MEDCHEM 562P 2014 - VITAMINS and Minerals

Part 1: Water Soluble Vitamins

Bill Atkins Ph.D. H172Q, 685 0379; winky@u.washington.edu

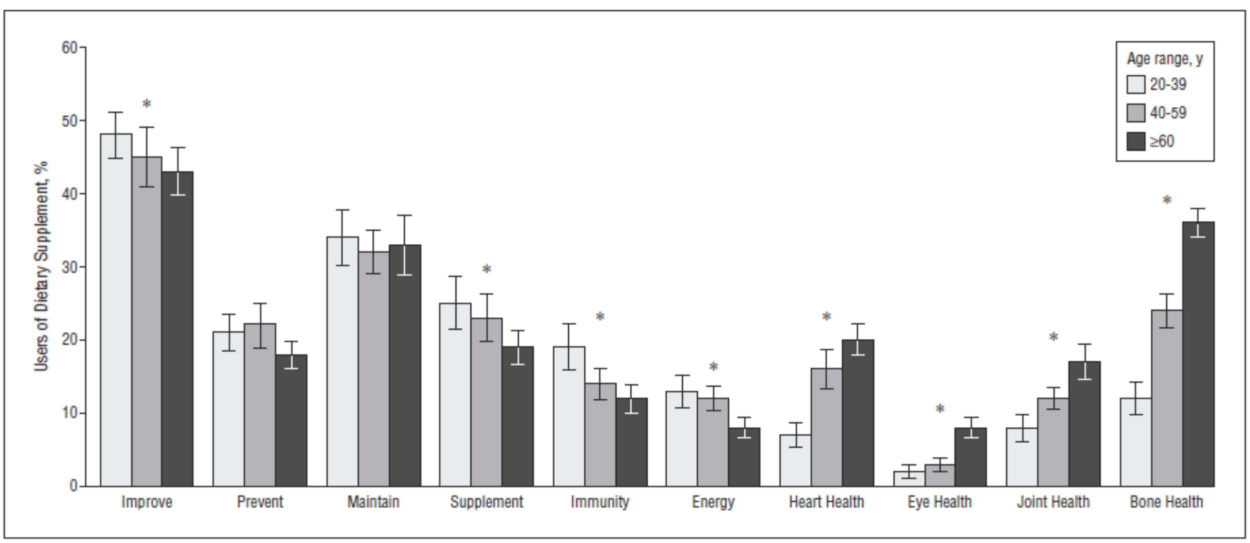
INTRODUCTION

I. Who takes vitamin/mineral supplements and why? [Bailey et al. *JAMA Intern Med* 173:355 (2013].

- It is estimated that ~50% of the adult population in the US takes some type of dietary supplement, typically to 'improve/maintain overall health'.
- >75% of products are used without care-provider recommendation.

Table 3. Prevalence of Use of Specific Types of Dietary Supplements and the Most Frequently Reported Motivation for Use of Each Product Type in Adults (≥20 Years) in the United States, 2007-2010[a]

Type of Supplement	Users, No.	Overall (n = 11 956)	Men (n = 5911)	Women (n = 6045)	Most Common Reported Motivation	Users Reporting Motivation, %
Multivitamin-mineral	3404	31.9 (0.8)	28.5 (1.1)	35.2 (0.9)[b]	To improve overall health	48 (1)
Calcium	1342	11.6 (0.6)	4.4 (0.4)	18.5 (0.9)[b]	For bone health	74 (2)
ω-3/fish oil	1032	9.8 (0.6)	9.3 (0.6)	10.3 (0.8)	For heart health, lower cholesterol	48 (2)
Botanical supplements	841	7.5 (0.5)	6.6 (0.5)	8.4 (0.6)[b]	To improve overall health	27 (2)
Vitamin C	764	7.1 (0.5)	6.6 (0.5)	7.6 (0.6)	To boost immune system, prevent colds	45 (3)
Multivitamin	632	5.7 (0.4)	4.7 (0.3)	6.6 (0.5)	To improve overall health	31 (2)
Vitamin D	542	4.9 (0.4)	3.0 (0.3)	6.8 (0.6)	For bone health	38 (2)
Vitamin E	439	3.7 (0.2)	3.1 (0.3)	4.3 (0.4)	To improve overall health	40 (3)
Joint supplements	430	4.0 (0.3)	4.0 (0.4)	4.1 (0.3)	For healthy joints, prevent arthritis	76 (3)
Vitamin B_{12}	408	3.3 (0.2)	2.5 (0.2)	4.0 (0.3)	To improve overall health	31 (3)
Iron	245	1.8 (0.1)	0.9 (0.2)	2.7 (0.2)	For anemia, low iron	67 (4)
Folic acid	194	1.5 (0.2)	1.0 (0.1)	2.0 (0.2)	Other reason	15 (4)
Protein/sports	155	1.6 (0.2)	1.9 (0.2)	1.3 (0.3)	To improve overall health	25 (4)
Fiber	109	1.1 (0.1)	0.8 (0.1)	1.3 (0.2)	For bowel/colon health	77 (5)
Potassium	119	0.9 (0.1)	0.7 (0.1)	1.2 (0.2)	For muscle related issues	24 (5)
Magnesium	125	1.1 (0.1)	0.9 (0.1)	1.4 (0.2)	To improve overall health	18 (4)
Vitamin B_6	106	0.9 (0.1)	0.7 (0.1)	1.1 (0.2)	To improve overall health	24 (5)
Vitamin A	103	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	For eye health	44 (6)
Niacin	70	0.7 (0.1)	0.9 (0.2)	0.4 (0.1)[b]	For heart health, lower cholesterol	77.1 (6)

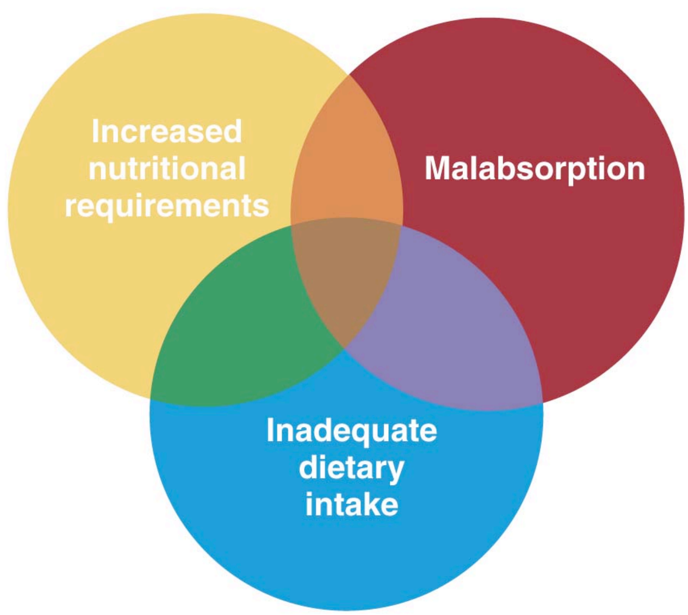


II. Multivitamins

- It is estimated that ~30% of the adult US population take multivitamins daily.
- A recent clinical trial of male physicians taking multivitamins concluded there was a very modest, but (statistically) significant, reduction in total cancers with daily multivitamin use (*NEJM*, 308:1871 (2012).
- Do we need to supplement diets with vitamins/multivitamins? Maybe…. in certain circumstances.

III. When are vitamin supplements worthwhile?

- *Inadequate intake* -- alcoholics, poor, elderly, dieters, poor diet
- *Increased needs* -- pregnancy, lactation, infants, smokers, injury, trauma, recovery from surgery, infection
- *Poor absorption* -- elderly, GI disorders, specific GI surgeries, e.g. gallbladder removal, gastric bypass, cystic fibrosis, severe diarrhea, drug-induced vitamin deficiencies – e.g. long term antibiotic use, cholestyramine, mineral oil



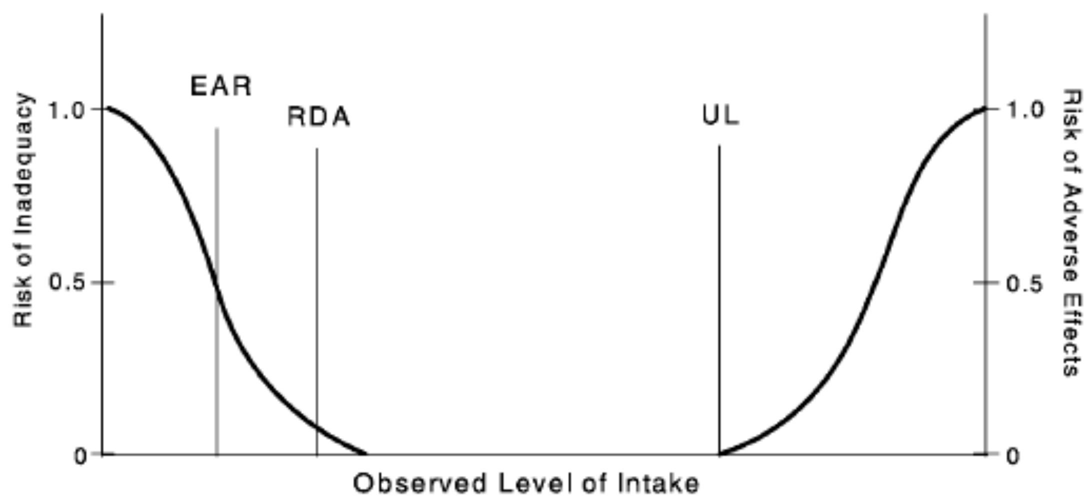
IV. Definitions

- Vitamins are *organic compounds* and minerals are *chemical elements* that are required as nutrients in small amounts by an organism.
- Vitamers are different forms of a particular vitamin, e.g. vitamins K1 and K2, vitamins D2 and D3, retinol and retinal, etc.

V. Reference Tables for Intake of Vitamins and Elements Intakes

DRI Reports are produced by the **Food & Nutrition Board of the Institute of Medicine, National Academies of Science.** http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables

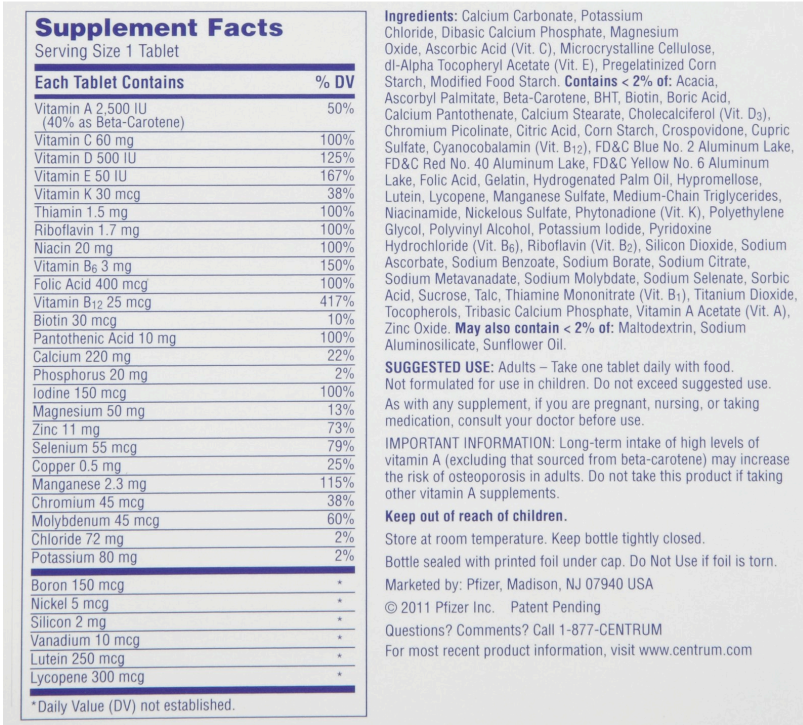
- Estimated average requirements (EAR): the average daily nutrient intake level estimated to meet the requirements of half of the healthy individuals in a group.
- Recommended Dietary Allowance (RDA): the average daily dietary intake level; sufficient to meet the nutrient requirements of nearly all (97-98%) healthy individuals in a group. Calculated from the EAR.
- Tolerable Upper Limit (UL): maximum adult daily intake unlikely to cause harm.



RDA= 1.2(EAR)

Daily Values (DVs) are set by the **FDA.**
http://ods.od.nih.gov/HealthInformation/dailyvalues.aspx

- Two groups: Daily Reference Values (DRVs) for energy-producing nutrients, e/g. fats, carbohydrates, protein etc. and Reference Daily Intakes (RDIs) for vitamins and minerals.
- A DV is often, but not always, similar to one's RDA for that nutrient.
- DV is primarily used for labeling purposes. % DV on label is based on 2,000 calorie/day diet for adults and children over 4 yrs.



Supplement Facts

Serving Size 1 Tablet

Each Tablet Contains	% DV
Vitamin A 2,500 IU (40% as Beta-Carotene)	50%
Vitamin C 60 mg	100%
Vitamin D 500 IU	125%
Vitamin E 50 IU	167%
Vitamin K 30 mcg	38%
Thiamin 1.5 mg	100%
Riboflavin 1.7 mg	100%
Niacin 20 mg	100%
Vitamin B_6 3 mg	150%
Folic Acid 400 mcg	100%
Vitamin B_{12} 25 mcg	417%
Biotin 30 mcg	10%
Pantothenic Acid 10 mg	100%
Calcium 220 mg	22%
Phosphorus 20 mg	2%
Iodine 150 mcg	100%
Magnesium 50 mg	13%
Zinc 11 mg	73%
Selenium 55 mcg	79%
Copper 0.5 mg	25%
Manganese 2.3 mg	115%
Chromium 45 mcg	38%
Molybdenum 45 mcg	60%
Chloride 72 mg	2%
Potassium 80 mg	2%
Boron 150 mcg	*
Nickel 5 mcg	*
Silicon 2 mg	*
Vanadium 10 mcg	*
Lutein 250 mcg	*
Lycopene 300 mcg	*

*Daily Value (DV) not established.

Ingredients: Calcium Carbonate, Potassium Chloride, Dibasic Calcium Phosphate, Magnesium Oxide, Ascorbic Acid (Vit. C), Microcrystalline Cellulose, dl-Alpha Tocopheryl Acetate (Vit. E), Pregelatinized Corn Starch, Modified Food Starch. **Contains < 2% of:** Acacia, Ascorbyl Palmitate, Beta-Carotene, BHT, Biotin, Boric Acid, Calcium Pantothenate, Calcium Stearate, Cholecalciferol (Vit. D_3), Chromium Picolinate, Citric Acid, Corn Starch, Crospovidone, Cupric Sulfate, Cyanocobalamin (Vit. B_{12}), FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, Folic Acid, Gelatin, Hydrogenated Palm Oil, Hypromellose, Lutein, Lycopene, Manganese Sulfate, Medium-Chain Triglycerides, Niacinamide, Nickelous Sulfate, Phytonadione (Vit. K), Polyethylene Glycol, Polyvinyl Alcohol, Potassium Iodide, Pyridoxine Hydrochloride (Vit. B_6), Riboflavin (Vit. B_2), Silicon Dioxide, Sodium Ascorbate, Sodium Benzoate, Sodium Borate, Sodium Citrate, Sodium Metavanadate, Sodium Molybdate, Sodium Selenate, Sorbic Acid, Sucrose, Talc, Thiamine Mononitrate (Vit. B_1), Titanium Dioxide, Tocopherols, Tribasic Calcium Phosphate, Vitamin A Acetate (Vit. A), Zinc Oxide. **May also contain < 2% of:** Maltodextrin, Sodium Aluminosilicate, Sunflower Oil.

SUGGESTED USE: Adults – Take one tablet daily with food. Not formulated for use in children. Do not exceed suggested use.

As with any supplement, if you are pregnant, nursing, or taking medication, consult your doctor before use.

IMPORTANT INFORMATION: Long-term intake of high levels of vitamin A (excluding that sourced from beta-carotene) may increase the risk of osteoporosis in adults. Do not take this product if taking other vitamin A supplements.

Keep out of reach of children.

Store at room temperature. Keep bottle tightly closed.

Bottle sealed with printed foil under cap. Do Not Use if foil is torn.

Marketed by: Pfizer, Madison, NJ 07940 USA

© 2011 Pfizer Inc. Patent Pending

Questions? Comments? Call 1-877-CENTRUM

For most recent product information, visit www.centrum.com

VI. Standardization

- Units of biological activity (IU) superceded, where known, by potencies based on weight (μg, mg) of the most active vitamer.
- IoM guidelines use weight.
- FDA labels use both.

VII. History and Discovery

1500 BC — Ancient Egyptians used liver - rich in vitamin A - applied to the eye to treat night blindness.

1536 — Jacques Cartier, exploring the St. Lawrence River, uses local native knowledge to save his men from scurvy by boiling the needles from cedar trees to make a vitamin C-rich tea.

1795 — British navy adds lemons to sailors' rations, 40 years after a Scottish naval surgeon, James Lind, had urged that citrus fruits be used to prevent scurvy.

1884 — Japanese navy eradicates beriberi - vitamin B1 deficiency- by feeding sailors meat and fruit in addition to polished white rice, which lacked the thiamine-rich husks.

1897 — Beriberi (a polyneuritis) was induced in birds fed only polished rice and reversed by feeding the rice polishings.

1911 — Casimir Funk isolates amine-containing concentrate containing thiamine from rice polishings, which was curative for polyneuritis in pigeons, and names it '**vitamine**' **for vital amine**.

1912 Xavier Mertz –Antarctic explorer – dies of vitamin A poisoning from ingesting sled dog liver after supplies are lost in a crevasse.

Year discovered	Vitamin	Source
1912	Vitamin B1	Rice bran
1912	Vitamin C	Lemons
1913	**Vitamin A**	**Milk/egg yolk**
1918	**Vitamin D**	**Cod liver oil**
1920	Vitamin B2	Eggs
1922	**Vitamin E**	**Wheat germ, Seed oils**
1926	Vitamin B12	Liver
1929	**Vitamin K**	**Alfalfa**
1931	Vitamin B5	Liver
1931	Vitamin B7	Liver
1934	Vitamin B6	Rice bran
1936	Vitamin B3	Liver
1941	Vitamin B9	Liver

VII. WATER SOLUBLE VITAMINS

A. Generalities

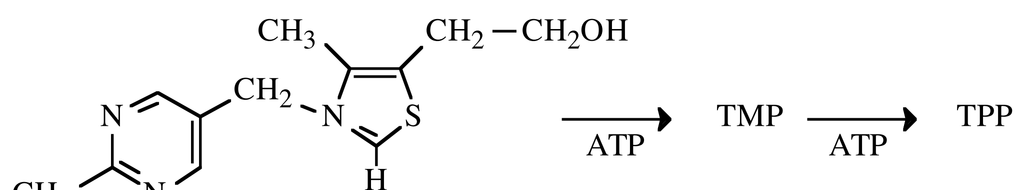
1. **Metabolism and storage** -- only B_{12} and folate are appreciably stored. In general, water soluble vitamins are excreted readily and are not stored. As a result, depletion is more of a problem than toxicity.

2. **Toxicity** -- only niacin and pyridoxine are at all toxic (in high conc.). In general, the water soluble vitamins have few toxicities.

The water soluble vitamins are coenzymes for various common biochemical reactions and their status can be readily determined by measuring the appropriate enzyme activities in blood. Typically, the enzyme activity is measured in the absence and the presence of exogenously added coenzyme, to determine whether the patient needs more of the vitamin.

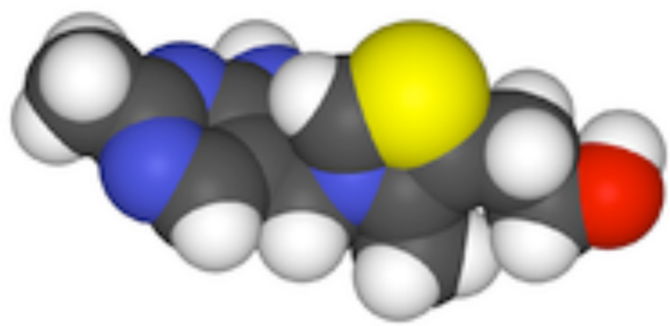
B. Thiamin -- (Vitamin B_1)

1. **Structure**



thiamin

Chemically, the structure includes a pyrimidine ring and a thiazole ring. The thiazole ring has received enormous attention from mechanistic biochemists - they have pondered the reason for the choice by nature of a sulfur atom in the ring. Imidazole rings and oxazole rings would also, in principle, be capable of catalyzing the relevant chemical reactions.



Space-filling model of Thiamin

2. **<u>Function</u> – used to harvest carbohydrates for energy**

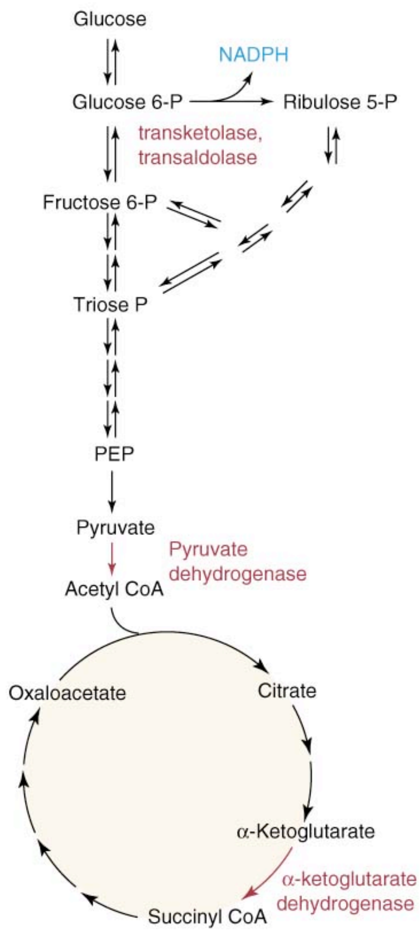


Figure 28.9. Summary of important reactions involving thiamine pyrophosphate.

a) **Oxidative decarboxylation of α-keto acids**

e.g.

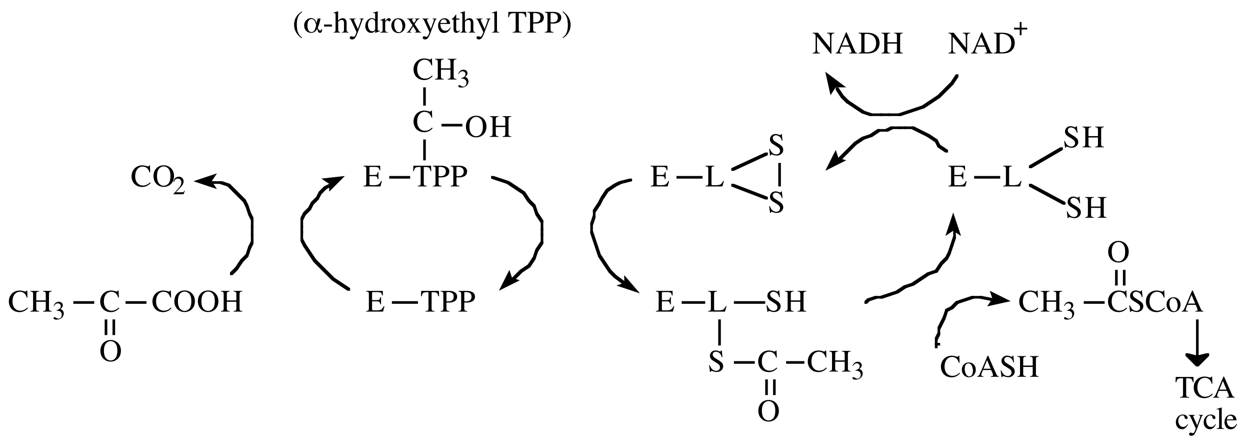
$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CO_2H \xrightarrow[\substack{\text{lipoic acid} \\ NAD^+ \\ \text{CoASH} \\ \text{pyruvate dehydrogenase complex}}]{\text{TPP}} CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-SCoA + CO_2 + NADH$$

e.g.

$$\alpha\text{-ketoglutaric acid} \xrightarrow[\substack{NAD^+ \\ \text{CoASH} \\ \text{lipoic acid} \\ \alpha\text{-ketoglutarate dehydrogenase complex}}]{\text{TPP}} \text{succinyl CoA} + CO_2$$

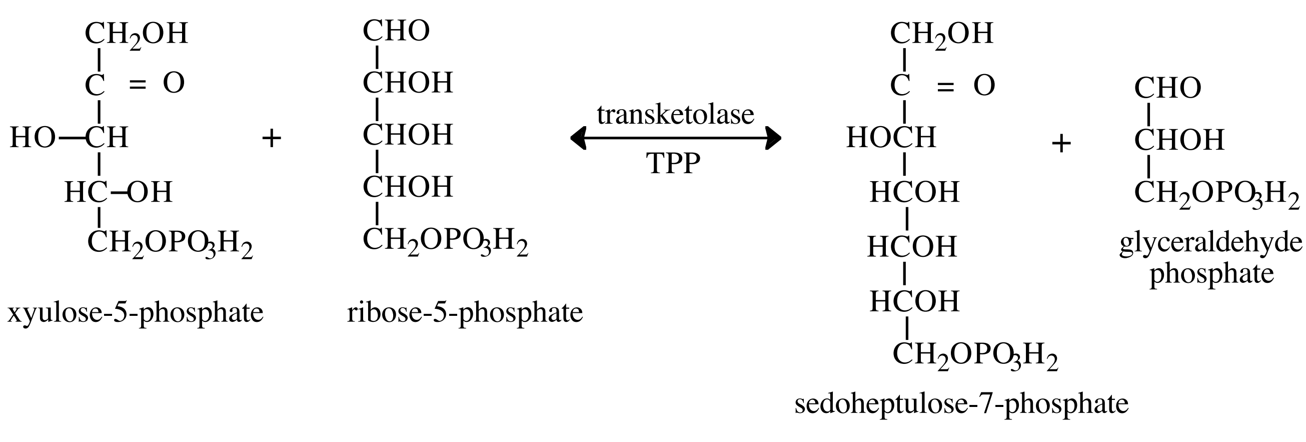
The decarboxylation is accomplished by a mitochondrial enzyme complex as shown below. L = lipoic acid, E = enzyme, TPP = thiamin pyrophosphate.

Pyruvate dehydrogenase complex in detail



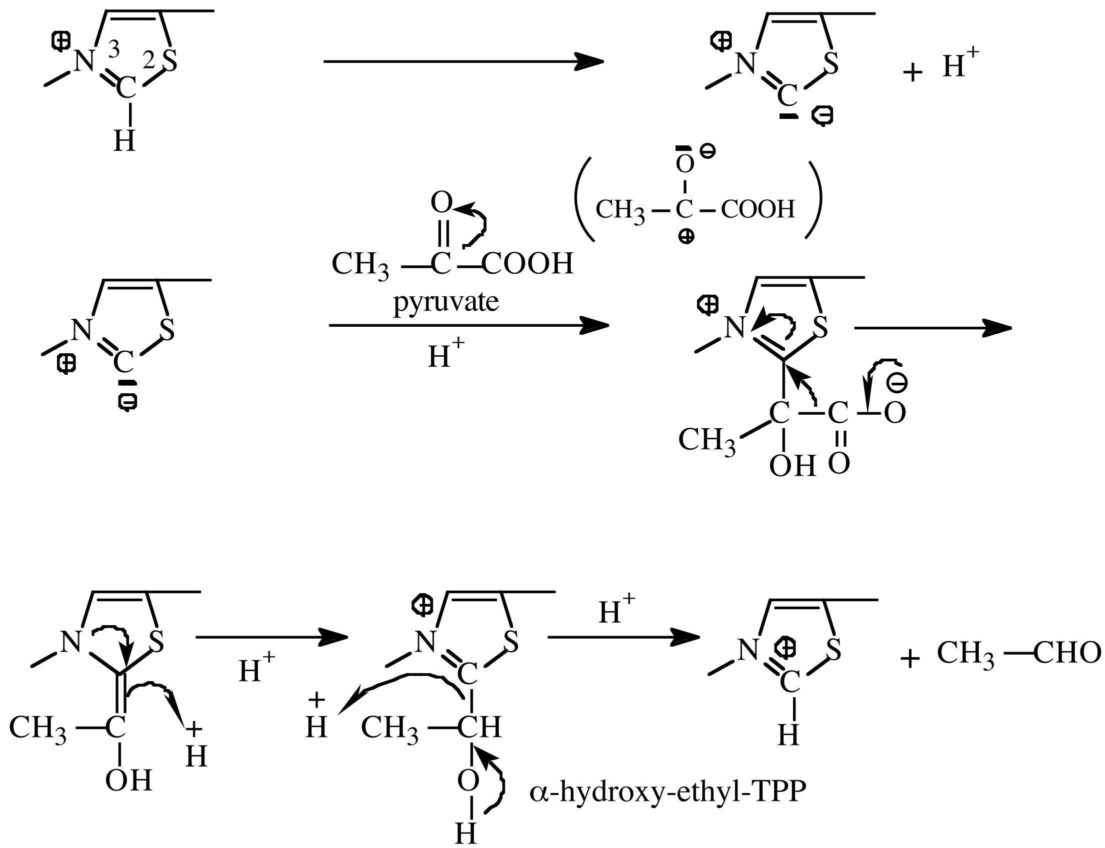
b) **Transfer of α-ketols** (pentose phosphate pathway) -- 10% of carbohydrate metabolized this way. This pathway provides pentoses for RNA and DNA synthesis and NADPH for the biosynthesis of fatty acids and other endogenous reactions.

e.g.



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

3. **Mechanism** – formation of adduct with C2 of thiazole ring.



‘Classic’ experiments support this mechanism, including facile exchange of solvent D2O at the C-2 position.

4. **Deficiency** – 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 (erythrocyte 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.

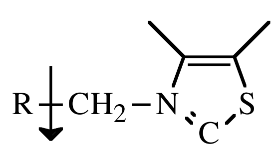
c) Thiamine and the alcoholic
   (i) intake low and alcohol blocks conversion of thiamin → TPP
   (ii) ↓ absorption - ↓ active transport
   (iii) ↓ storage
   (iv) increased fluid intake and urine flow causes thiamin washout
   (v) involved in fetal alcohol syndrome.

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 irriversible in part.

e) Factors → B_1 deficiency
   (i) ↑ carbohydrate intake -- TPN, alcoholics
   (ii) ↓ absorption -- ulcerative colitis, etc., alcoholism
   (iii) ↓ intake -- poor diet, geriatrics, breast fed infant from B_1 deficient mother, etc.
   (iv) alcoholism.

f) Cellular uptake – Intestinal cells contain a thiamin specific receptor/transporter (hTHTR) which appears to specifically pump thiamin and not TPP. After cellular uptake, thiamin is converted to TPP. Polymorphisms in the gene encoding hTHTR are known and may contribute to thiamin-responsive megaloblastic anemia. Once in the circulation specific transport proteins may 'store' TPP and control its circulation (hypothesized), but most is bound to Albumin. Most ends up in skeletal muscle, brain, heart, liver.

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 or processing of rice and flour, the thiamin is lost. 'Whole' wheat or rice contains ~10 times as much Thiamin as white wheat or rice. 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) transkelotase 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	?
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.

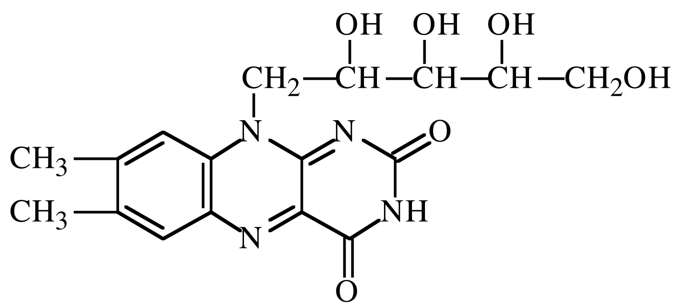
12. Patient Counseling/ Patient Use Issues

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 at higher doses
d) Benefit in high doses in rare thiamin-responsive inborn errors of metabolism
e) Uncertain benefit as a mosquito repellant (if true, 1-2 week onset)
f) Nontoxic.

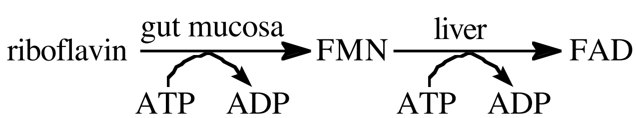
C. **Riboflavin (Vitamin B_2)**

Like Vitamin B_1, Riboflavin is highly water soluble, and it is difficult to achieve toxic levels in the body – excess vitamin is efficiently eliminated renally. It used as an additive in many enriched foods and can be produced in huge, industrial scale, quantities by expression of the biodynthetic enzymes in fungi or bacteria. These genetically engineered organisms may appear bright yellowish-orange, which is the color of Riboflavin.

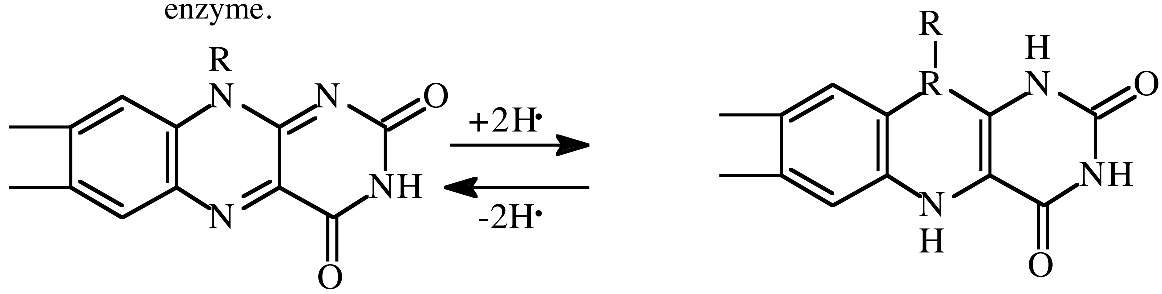
1. **Structure**



<u>FMN</u> = riboflavin monophosphate
<u>FAD</u> = flavin adenine dianucleotide
} riboflavin coenzymes



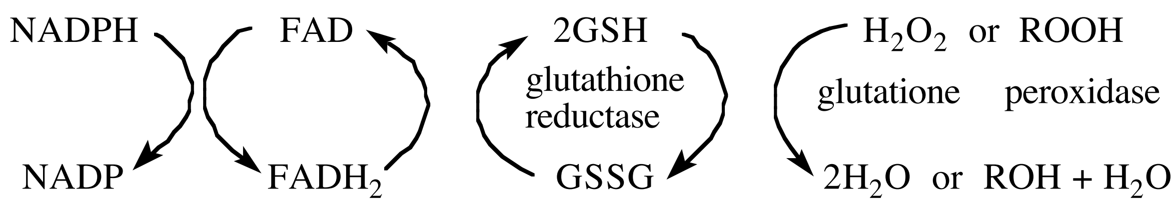
2. **Function** – redox, tissue respiration, H transfer as flavin containing enzyme.



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 B_2 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

a) Usually > 30% destroyed by cooking
b) Labile to light

c) More stable in acid than alkali in absence of light.

6. Use

a) Deficiency states. Is a component of most multivitamin mixtures.
b) New – may help in migraine headache prevention.
c) New – high intake associated with lower risk for cataracts and a 3mg supplement reduced risk.

7. Requirements

a) DV = 1.7 mg
b) "Average" U.S. diet contains 2 mg for males and 1.5 mg for females
c) Diagnosis – erythrocyte glutathione rreductase activity
d) No UL value

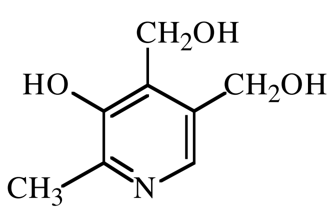
8. Patient Counseling/ Patient Use Issues

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

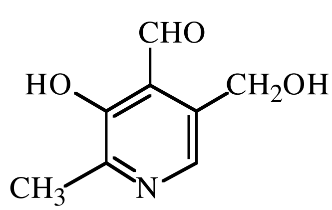
D. Vitamin B_6

1. Structure

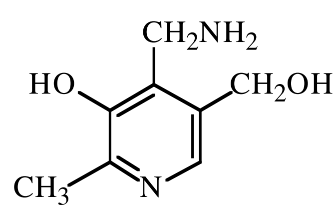
pyridoxine (P)



pyridoxal (PL)



pyridoxamine (PN)



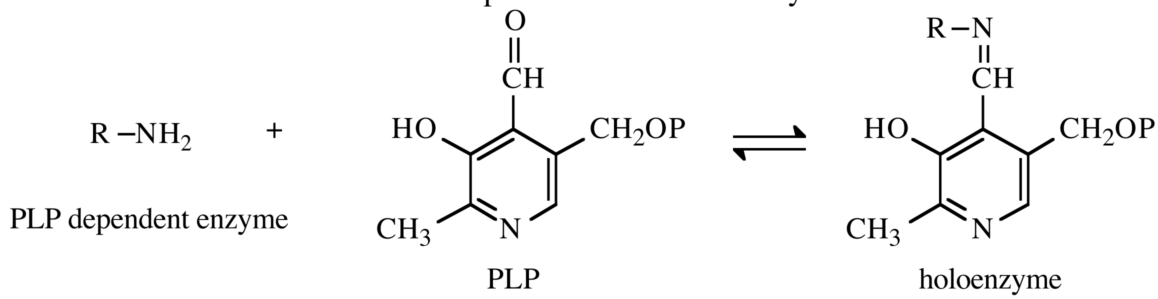
Pyridoxine is a commonly used term for this vitamin, but all 3 are equally active so vitamin B_6 is a better term to use.

Three phosphorylated forms are present also:

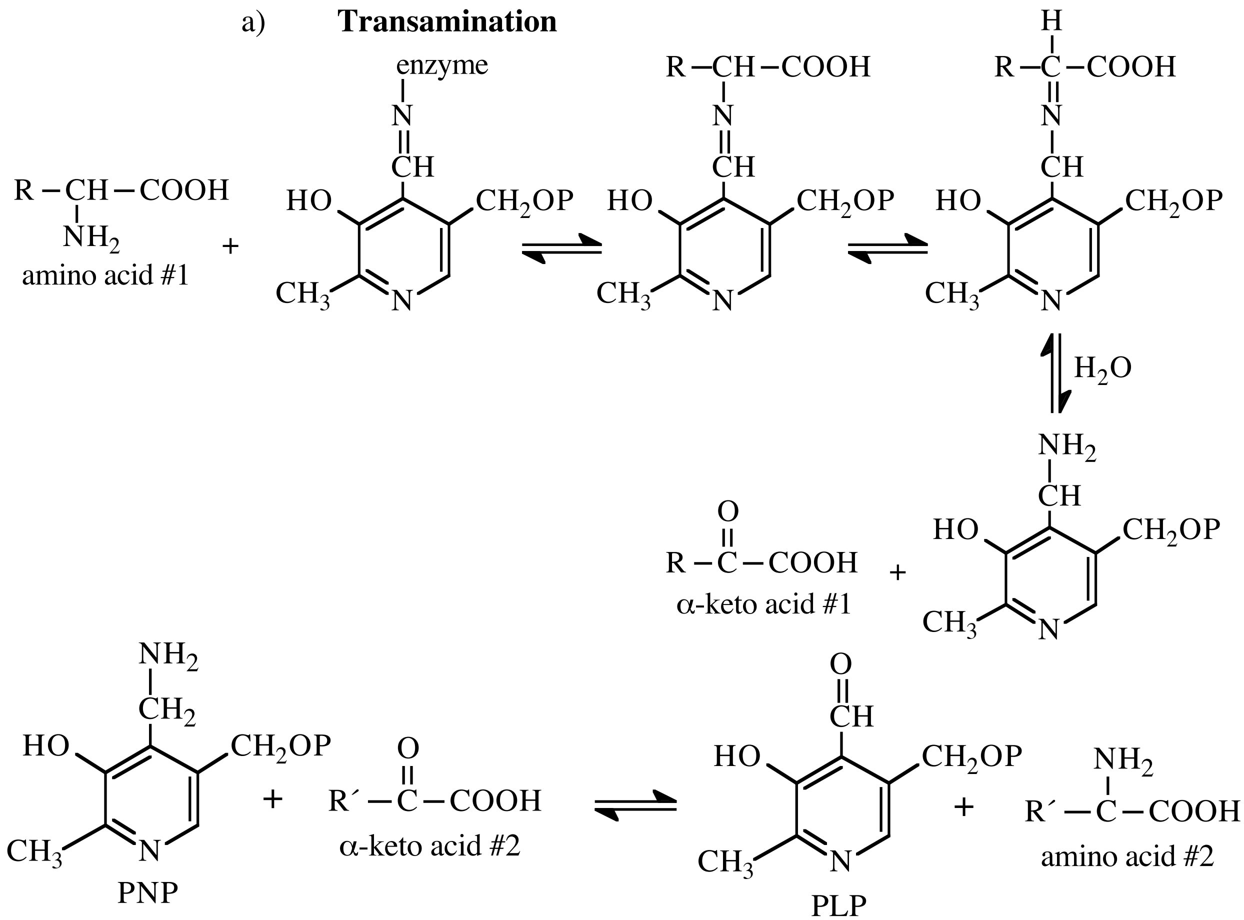
$$P-PO_4 \underset{FMN}{\rightleftharpoons} PLP \underset{FMN}{\leftrightharpoons} PNP$$

Coenzyme = pyridoxal-5-phosphate “PLP”

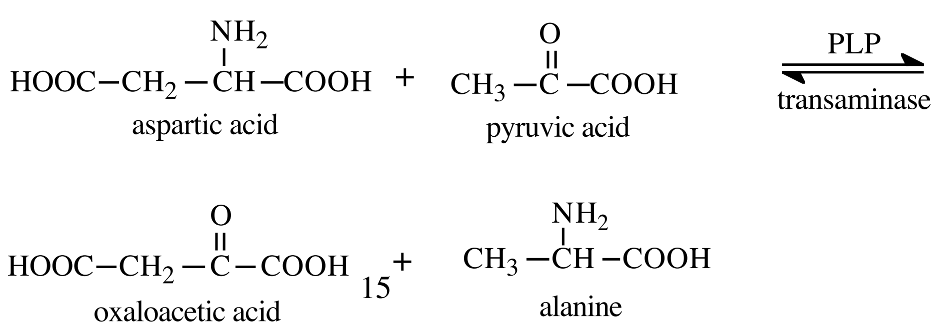
2. **Function** – participates in over 140 enzymatic reactions by forming a Schiff base with the terminal amino group of lysine in the enzyme. It is estimated that this corresponds to ~4% of all enzymatic reactions known.



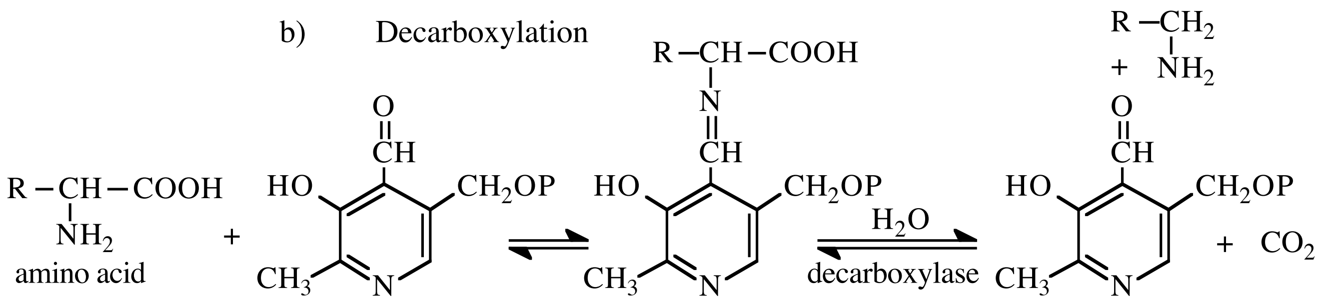
a) **Transamination**



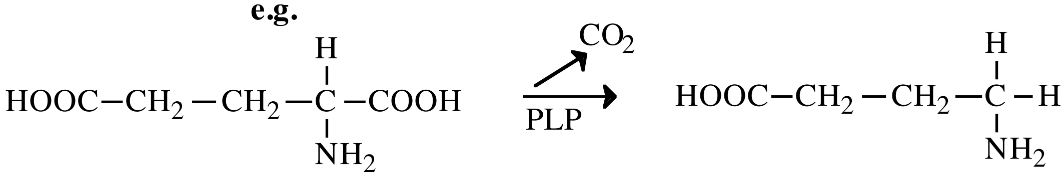
e.g. glutamate-aspartate transaminase



b) Decarboxylation



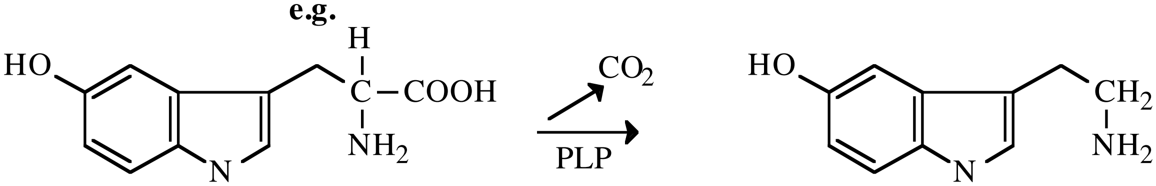
e.g.



glutamic acid

γ-amino butyric acid
(GABA)

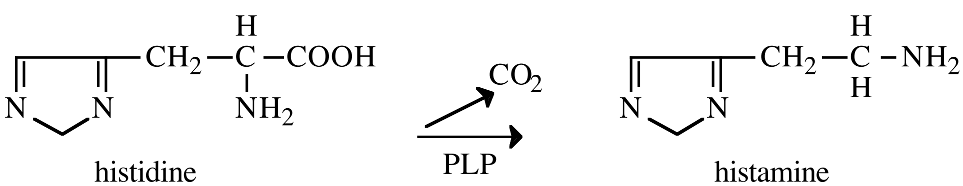
e.g.



5-hydroxytryptophan

5-hydroxytryptamine
(serotonin)

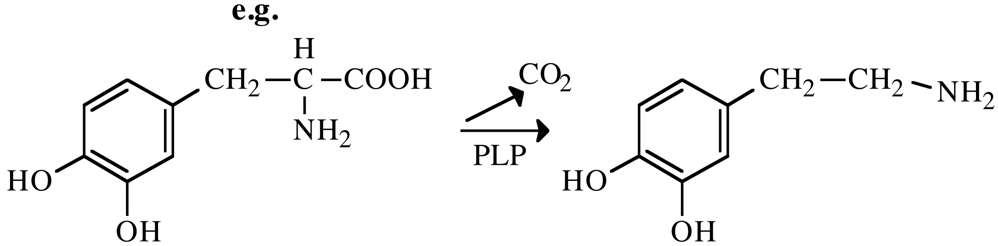
e.g.



histidine

histamine

e.g.



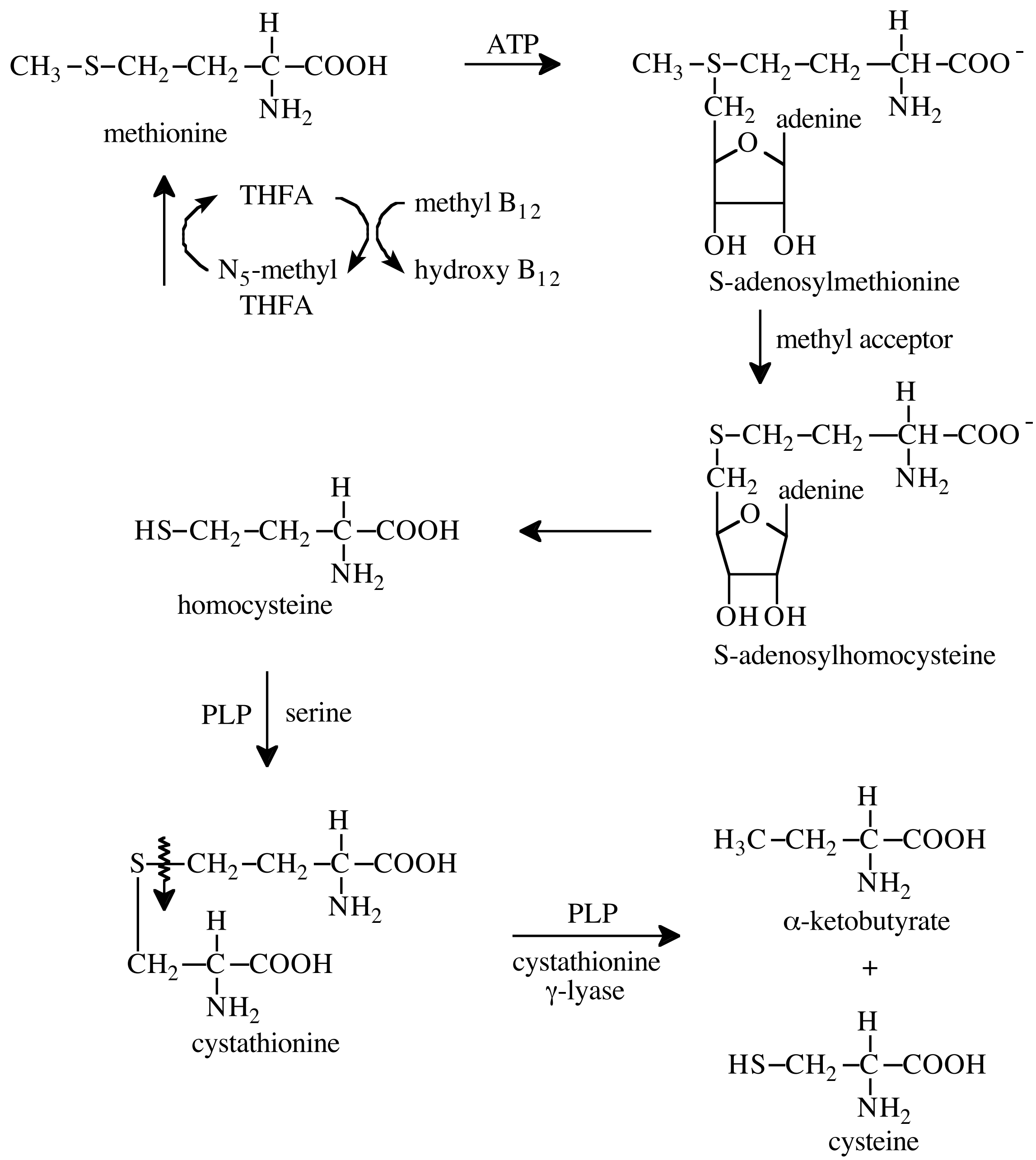
DOPA

DOPAMINE

<u>Note</u>: B_6 contraindicated in levo-DOPA therapy because B_6 enhances peripheral decarboxylation of levo-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. The anti-Parkinsons's drug Sinemet® contains levo-DOPA and carbidopa (A DOPA

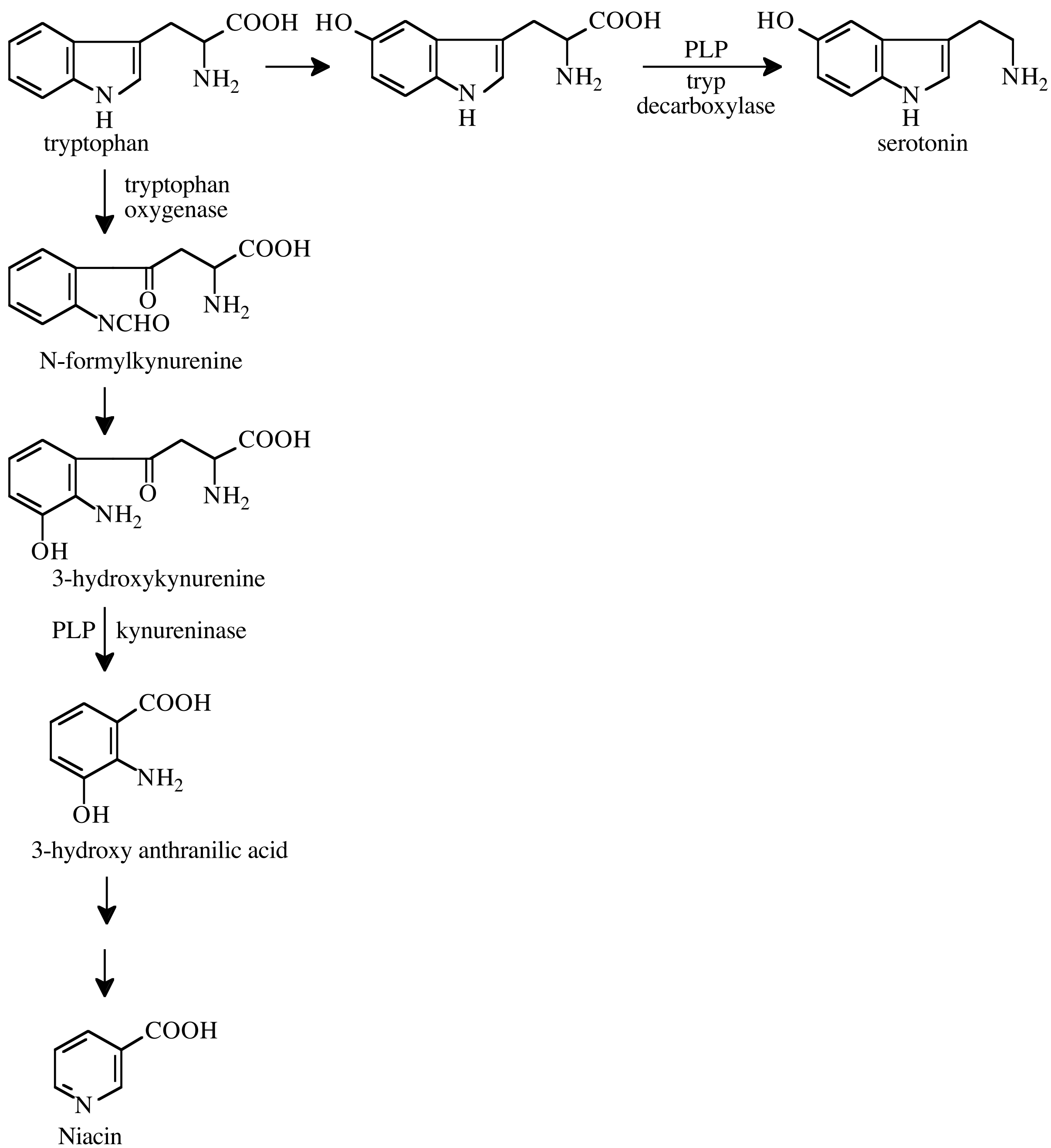
decarboxylase inhibitor) -- therefore, no interaction.

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



d) 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.

e) B_6 involved in tryptophan metabolism to serotonin and niacin.

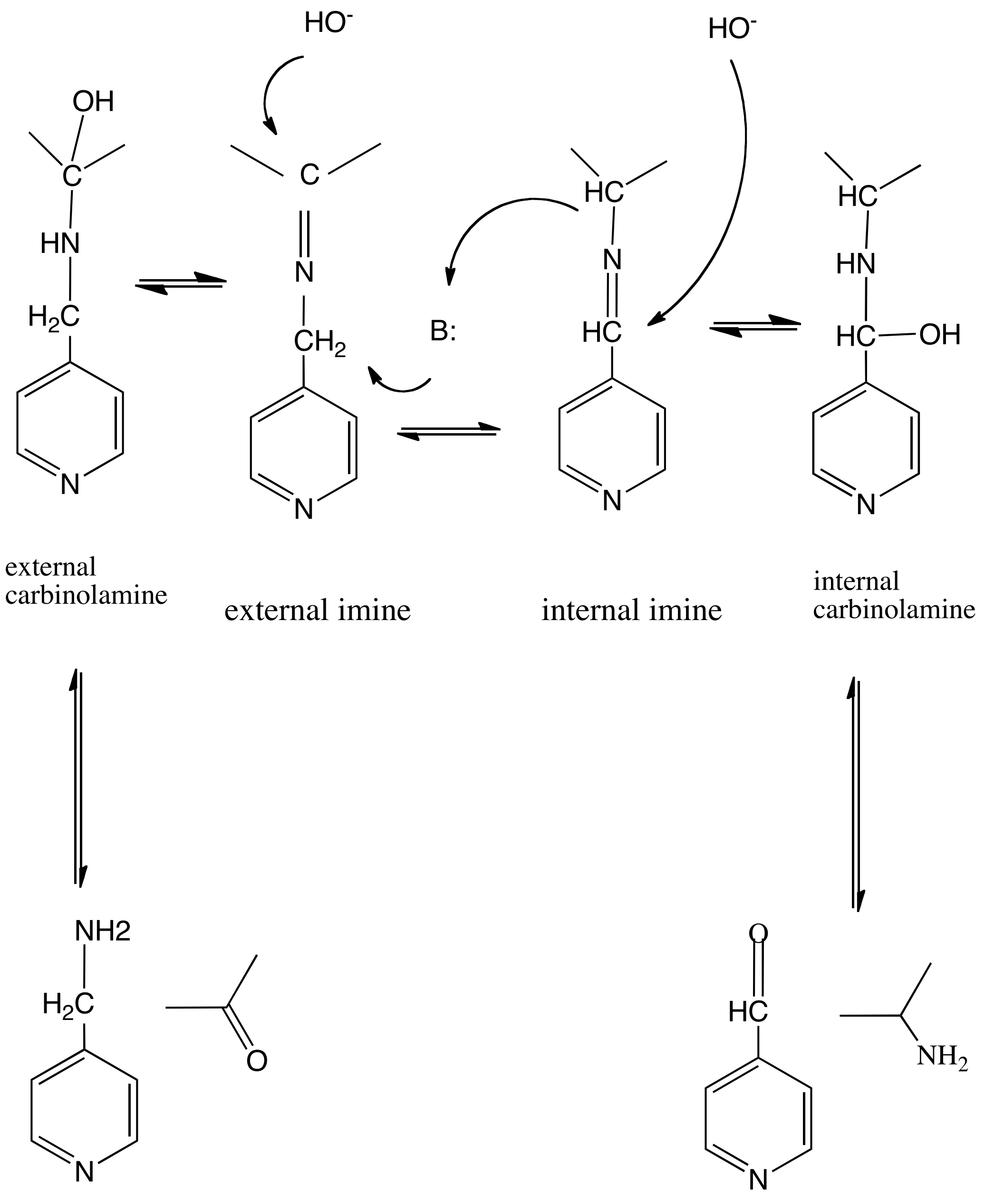


f) Other reactions requiring B_6:

(i) Glycogen phosphorylase (release of glucose in muscle)
(ii) Heme biosynthesis

(iii) Nucleic acid biosynthesis (via SAM)

SUMMARY of Pyridoxal/pyridoxamine reactions



hydrolysis of Imine leads to incorporation of 'oxygen atom'

H_2O attacks carbon atom of the imine, that carbon gets an oxygen

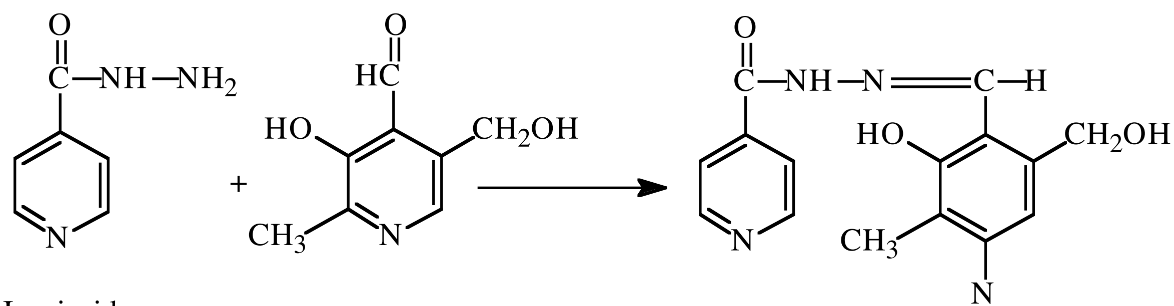
PLP enzymes control which carbon atom gets the oxygen atom by switching between the external imine and the internal imine. This accounts for their versatility.

3. **Deficiency**

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

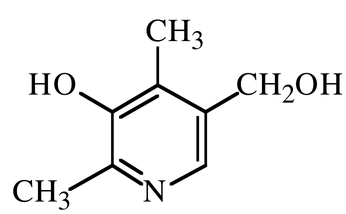
b) Iatrogenic B_6 deficiencies

(i) 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

(ii) 4-Deoxypyridoxine – (experimental only)



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

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

4. **Source** – milk, meats, legumes, tuna, whole grains, beans.

5. **Stability** – 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. In some trials vitamin B6 combined with lipoic acid worked – effects are modest!

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 B_{12} for optimum lowering action.

g) Nausea and vomiting in pregnancy-Helpful in high doses. PremesisRx contains 75mg sustained release B_6 (plus 12ug B_{12}, 1mg folic acid and 200mg calcium) or 25mg of generic B_6 TID is less expensive. It does not contain Iron. PremesisRx is contraindicated for patients on Fluorouracil – FU side effects may be increased by PremesisRx. Not used in the USA any longer.

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

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. <u>Patient Counseling/ Patient Use Considerations</u>

a) Routine single dose supplementation usually not needed. Use a multivitamin to get needed B_6.

b) Sometimes used, with limited evidence, for carpal 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, 25 mg TID or use PremensisRx which is FDA approved for this.

f) Used with B_{12} and folic acid in high homocysteine.

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