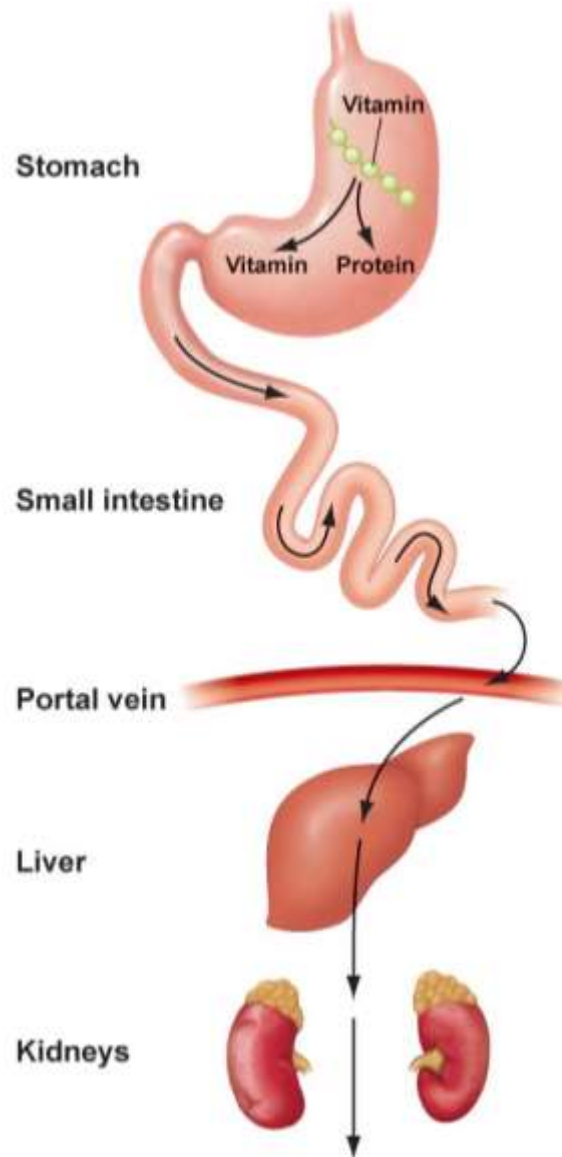


Vitamins

Classification

- Vitamins are classified into two major groups:
 - **Fat-soluble** (4 fat soluble) Vitamin A, D, E, K.
 - **Water-soluble** (9 water soluble)
 - B₁ (thiamine)
 - B₂ (riboflavin)
 - B₃ or Vitamin P or Vitamin PP (niacin)
 - B₅ (panthotenic acid)
 - B₆ (pyridoxine and pyridoxamine)
 - B₇ or Vitamin H (biotin)
 - B₉ or Vitamin M (folic acid)
 - B₁₂ (cobalamin)
 - Vitamin C

Digesting and absorbing water-soluble vitamins



a Vitamins are hydrolyzed in the stomach from the protein complexes found in food.

b Most of the water-soluble vitamins are absorbed in the upper small intestine with the exception of vitamin B₁₂, which is absorbed in the ileum.

c The water-soluble vitamins are absorbed directly into the portal vein and transported to the liver, where they are either stored (B₁₂) or sent out into circulation.

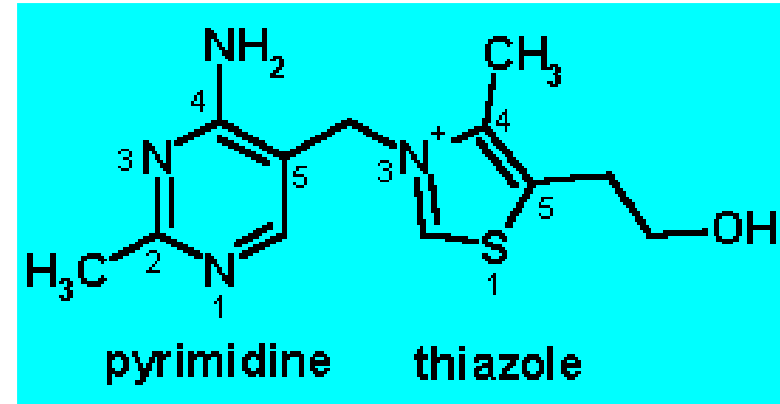
d Excess water-soluble vitamins are excreted through the kidneys in the urine.

Thiamin (B 1)

Chemistry:

- A substituted **pyrimidine** joined by a methylene bridge to a substituted **thiazole**.

Requirements: 1-1.5 mg/day for adults.
(Higher needs in pregnancy, high CHO diet)



Sources:

- **Plant sources:** whole grains (unrefined cereal grains), beans, peas, nuts and bran.
- **Animal sources:** liver, heart, kidney and milk.
- **Yeast**

Activation (Co-enzyme):

- Conversion of thiamin to its active form **thiamin pyrophosphate (TPP)**

Absorption

- Thiamine is released by the action of pyrophosphatase
- At low concentrations, the process is **carrier-mediated**.
- At higher concentrations, absorption also occurs via **passive diffusion**.
- It can be inhibited by **alcohol consumption**.
- On serosal side of the intestine, its transport is **Na⁺-dependent ATPase**.
- The majority of thiamine in serum is bound to proteins, mainly **albumin**.
- Approximately 90% of total thiamine in blood is in **RBCs**.

Cellular uptake

- Thiamine uptake and secretion appears to be mediated by a soluble thiamine transporter that is **dependent on Na⁺ [Thiamin transporter-1 & 2 (human THTR-1 & 2)]**.

Storage: of thiamine occurs in muscle, heart, brain, liver, and kidneys.

Excretion: Thiamine and its metabolites are excreted in **urine**.

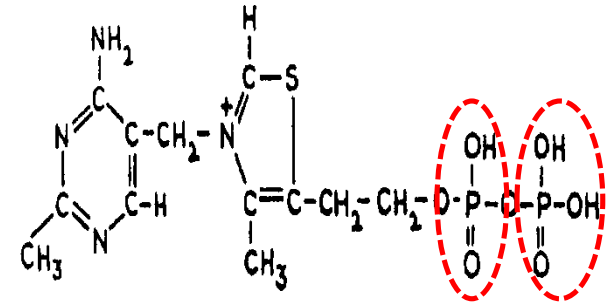
Thiamin: activation

Thiamin

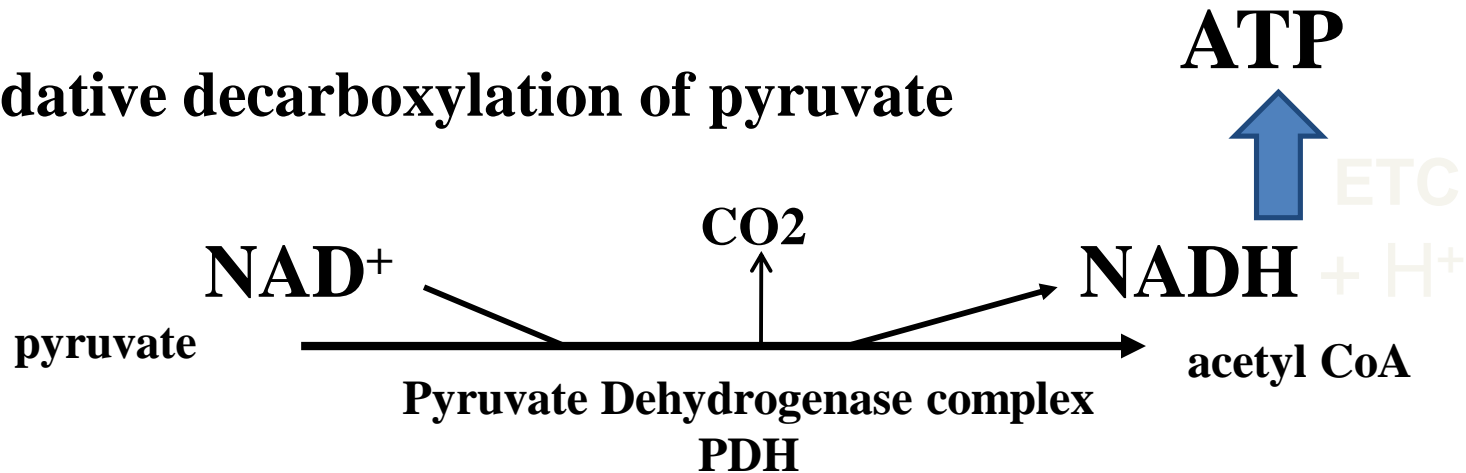
ATP-dependent thiamin
diphosphotransferase

Brain, liver

TPP



Oxidative decarboxylation of pyruvate



Vitamins (thiamin, lipoic, riboflavin, Niacin, pantothenic acid)

Co enzymes (TPP, Lipoamide, FAD, NAD^+ , CoASH)

Functions

- TPP serves as a coenzyme transferring an **activated aldehyde unit** in the following enzymatic reactions:
 1. **Oxidative decarboxylation** of α -keto acids.
 2. **Transketolase reaction** (pentose phosphate pathway; PPP). It is used for the biosynthesis of pentose sugars deoxyribose and ribose.
 3. **Acetylcholine synthesis** which is one of neurotransmitters and for myelin synthesis.
- **Important in:**
 - Producing **energy from carbohydrates**
 - **Nerve function**
 - **Muscle function**
 - **Appetite**
 - **Growth**
- **Therapy:** It can be used for treatment of Heart failure & Alzheimer disease.

Deficiency

Causes:

- **Low intake, malabsorption , and/ or defective phosphorylation** to TPP.
- **Antithiamine factors** : These are enzymes present in the viscera of shell fish and many microorganisms . They cause cleavage of thiamin producing pyrimidine and thiazole rings so they are called **thiaminases**. These antithiamine factors cause an isolated thiamine deficiency. **Plant** thiamine antagonists are heat-stable; for examples **caffeic acid**, and **tannic acid**. These compounds interact with the thiamine to oxidize the thiazole ring, thus rendering it unable to be absorbed.
- **Alcoholism** : Chronic alcoholism gives the manifestation of moderate thiamine deficiency. This is called **Wernike korsacoff** , **syndrome**. Alcohol interferes with absorption
- **Excessive loss** (diuretics).

Manifestations of thiamine deficiency

1. **Mild deficiency:** leads to
 - Gastrointestinal complaints
 - Weakness.

2. **Moderate deficiency:**
Wernike korsacoff , syndrome

- Peripheral neuropathy.
- Mental abnormalities.

3. **Severe thiamin deficiency**

A. Beriberi

- **Dry beriberi** is characterized by advanced neuromuscular symptoms:
 - Atrophy and weakness of the muscles
 - Peripheral neuropathy
 - Memory loss.
- **Wet beriberi:** the previous symptoms (dry beriberi) are coupled with oedema.

B. Wernike korsacoff , syndrome

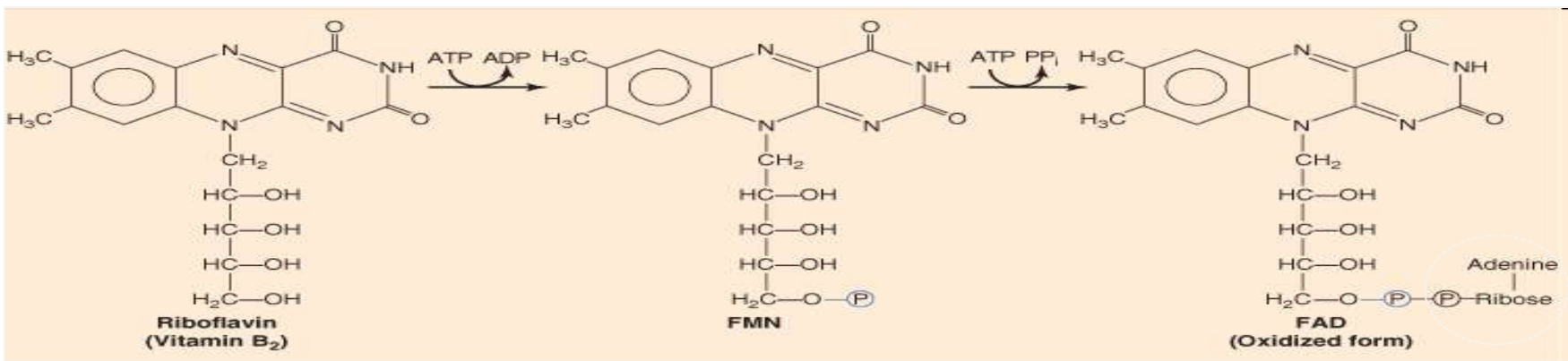
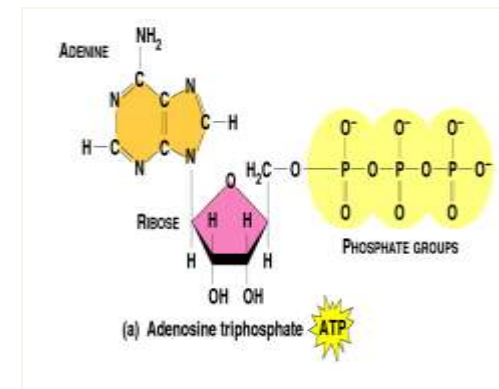
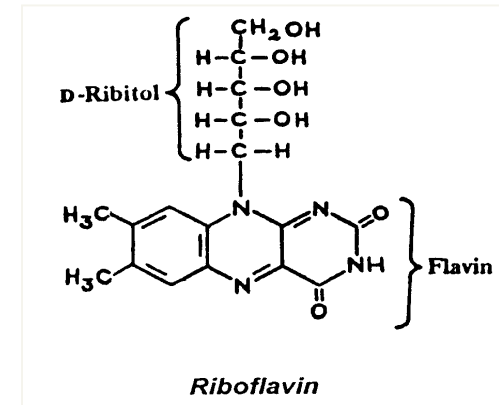


Riboflavin (B 2)

Chemistry: It consists of a **flavin ring** attached to the sugar alcohol **D- ribitol**.

Co enzyme forms

- Flavin mononucleotide (**FMN**) is formed by ATP-dependent phosphorylation of riboflavin.
- Flavin adenine dinucleotide (**FAD**) is synthesized by a further reaction with ATP in which the AMP moiety of ATP is transferred to FMN. Biosynthesis of FMN and FAD occurs in most tissues.



Absorption

- In diet, riboflavin (RF) exists in the free and FMN and FAD forms. They are **hydrolyzed to free Rf** by intestinal phosphatases.
- RF absorption in the **intestines** involve a **specific carrier-mediated mechanism for Rf uptake** located at the apical membrane & across the BLM.
- Both **RFT-1** (RF transporter1) and **RFT-2** are expressed in **intestine**.
- **RFT-3** is more **brain-** specific.
- Riboflavin in **blood** associates with **albumin or globulins**.

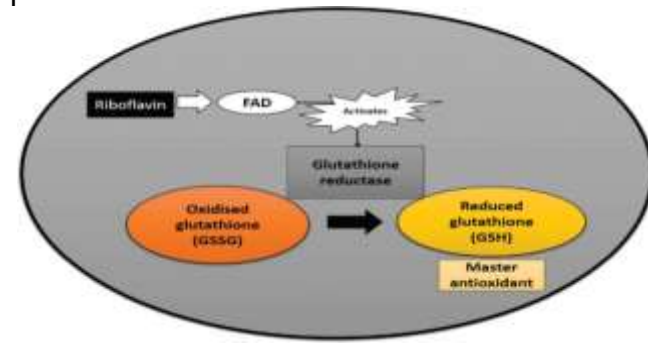


Sources

- **Animal origin:** liver and beef, milk, dairy products, fish, eggs, nuts
- **Yeast**
- **Plant origin:** Green leafy vegetables, nuts, of smaller quantities in cereals.

Function:

- **Involved in energy metabolism (ATP production):** Participate in
 - Oxidative decarboxylation
 - Citric acid cycle
 - Beta-oxidation of fatty acids
 - Electron transport
- **Associated with antioxidant glutathione reductase** (utilizes an **FAD** prosthetic group and **NADPH** to reduce GSSG to two GSH.)



1. Chemical **structure** of vitamin B2 is

[flavin + ribitol], fluorescent, light sensitive, heat stable.

2. Active form (**Co-enzyme**) of vitamin B2 is

[FMN & FAD]

3. Its **function** is to act as

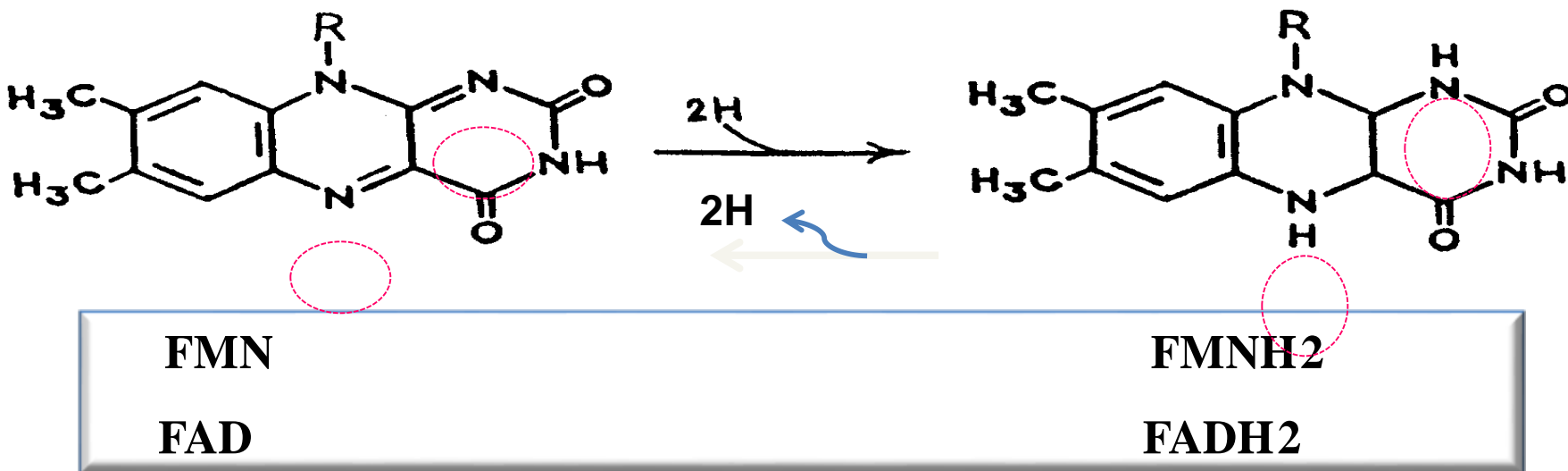
[prosthetic groups of oxidoreductases]

4. **Reactions** requiring **FAD** are:

a- [**oxidative decarboxylation** of a keto acids as PDH] \longrightarrow Energy (ATP)

b- [C.A.C.] \longrightarrow Energy (ATP)

c- [β -oxidation of F.A.] \longrightarrow Energy (ATP)



symptoms of deficiency

Related to Energy production (skin & mucous membrane inflammation).

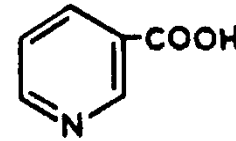
- **Glossitis & angular stomatitis** (Inflammation of the lining of mouth and tongue).
- Keratitis , dermatitis (Dry and scaling skin).
- **Cheilosis** (cracked and red lips).
- **Ocular manifestations (vascularization of cornea)**



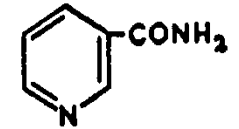
N.B. :

- Deficiency occurs in **newborn infants with hyperbilirubinemia** who are treated by phototherapy.

Niacin (B 3)



Niacin (nicotinic acid)



Niacinamid
(nicotinamide)

Chemistry:

- Nicotinic acid is a carboxylic acid derivative of pyridine.

Synthesis: PLP (vit. B6)

- **Tryptophan** → → → → → → **Niacin (vit. B3)** (insufficient)
- most people require dietary sources of both tryptophan and niacin.

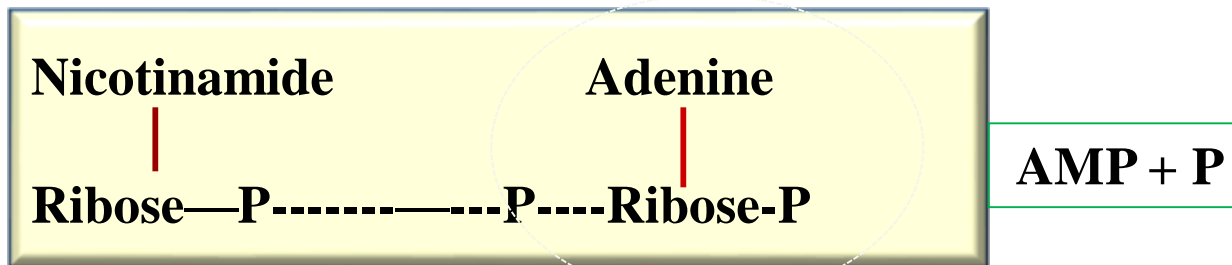
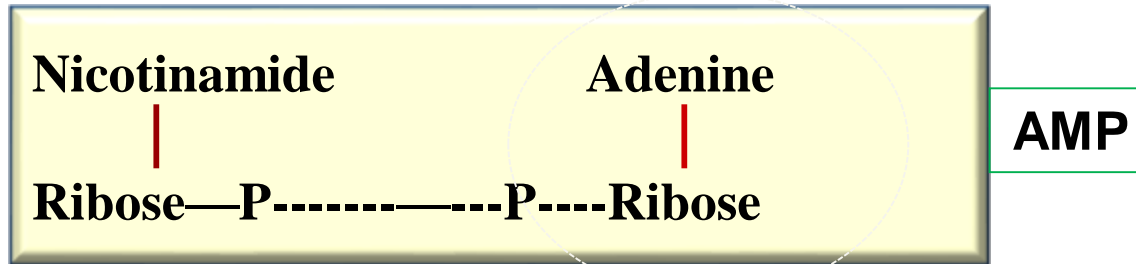
Sources:

- Food stuffs containing nicotinic acid: as B₁
- Tryptophan containing proteins

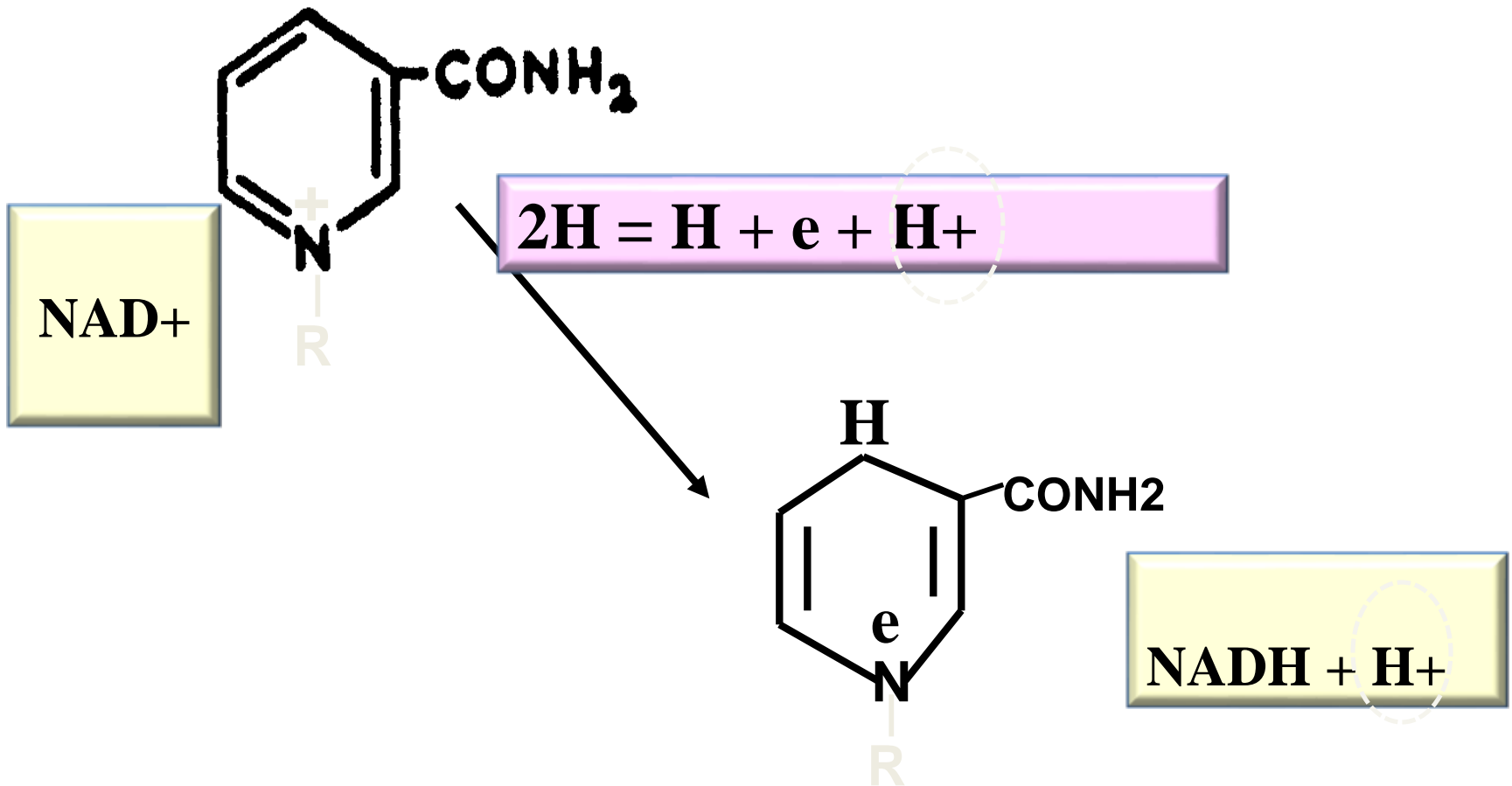
Functions: niacin required for the synthesis of NAD⁺ (nicotinamide adenine dinucleotide) and NADP⁺ (nicotinamide adenine di-nucleotide phosphate)

- NAD⁺ and NADP⁺ are coenzymes of many oxidoreductase enzymes.
- Generally, NAD⁺-linked dehydrogenases catalyze oxidoreduction reactions in **oxidative pathways**, e.g. the citric acid cycle.
- Whereas NADP⁺-linked dehydrogenases are often found in pathways concerned with **reductive synthesis** e.g. the pentose phosphate pathway.
- $\text{NAD}^+ + \text{AH}_2 \longrightarrow \text{NADH} + \text{H}^+ + \text{A}$

Structure of NAD⁺



reduction of NAD⁺



- **Reactions** requiring **NAD⁺** are:
 - a- [oxidative decarboxylation of a keto acids as PDH] → Energy (ATP)
 - b- [C.A.C.] → Energy (ATP)
 - c- [β oxidation of F.A.] → Energy (ATP)

- **Reactions** requiring co-enzyme **NADP⁺** as:
 - Glucose-6-phosphate dehydrogenase (NADP⁺)
 - Folate reductase (NADPH+H⁺)

intestinal niacin absorption process: intracellular **protein-tyrosine-kinase-mediated pathway** regulates vitamin uptake.

Deficiency

Causes of deficiency:

- in elderly on very restricted diet.
- malabsorption.
- in maize-dependant population.
- in vit. B6 def.
- Hartnup disease (decreased tryptophan absorption)
- Malignant carcinoid syndrome (increased tryptophan metabolism to serotonin)
- INH (anti-TB) (decreased B6)

Clinical use: Treatment of hyperlipidemia

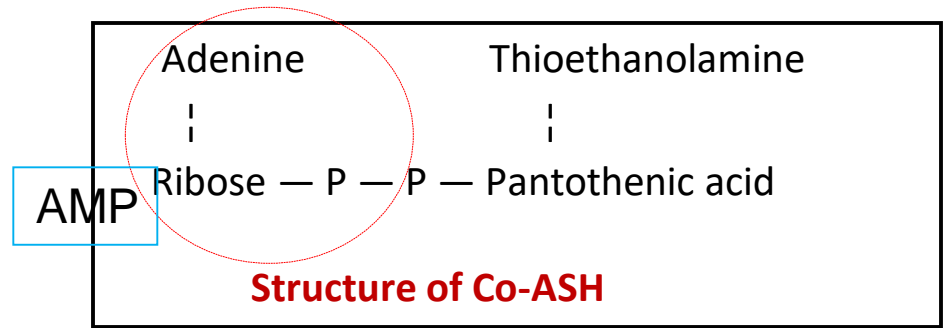
- Deficiencies found in southeast if subsisting on diet of corn ; niacin is bound by protein. Pellagra is very rare now
- **Deficiency:**
- **Milder deficiencies of niacin** cause:
 - Poor appetite, fatigue.
 - Dermatitis, Diarrhea.
- **Severe deficiencies** lead to **pellagra** which is characterized by “the four D_s”: dermatitis, diarrhea, dementia (lack of concentration) and death.
- Dermatitis is usually seen in skin areas exposed to sun light and is symmetric.
- The neurologic symptoms start by nervous disorders and mental disturbances.



Pantothenic acid (B 5)

Absorption

- For the intestinal cells to absorb pantothenic vitamin, it must be converted into free pantothenic acid.
- Free **Pantothenic acid** and **Biotin** are absorbed into intestinal cells via a saturable, sodium-dependent active transport system. [**Sodium-dependent multivitamin transporter (SMVT)**]
- At high levels of intake, when this mechanism is saturated, some pantothenic acid may also be absorbed via passive diffusion. As intake increases 10-fold, however, absorption rate decreases to 10%.



6- Sources are: [as B1]

7- Reactions requiring CoASH:

- a- oxidative decarboxylation of a keto acids \longrightarrow Energy.
- b- oxidation of Fatty acid
- e- acetylating reactions as acetyl choline.

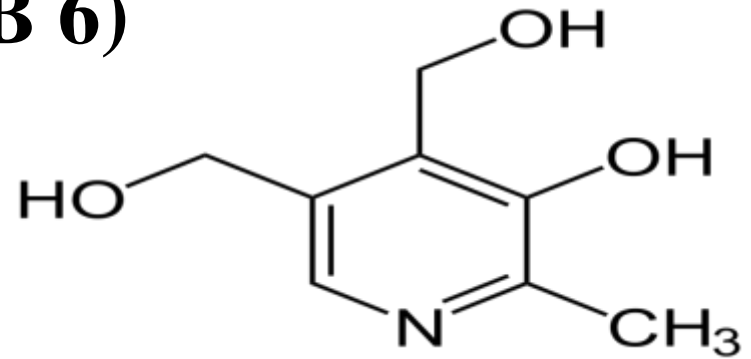
8- Reaction requiring ACP is : [Fatty acids synthesis]

- **Destruction:** Easily destroyed by food processing.
- **Functions:** Part of **coenzyme A** used in **energy metabolism**.
- **Deficiency: rare** because it is very widespread in natural food.
 - Nausea, vomiting. -Easy fatigability. -Dermatitis.
 - Depression, neurological symptoms (disorders of the synthesis of acetylcholine). Numbness, muscle cramps, inability to walk.
 - **Burning foot syndrome** (severe burning and excessive sweating).

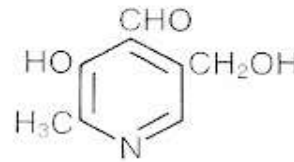
Pyridoxine (B 6)

Chemistry:

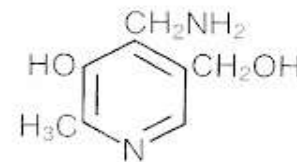
- It is a water soluble vitamin
- A pyridoxine derivative
- Consists of 3 closely related compounds equally effective as precursors of its coenzyme PLP (pyridoxal phosphate)



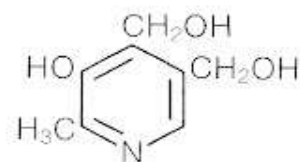
- Pyridoxine (alcohol)
- Pyridoxal (aldehyde)
- Pyridoxamine (amine)



Pyridoxal

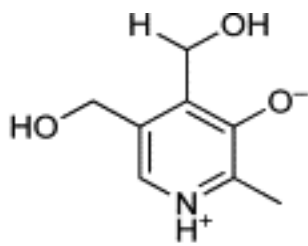


Pyridoxamine

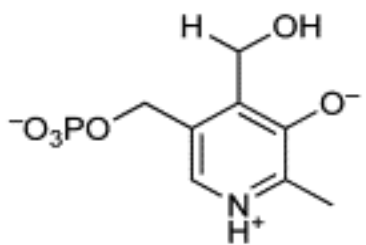


Pyridoxine

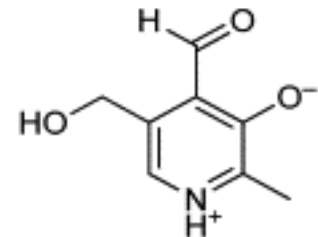
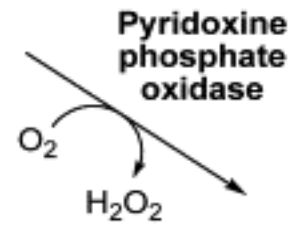
- Pyridoxamine is mostly present in plants
- Pyridoxal & pyridoxine is present in animal foods
- Pyridoxine can be converted into pyridoxal & pyridoxamine
- Pyridoxal phosphate (PLP) is the active form of Pyridoxine
- PLP is synthesized by pyridoxal kinase, utilizing ATP



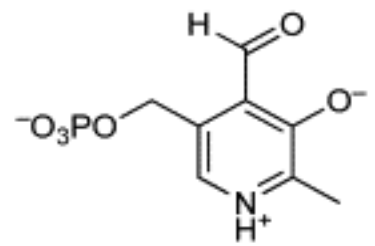
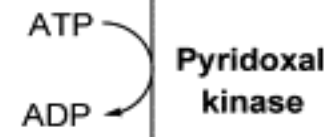
Pyridoxine



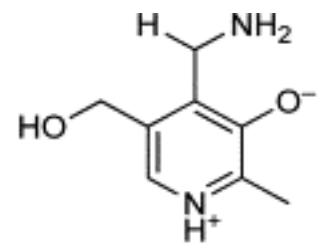
Pyridoxine 5'-phosphate



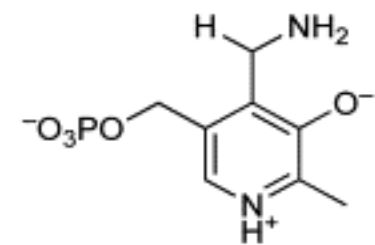
Pyridoxal



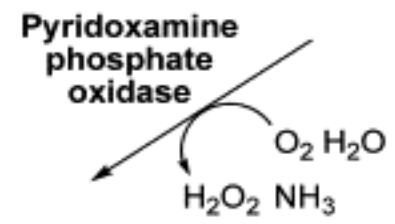
Pyridoxal 5'-phosphate



Pyridoxamine



Pyridoxamine 5'-phosphate



Metabolism

Absorption: It occurs in proximal jejunum by passive diffusion

- In the mucosal cells, all forms of pyridoxine is converted into pyridoxal
- Transport: It transported in the circulation bound to albumin
- Storage: It is stored in the tissues as its coenzyme form, PLP
- Mainly stored in liver, brain, kidney & muscle
- Excretion: 4 – pyridoxic acid excreted in urine

Biochemical functions

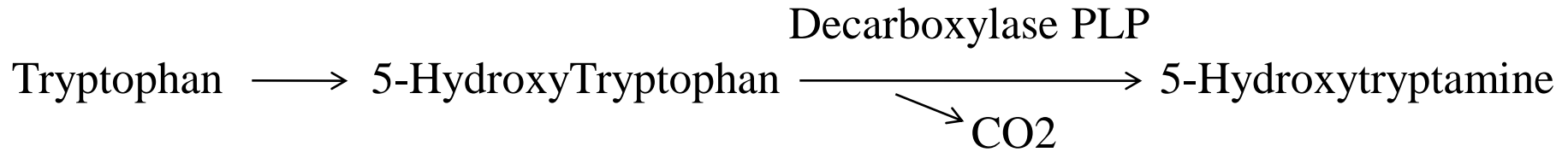
- PLP is the coenzyme of B6 is found attached to ϵ –amino group of lysine in the enzyme
- PLP is associated with Amino acid metabolism
- PLP is involved in:
 - 1- Transamination
 - 2- Decarboxylation
 - 3- Deamination
 - 4- Transsulfuration
 - 5- Condensation

Transamination

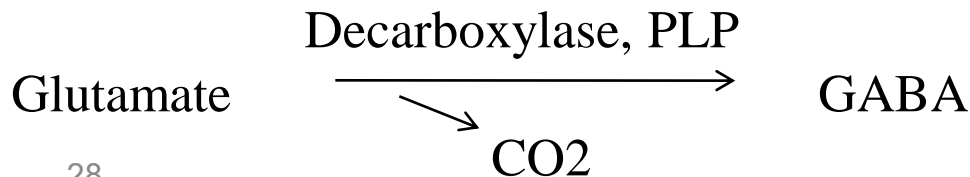
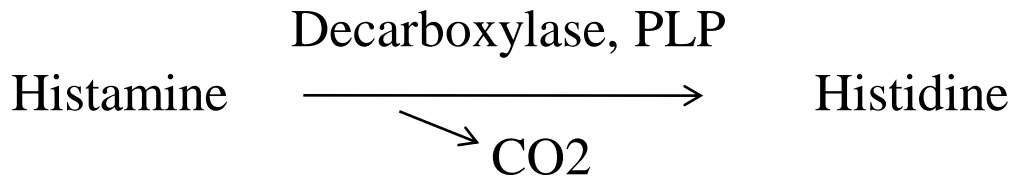
- PLP is involved in transamination reaction converting amino acids to keto acids
- Keto acids enter the TCA cycle and get oxidized to generate energy
- During transamination, PLP interacts with amino acids to form Schiff base
- The amino group is handed over to PLP to form Pyridoxamine phosphate and ketoacid is liberated.

Decarboxylation

- α - Amino acids undergo decarboxylation to form respective amines
- The reaction is carried out by decarboxylases which require PLP
- 1- Serotonin produced from tryptophan is important in nerve impulse transmission. It regulates sleep, behavior, blood pressure.

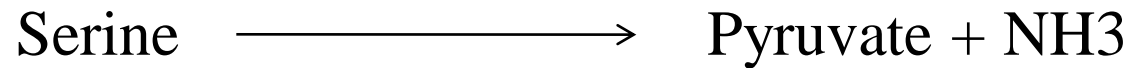


- 2- Histamine is vasodilator lowering blood pressure
- It stimulates gastric HCl secretion and is involved in inflammation and allergic reactions
- 3- Glutamate on decarboxylation gives GABA which inhibits transmission of nerve impulses



- PLP Plays an important role in metabolism of sulfur containing A.A.s
- Transsulfuration from homocysteine to serine occurs in the synthesis of cysteine
- PLP dependent enzyme cystathionine synthase
- Deamination of hydroxyl group containing A.A.s requires PLP

PLP, dehydratase



- Synthesis of serine from glycine require PLP.
- Glycogen phosphorylase contains PLP for converting glycogen to glucose 1-phosphate
- PLP is needed for the absorption of amino acids from intestine
- B6 is useful to prevent urinary stone formation

RDA (Recommended Dietary allowance) of vitamin B 6

- Adult men – 2 - 2.2 mg/day
- Adult women - 2.0 mg/day
- Pregnancy and lactation - 2.5 mg/day

Dietary sources:

- Animal sources: egg yolk, fish, milk, meat
- Vegetable sources: wheat, corn, cabbage, roots & tubers

Deficiency

- Decreased dietary intake
- Alcoholism
- Impaired absorption
- Antivitamins: chronic administration of drugs such as isoniazid and penicillamine

Clinical features

- Neurological manifestations due to B6 deficiency, serotonin, epinephrine, norepinephrine and GABA are not produced properly

- The synthesis of niacin from tryptophan is impaired
- Xanthurenic acid, produced in high quantities is excreted in urine and can be used as reliable index of B6 deficiency
- Decreased Hb levels, associated with hypochromic microcytic anemia seen in B6 deficiency

Toxicity of B6

- Excess use of B6 (2.5 g/day) may lead to sensory neuropathy
- It is manifested by imbalance, numbness, muscle weakness and nerve damage

Biotin (B 7)

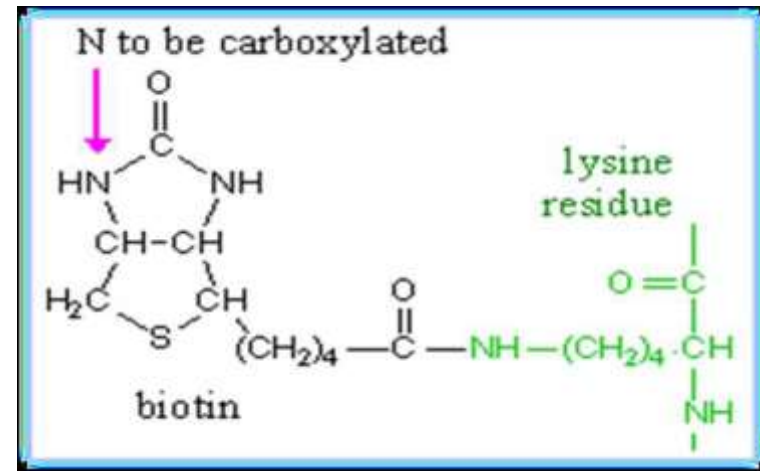
- It is formerly known as anti-egg white injury factor or vitamin H
- It is water soluble sulfur containing B-complex vitamin
- Biotin mainly participates in the carboxylation reactions

Chemistry

- It is a heterocyclic sulfur containing monocarboxylic acid
- Biotin is imidazole derivative formed by fusion of imidazole and thiophene rings with a valeric acid side chain
- Biotin covalently bound to ϵ – amino group of lysine to form biocytin

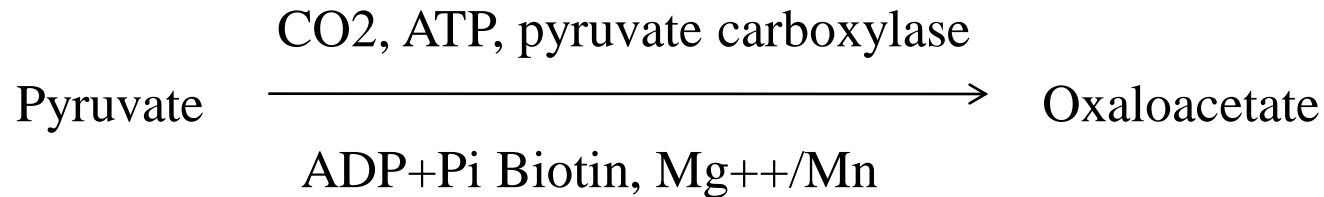
Coenzyme form

- Biocytin is the coenzyme form of Biotin
- Biotin is a prosthetic group of carboxylase



Biochemical functions

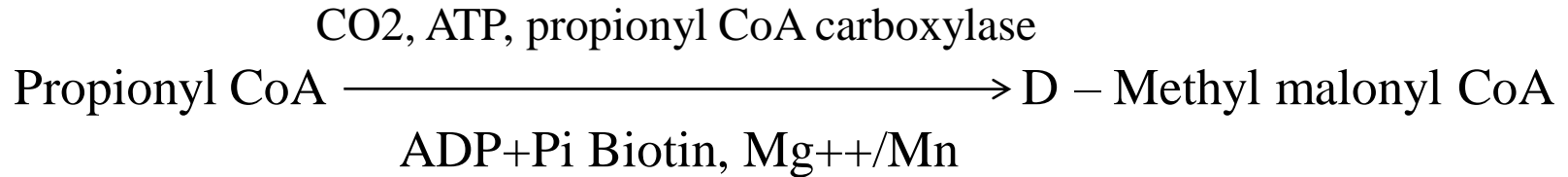
- Biotin is required for carboxylation reactions
- Biotin is required for the enzymes
 - Pyruvate carboxylase
 - Acetyl CoA carboxylase
 - Propionyl carboxylase
 - β - Methyl crotonyl CoA carboxylase
- Pyruvate carboxylase catalyzes conversion of pyruvate to oxaloacetate



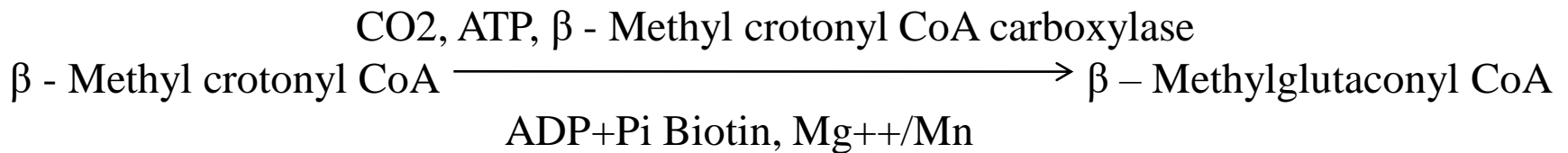
- Acetyl CoA carboxylase catalyzes the formation of malonyl CoA from acetyl CoA, the reaction provides acetate molecule for fatty acid synthesis



- Propionyl CoA carboxylase catalyzes the formation of D – Methyl malonyl CoA from propionyl CoA (from odd chain FA & methionine)
- It is required for entry of Propionyl CoA to TCA cycle via succinyl CoA



- β - Methyl crotonyl CoA carboxylase catalyzes the formation of β – Methylglutaconyl CoA from β - Methyl crotonyl CoA
- It is essential for leucine catabolism



- Not all carboxylation reactions in the biological system are biotin dependent, few carboxylation reactions which do not require biotin
- Formation of carbamoyl phosphate in urea cycle
- Incorporation of CO₂ in purine synthesis

Dietary sources

- Rich sources are eggs, liver, kidney, & yeast, pulses, nuts, vegetables
- Poor sources are cereals & dairy products

RDA

- Adults - 200 – 300 mg/day

Deficiency

- Biotin deficiency is generally not seen in man because of
 - 1- Its wide distribution in foods
 - 2- Synthesis of vitamin by the bacterial flora in the gut

Clinical features

- Severe dermatitis, weakness, & nausea
- In animals muscle weakness, dermatitis & loss of hair around the eye

- Avidin-biotin system is commonly utilized for detection of pathogenesis in ELISA test
- DNA is generally labelled by radioactive nucleotides
- Recently, biotin labelling of DNA is becoming more popular
- Biotin is added to nucleotides, which will be incorporated into the newly synthesized DNA
- The fixed biotin can be identified by reaction with Avidin
- Intake of 20 raw eggs/day will produce Biotin deficiency in humans
- Prolonged use of antibacterial drugs such as sulfonamides

Biotin antagonists

- Avidin (Raw egg white injury factor)
- Raw egg white injury factor is a heat labile protein known as avidin and is present in raw egg white
- Avidin binds to biotin & makes its unavailable for absorption
- Avidin is inactivated by boiling the eggs & biotin is readily absorbed when boiled eggs are used in the diet
- One molecule of avidin can combine with four molecules of biotin
- Egg white contains Avidin & egg yolk contains biotin
- The affinity of Avidin to biotin is greater than most of the usual antigen-antibody reactions