 2 mg for males and 1.5 mg for females
Diagnosis – erythrocyte glutathione reductase activity
No UL value

8. Patient Counseling/ patient use issues

a. Routine single dose supplementation is not needed. Use a multivitamin to get needed riboflavin
b. Possible use in preventing migraine headaches. Use 400mg/d
c. Will turn urine bright yellow in doses higher than the DV
d. Nontoxic

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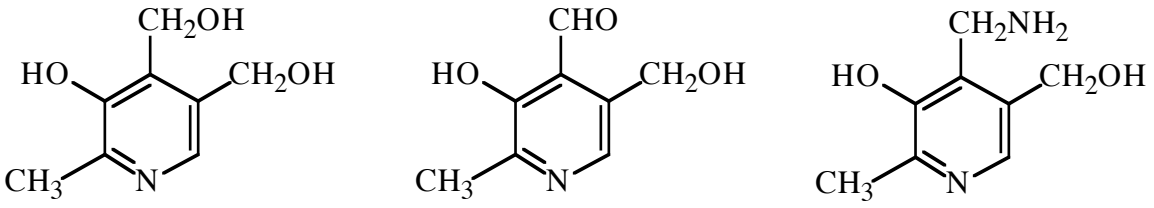
D. Vitamin B_6

1. Structure

pyridoxine (P) pyridoxal (PL) pyridoxamine (PN)

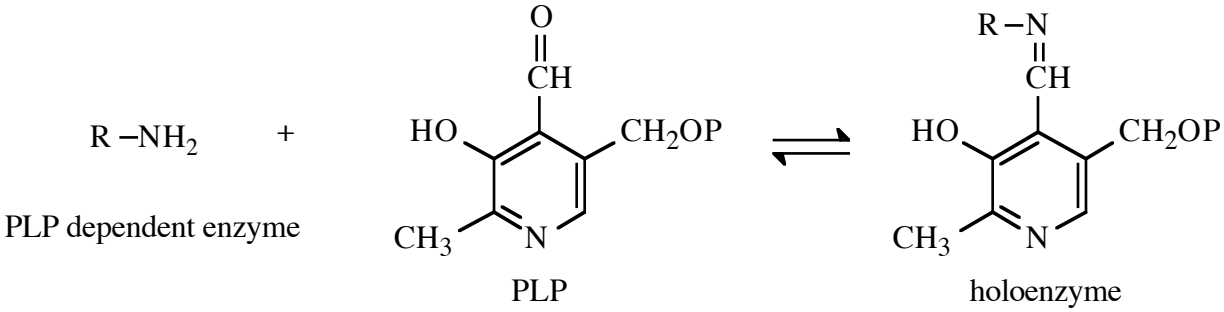


Pyridoxine is a commonly used term for this vitamin, but all 3 are equally active so vitamin B_6 is a better term to use.

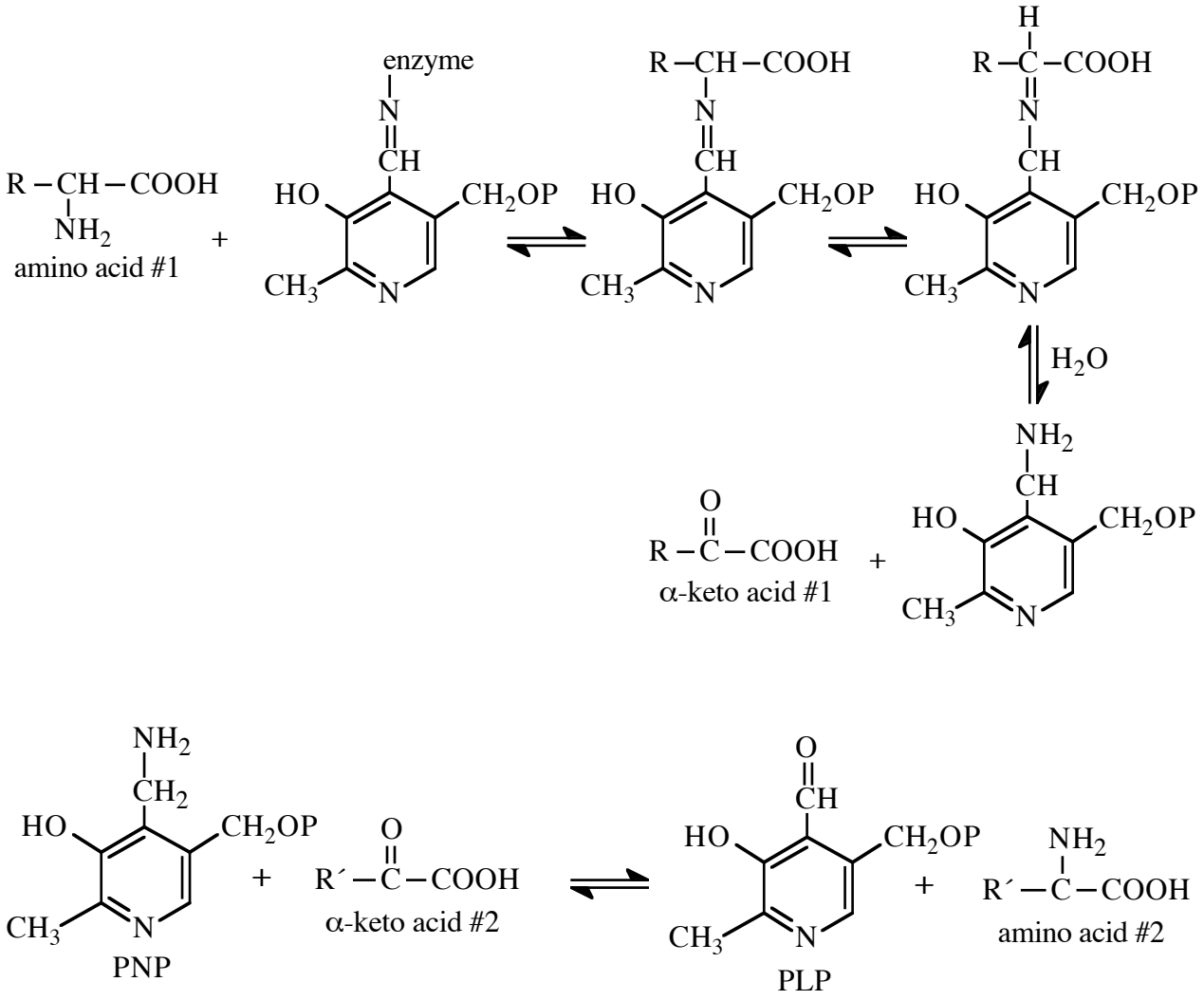
Three phosphorylated forms are present also

Coenzyme = pyridoxal-5-phosphate "PLP"

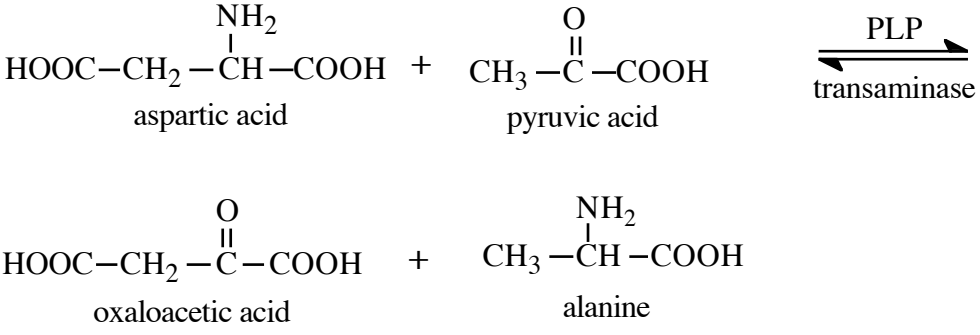
2. **Function** –participates in over 100 enzymatic reactions by forming a Schiff base with the terminal amino group of lysine in the enzyme.



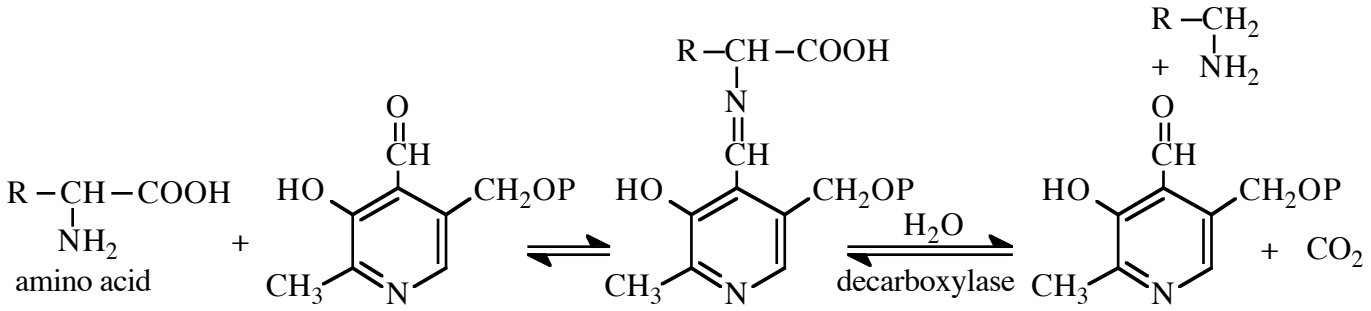
b. Transamination



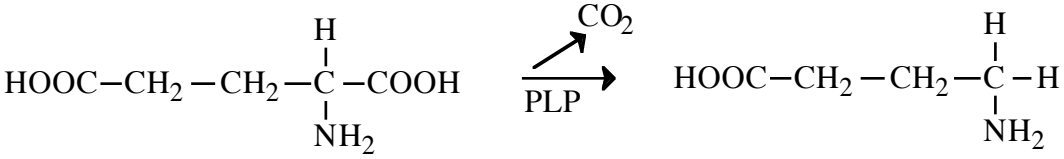
e.g. glutamate-aspartate transaminase



c. Decarboxylation



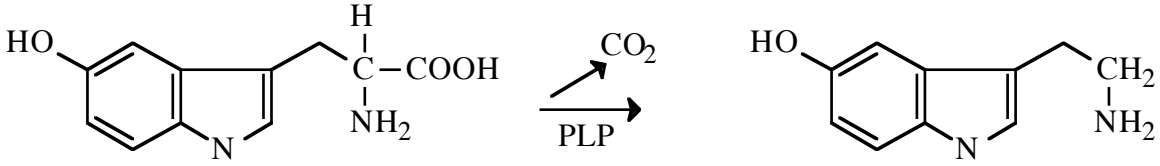
e.g.



glutamic acid

γ-amino butyric acid (GABA)

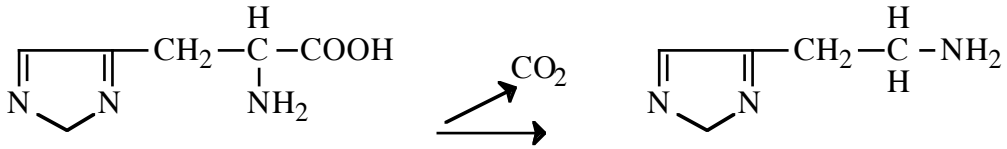
e.g.



5-hydroxytryptophan

5-hydroxytryptamine (serotonin)

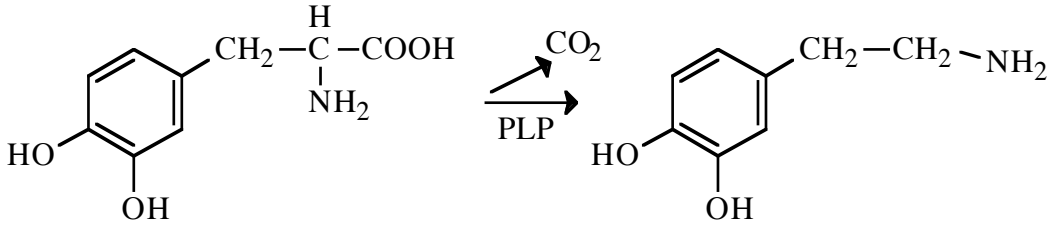
e.g.



histidine

histamine

e.g.



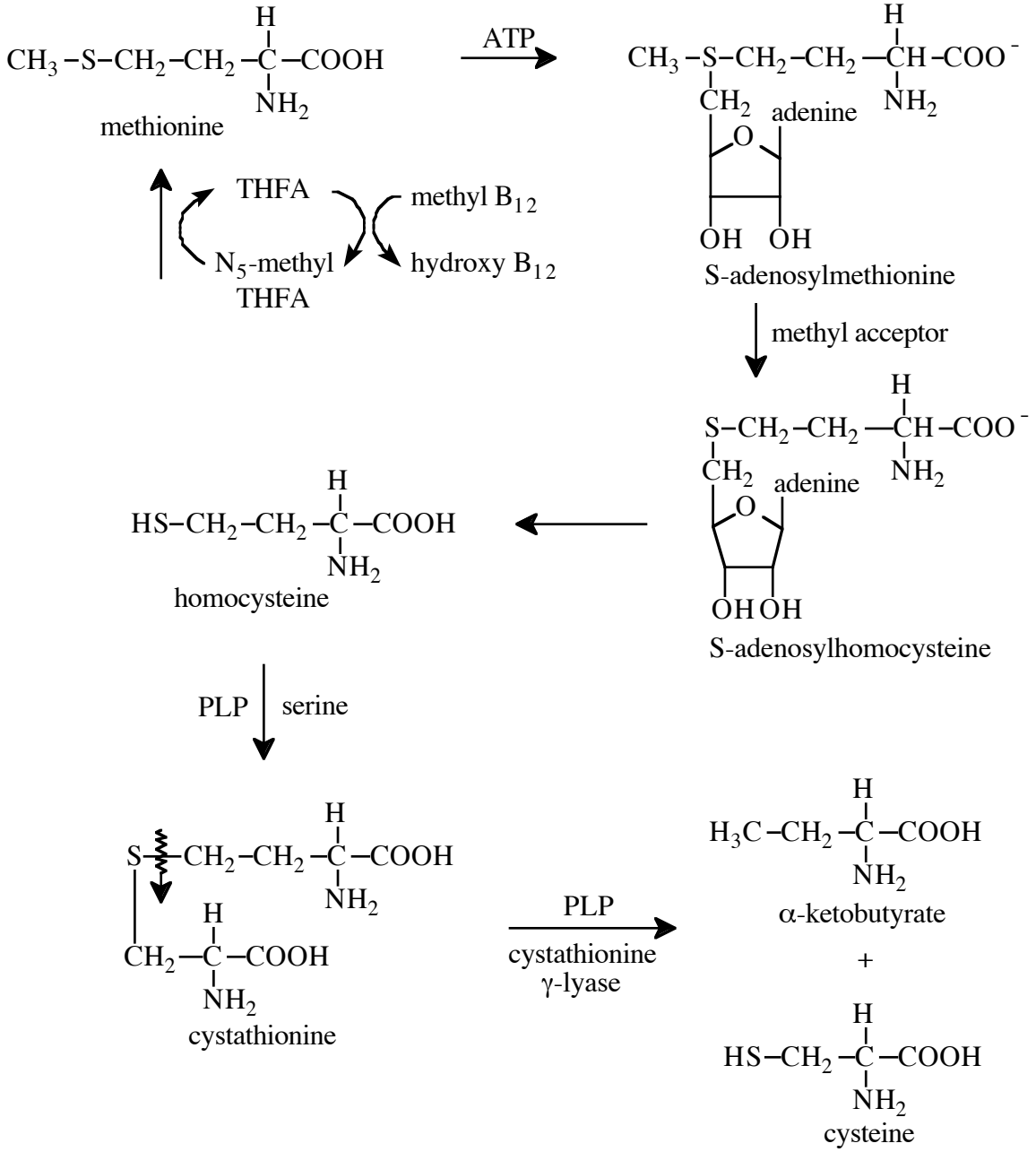
DOPA

DOPAMINE

Note: B_6 contraindicated in l-DOPA therapy because B_6 enhances peripheral decarboxylation of l-DOPA to dopamine which will not cross Blood Brain Barrier; Larobec® (Roche) contains no pyridoxine and can be used if multivitamin supplementation is desired for patient on l-DOPA.

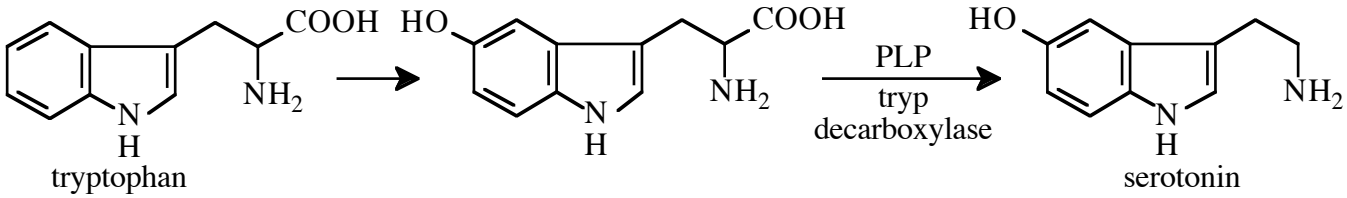
Sinemet® contains l-DOPA and carbidopa (A DOPA decarboxylase inhibitor) -- therefore, no interaction.

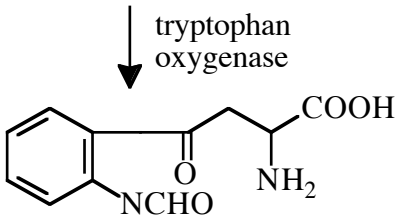
d. B_6 and sulfur amino acid metabolism. (Note: elevated homocysteine is an independent risk factor for cardiovascular disease and birth defects.)



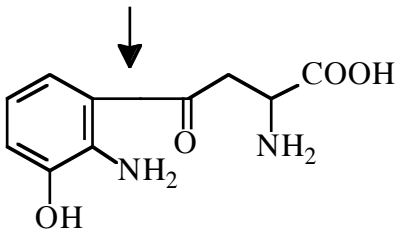
e. B_6 involvement in methionine formation (and S-adenosyl methionine) makes it indirectly involved in methylation. Hence B_6 is indirectly involved in lipid metabolism and nucleic acid formation and immune function.

f. B_6 involved in tryptophan metabolism to serotonin and niacin

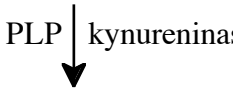


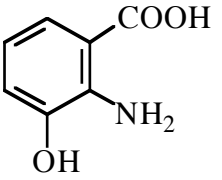


N-formylkynurenine

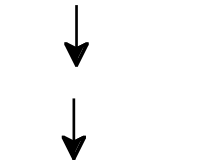


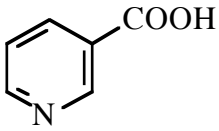
3-hydroxykynurenine





3-hydroxy anthranilic acid





Niacin

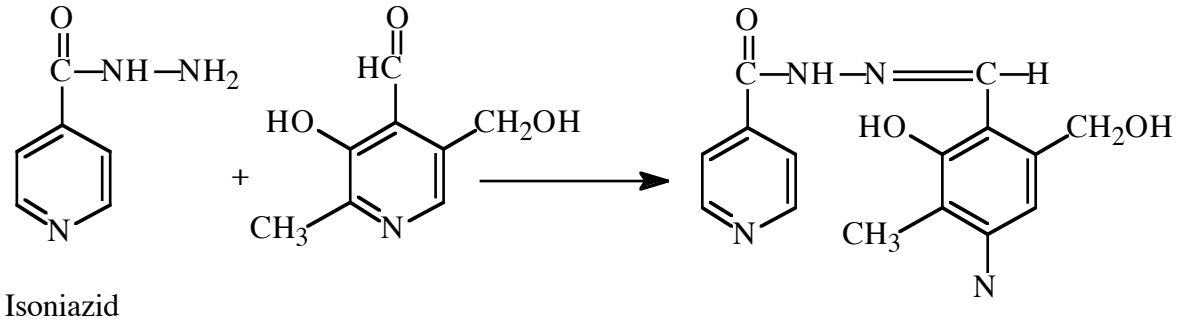
g. Other reactions requiring B6
Glycogen phosphorylase (release of glucose in muscle)
Heme biosynthesis
Nucleic acid biosynthesis (via SAM)

3. <u>Deficiency</u>

a. Not seen usually and, if seen, is associated with other vitamin deficiencies or is iatrogenic; symptoms include rash, peripheral neuritis, anemia and possible siezures. Deficiency diagnosed by low plasma PLP and low transaminase activities (±PLP).

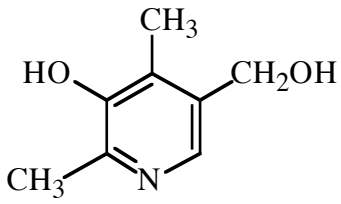
b. Iatrogenic B_6 deficiencies

1) Isoniazid -- antituberculosis drug -- forms Schiff base with B_6. Can get neuritis and convulsions. 25-300 mg/d B_6 given to prevent B_6 deficiency.



Isoniazid

2) 4-Deoxypyridoxine --(experimental only)



Symptoms -- Skin lesions on face, glossitis, stomatitis, convulsive seizures (↓ GABA?), anemia (↓ heme synthesis?).

3) Oral contraceptives.- older high dose Ocs can affect B6 but not a problem now.

4. **<u>Source</u>** -- milk, meats, legumes, tuna, whole grains, beans

5. **<u>Stability</u>** -- pyridoxine is stable; some loss on cooking, especially with meats, due to Schiff base formation and decrease of the pyridoxal in the foods.

6. **Diagnosis of deficiency** -- measure erythrocyte transaminases.

7. **Use** --

a) routine use in multivitamin products
b) in INH therapy
c) certain inborn errors of metabolism

Name	Symptoms	Dose of B_6	Problem
B_6--dependent infantile convulsions	Clonic and tonic seizures	10-25 mg/day	Defective glutamic acid decarboxylase; possible GABA depletion
B_6--responsive anemia	Microcytic, hypochromic anemia	100 mg/day	Defective hemoglobin synthesis
Xanthurenic acidurea	Mental retardation	25-100 mg/day	Defective tryptophan metabolism due to faulty kyureninase, xanthurenic acid spills into urine
Homocystinurea	Mental retardation Early heart disease	25-500 mg/day	Defective cystathionine synthetase homocysteine appears in urine
Cystathionurea	Mental retardation	25-500 mg/day	Defective cystathionase

d) PMS (50-500 mg/d) -- evidence is uneven. PLP is known to bind to steroid receptors.

e) carpal tunnel syndrome -- evidence is uneven. It seems to work for some. A trial of B_6 100-200 mg/d for 6 mos. may be worthwhile.

f) use in lowering homocysteine levels (see sulfur amino acid scheme above). High homocysteine may be an independent risk factor for cardiovascular disease but this is now controversial. Combine with folic acid and B12 for optimum lowering action.

g) Nausea and vomiting in pregnancy-Helpful in high doses. PremesisRx contains 75mg sustained release B6 (plus 12ug B12, 1mg folic acid and 200mg calcium) or 25mg of generic B6 TID is less expensive

8. **Requirement** -- DV = 2 mg; UL = 100mg

9. **Toxicity**

a. > 200 mg/day can decrease prolactin levels

b > 1-2 g/day can cause serious neuropathy by an unknown mechanism. Recommendation: avoid long term use in doses above 200 mg.

10. Patient counseling/patient use considerations

a. **Routine single dose supplementation is usually not needed. Use a multivitamin to get needed B6**

b. **Sometimes used, with limited evidence, for carpel tunnel syndrome, PMS, and depression on OCs**

c. **Rare use in high doses for inborn errors**

d. **Sometimes used to prevent neuropathy with isoniazid**

e. **For nausea and vomiting of pregnancy. 25mg TID or use PremensisRx which is FDA approved for this.**

f. **Used with B12 and folic acid in high homocysteine**

g. **Keep doses <200mg/d to avoid neuritis**