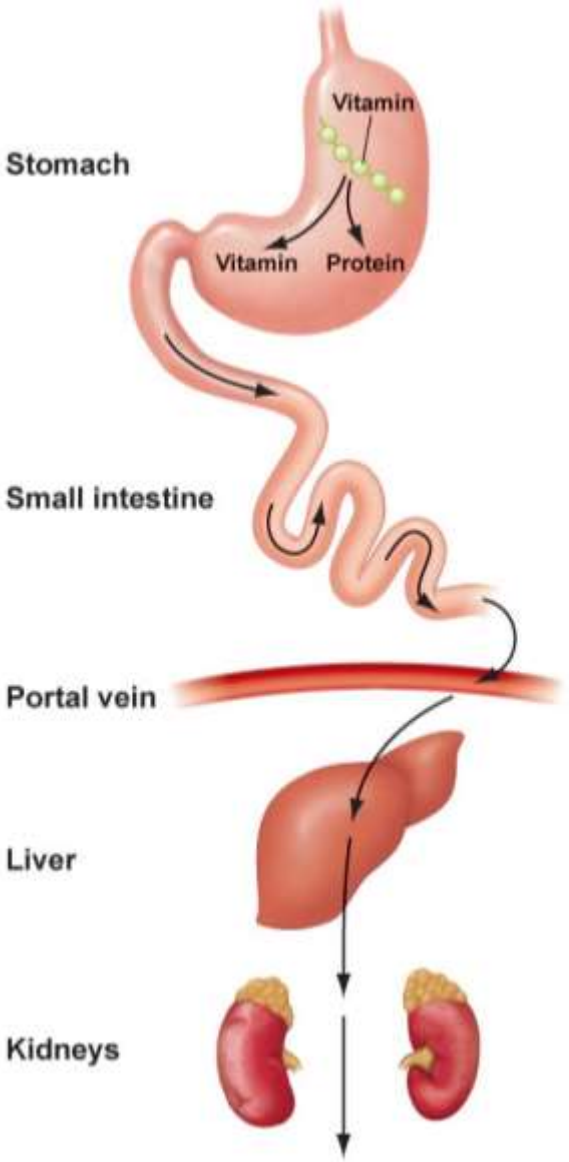
Classification

- Vitamins are classified into two major groups:
  - **Fat-soluble** (4 fat soluble) Vitamin A, D, E, K. AKED اكيد
  - **Water-soluble** (9 water soluble)
    - B_1 (thiamine)
    - B_2 (riboflavin)
    - B_3 or Vitamin P or Vitamin PP (niacin) or nicotinic acid
    - B_5 (panthotenic acid)
    - B_6 (pyridoxine and pyridoxamine)
    - B_7 or Vitamin H (biotin)
    - B_9 or Vitamin M (folic acid)
    - B_{12} (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 B_{12}, 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 (B_{12}) or sent out into circulation.

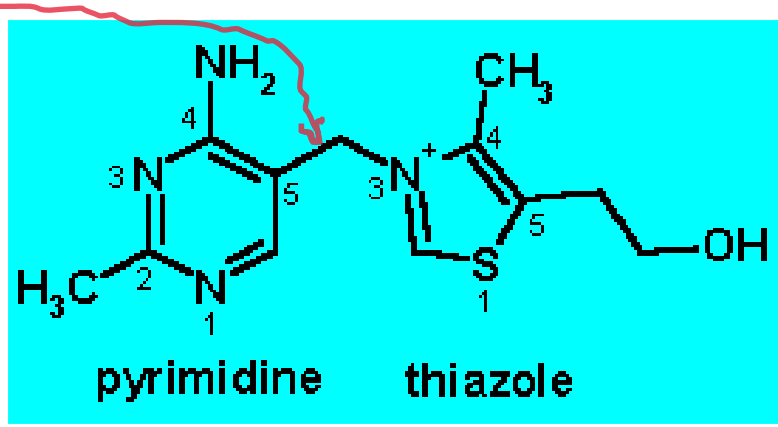
d Excess water-soluble vitamins are excreted through the kidneys in the urine.

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**. called general carrier
- Approximately 90% of total thiamine in blood is in **RBCs.**

Cellular uptake

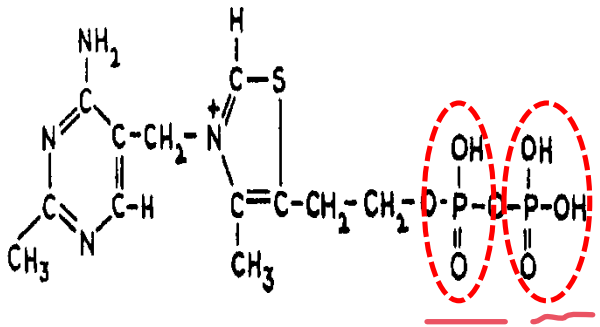
- Thiamine uptake and secretion appears to be mediated by a soluble thiamine transporter that is **dependent on Na^+ [Thiamin transporter-1 & 2 (**human THTR-1 & 2)].

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

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

Thiamin: activation

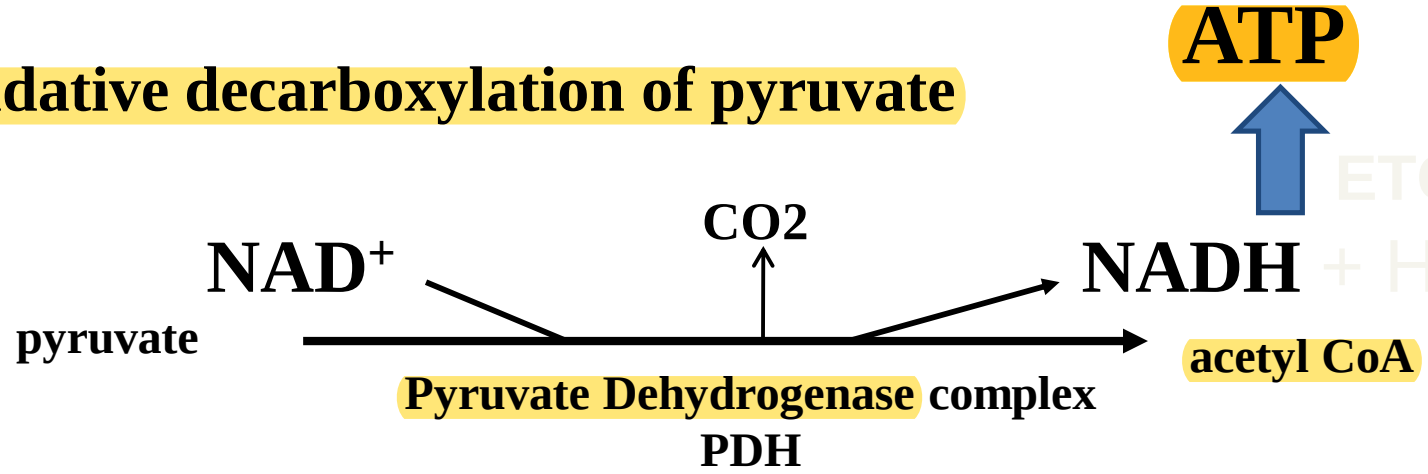
Thiamin → (ATP-dependent thiamin diphosphotransferase; Brain, liver) → **TPP**



2 phosphate groups

Thiamine + ATP → TPP + AMP (EC 2.7.6.2).

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.

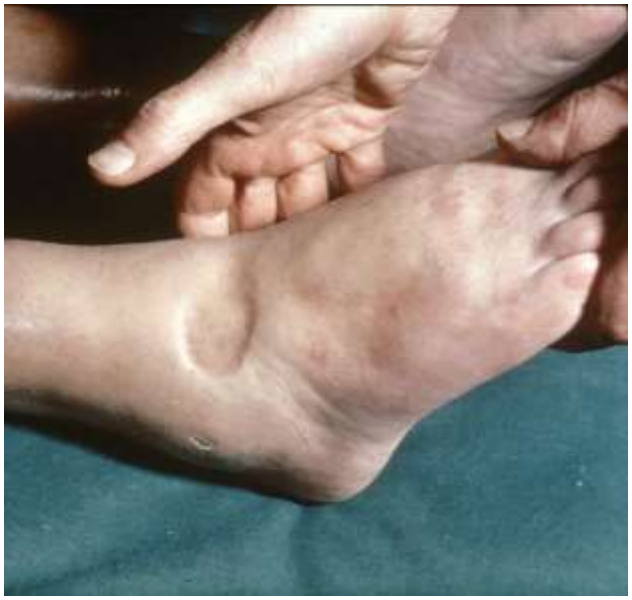
- **Important in:** Vitamin B1 is important in these things:
  - Producing **energy from carbohydrates**
  - **Nerve function**
  - **Muscle function**
  - **Appetite**
  - **Growth**
- **Therapy:** It can be used for treatment of Heart failure & Alzheimer disease.

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.

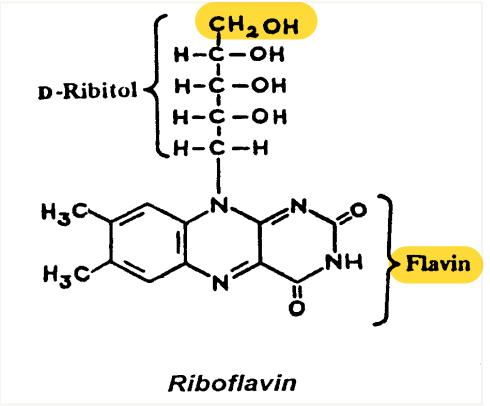
3. **Severe thiamin deficiency**

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

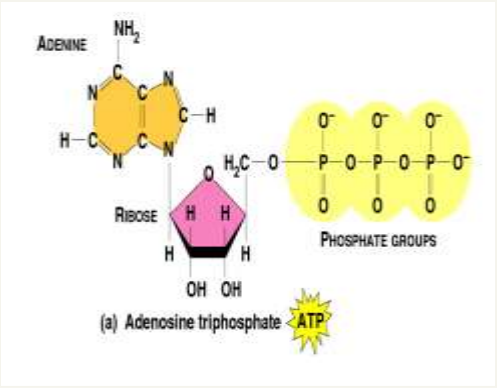
Riboflavin (B 2)

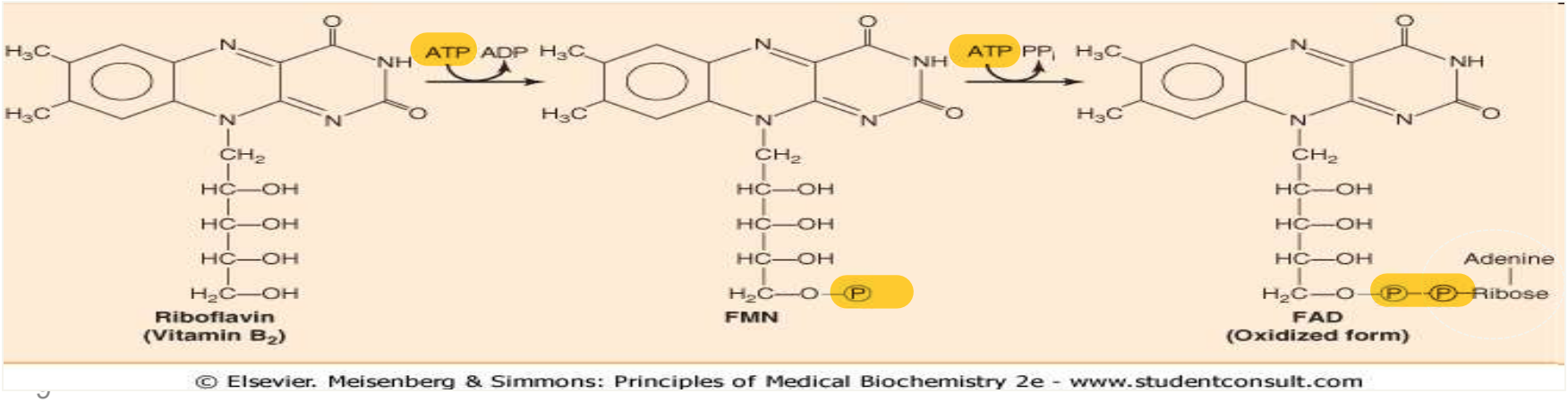


Chemistry: It consists of a **flavin ring** attached to the sugar alcohol **D- ribitol.**

Co enzyme forms

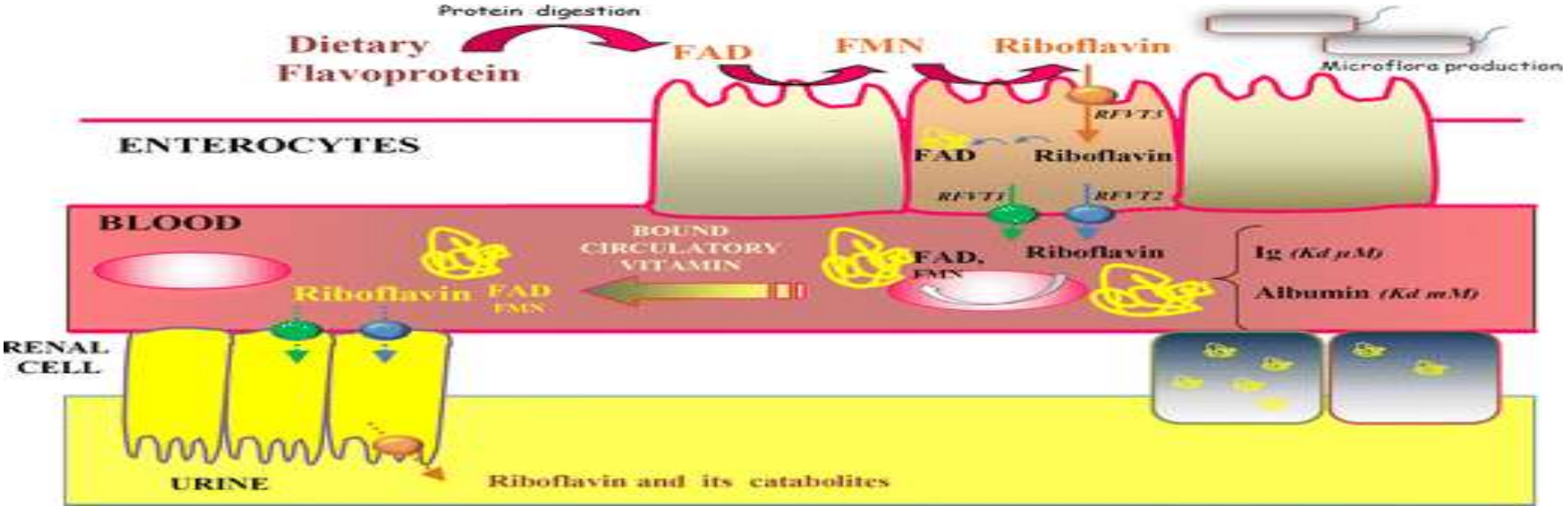
- Flavin mononucleotide (**FMN**) is formed by ATP-dependent phosphorylation of riboflavin.
- Flavin adenine dinucleotide (**FAD**) is synthesized by a further reaction with ATP in which the AMP moiety of ATP is transferred to FMN. Biosynthesis of FMN and FAD occurs in most tissues.





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.

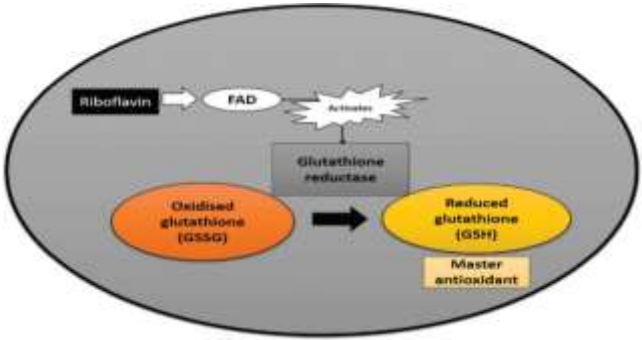
Function:

- **Involved in energy metabolism (ATP production):** Participate in
  - Oxidative decarboxylation
  - Citric acid cycle
  - Beta-oxidation of fatty acids
  - Electron transport

similar to B1 and are involved in energy

- **Associated with antioxidant glutathione reductase** (utilizes an **FAD** prosthetic group and **NADPH** to reduce GSSG to two GSH.)

GS–SG + NADPH + H^+ → 2 GSH + $NADP^+$



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]

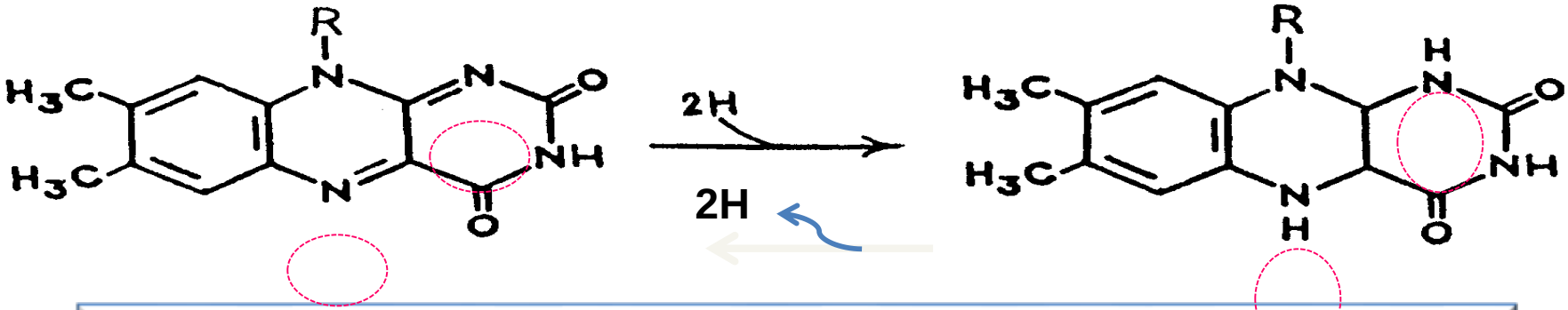
4. **Reactions** requiring **FAD** are:

a- **[oxidative decarboxylation of a keto acids as PDH → Energy (ATP)**

b- **[C.A.C.] → Energy (ATP)**

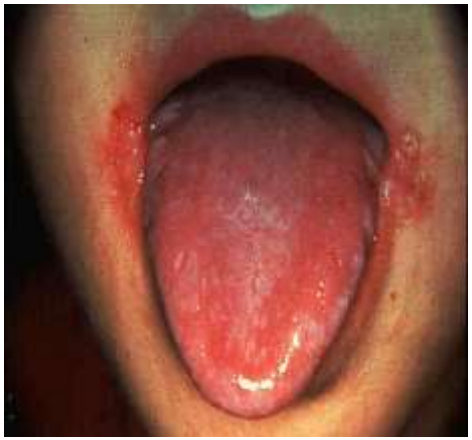
c- **[β -oxidation of F.A.] → Energy (ATP)**

fatty acids



FMN	**FMNH2**
FAD	**FADH2**

symptoms of deficiency



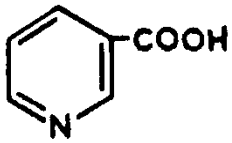
Related to Energy production (skin & mucous membrane inflammation).

- **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)**

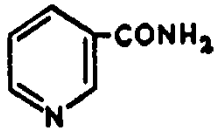
N.B. :

- 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:

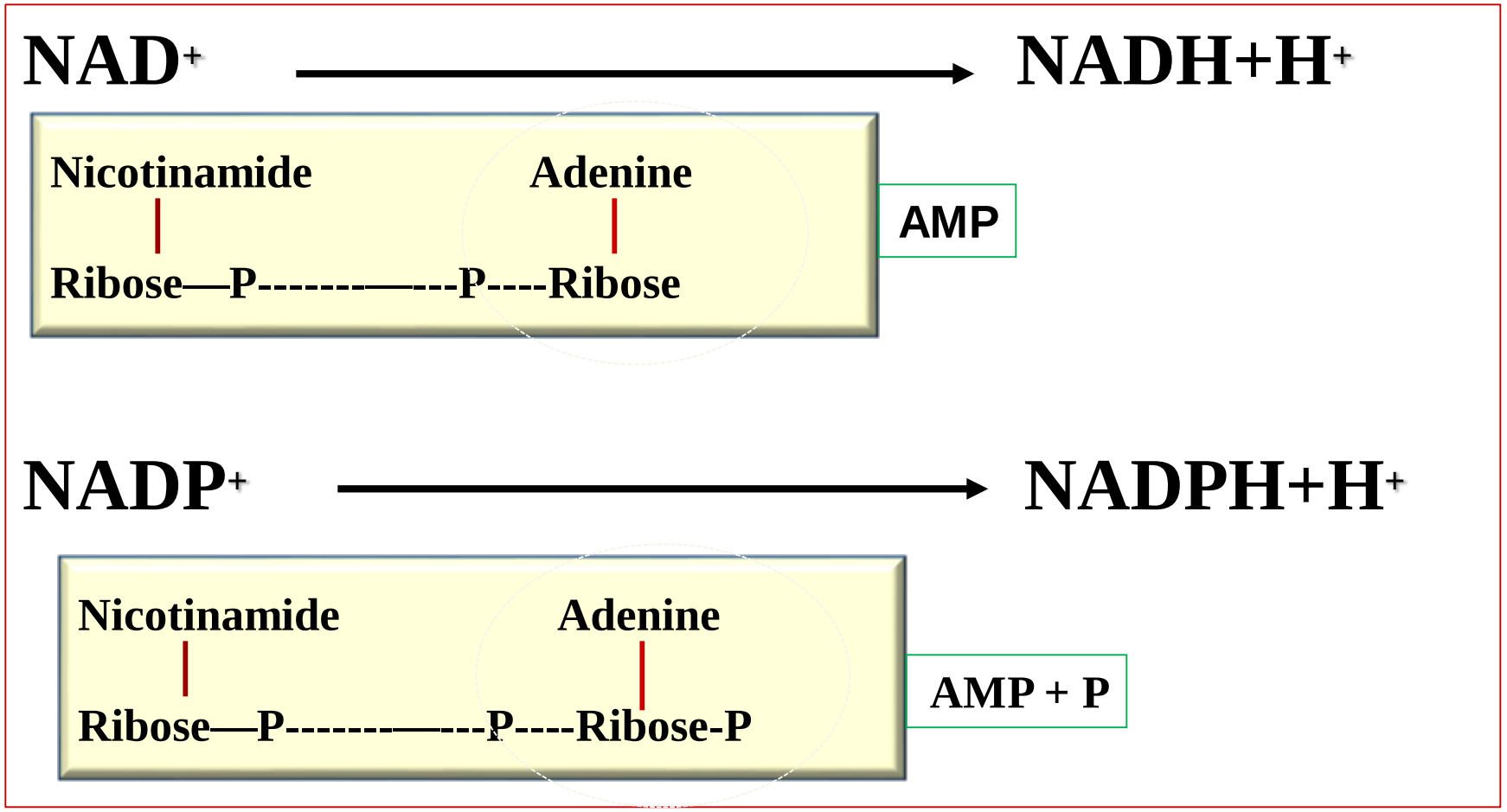
- Food stuffs containing nicotinic acid: as B_1
- Tryptophan containing proteins

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.
- $NAD^+ + AH_2 \longrightarrow NADH + H^+ + A$

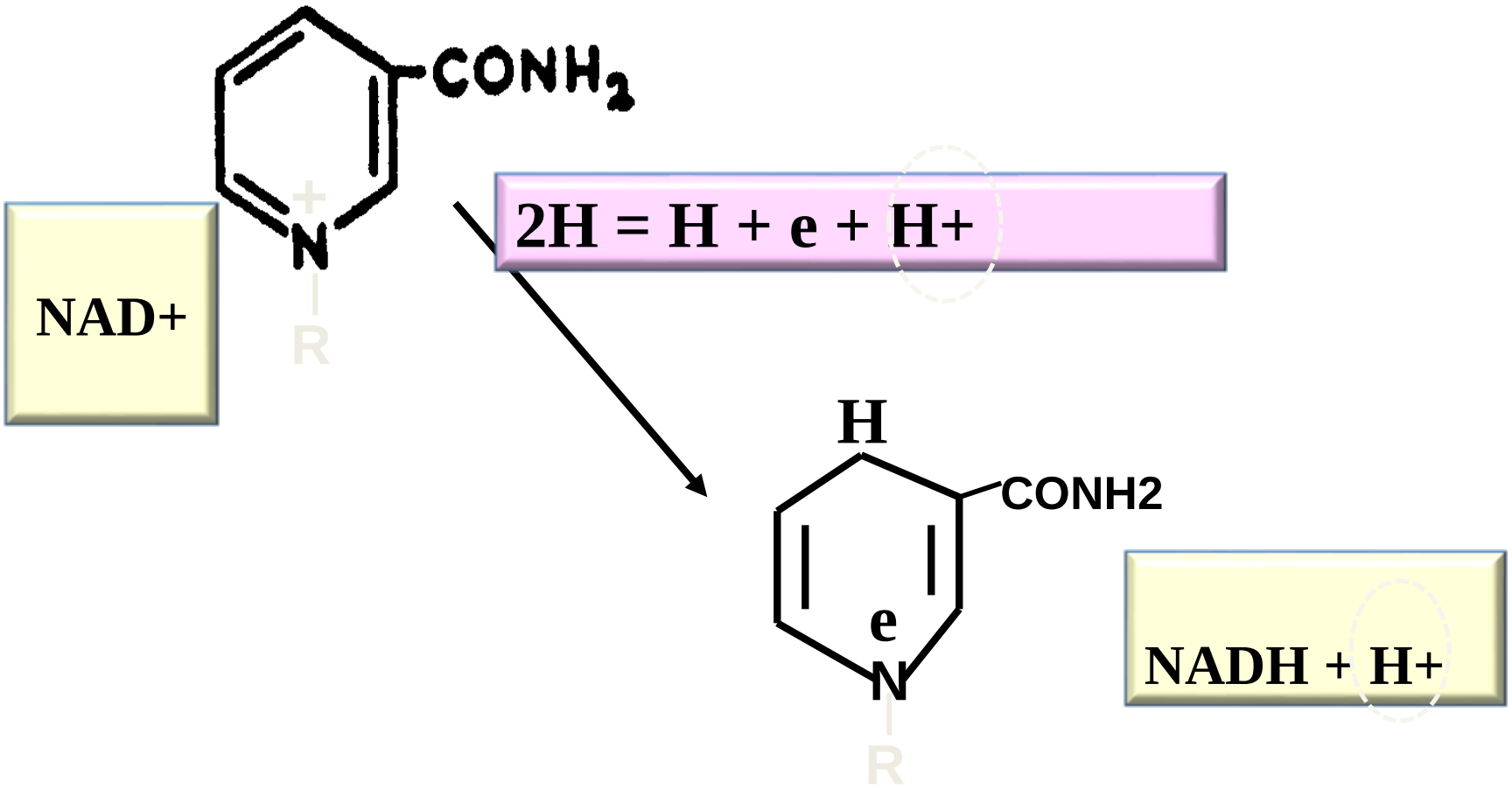
not explained

Structure of NAD+



not explained

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+)

reductive reactions

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

Deficiency

Causes of deficiency: main purposes : inadequate intake and malabsorption

- 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. Pelagra 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

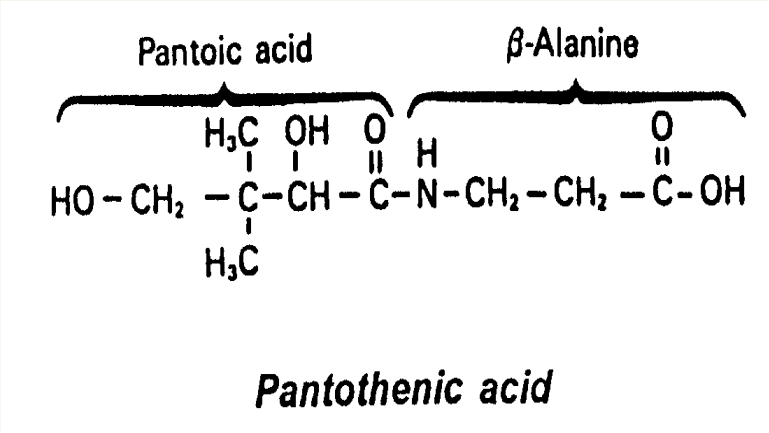
- For the intestinal cells to absorb pantothenic vitamin, it must be converted into free pantothenic acid.
- Free **Pantothenic acid** and **Biotin** are absorbed into intestinal cells via a saturable, sodium-dependent active transport system. **[Sodium-dependent multivitamin transporter (SMVT)]**

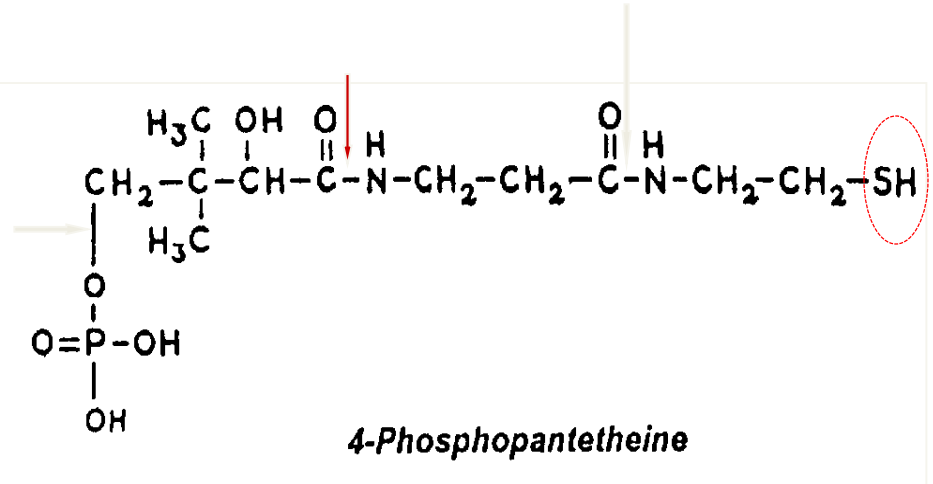
- At high levels of intake, when this mechanism is saturated, some pantothenic acid may also be absorbed via passive diffusion. As intake increases 10-fold, however, absorption rate decreases to 10%.

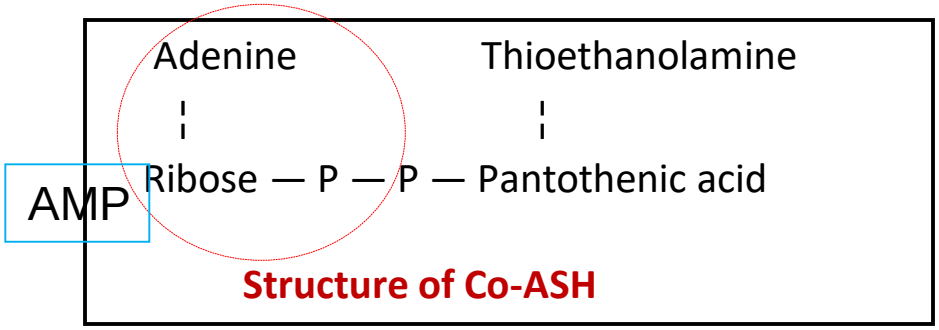
1. Chemical **structure** is …….. **[Pantoic & β- Alanine]**
2. **Active pantothenic** acid is …….. **[4-phosphopantotheine]**
3. Active form enters in the structure of ……

- **CoASH** = 4-phosphopantotheine + AMP
- **ACP**; acyl carrier protein

4. Its **active** group is: ……. **[Thiol group]**
5. Its **function as is: [Carrier of acyl radicals].** coenzyme A used in energy metabolism







6- Sources are: **[as B1]**

7- Reactions requiring **CoASH:**

a- oxidative decarboxylation of a keto acids ⟶ Energy.

b- oxidation of Fatty acid

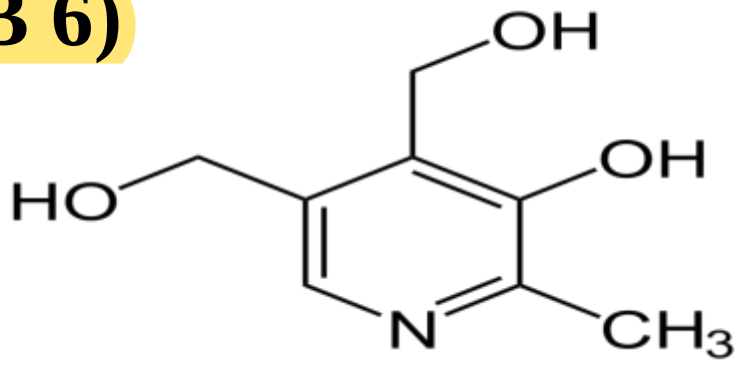
e- acetylating reactions as acetyl choline.

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.

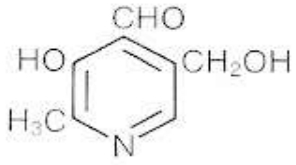
- Nausea, vomiting. -Easy fatigability. -Dermatitis.
- Depression, neurological symptoms (disorders of the synthesis of acetylcholine). Numbness, muscle cramps, inability to walk.
- **Burning foot syndrome** (severe burning and excessive sweating).

Pyridoxine (B 6)

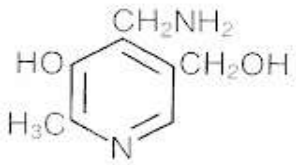


Chemistry:

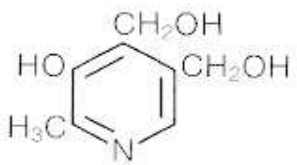
- It is a water soluble vitamin
- A pyridoxine derivative
- Consists of 3 closely related compounds equally effective as precursors of its coenzyme PLP (pyridoxal phosphate)
  - Pyridoxine (alcohol)
  - Pyridoxal (aldehyde)
  - Pyridoxamine (amine)



Pyridoxal

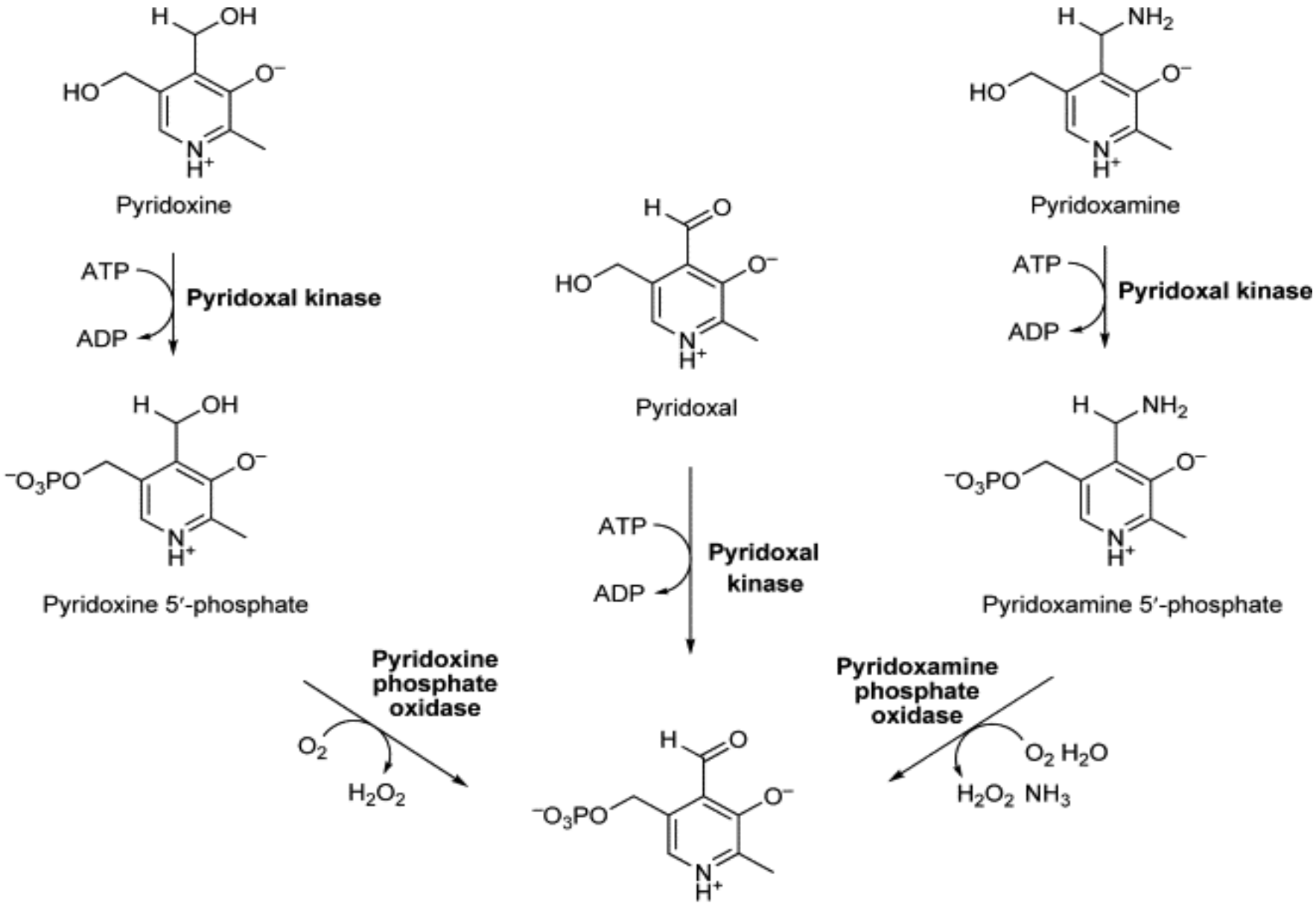


Pyridoxamine



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
ATP
ADP
Pyridoxal kinase
Pyridoxine 5′-phosphate
Pyridoxal
Pyridoxamine
Pyridoxal kinase
Pyridoxamine 5′-phosphate
Pyridoxine phosphate oxidase
Pyridoxamine phosphate oxidase
Pyridoxal 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

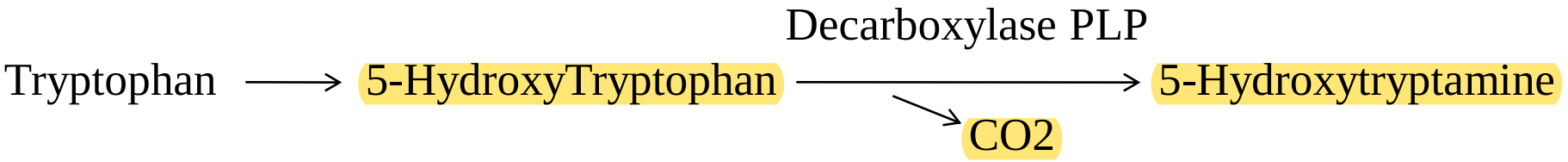
Transamination

- 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

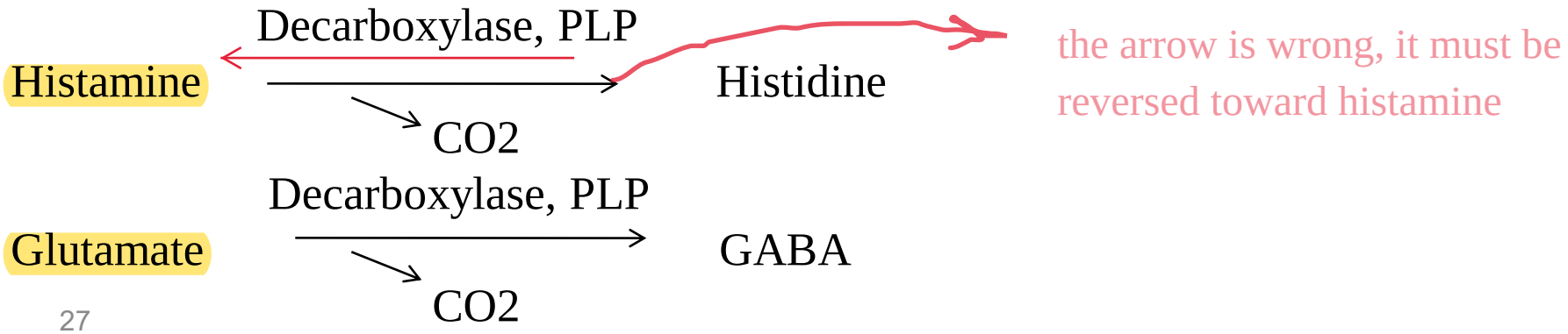
1- Serotonin produced from tryptophan is important in nerve impulse transmission. It regulates sleep, behavior, blood pressure.



2- Histamine is vasodilator lowering blood pressure

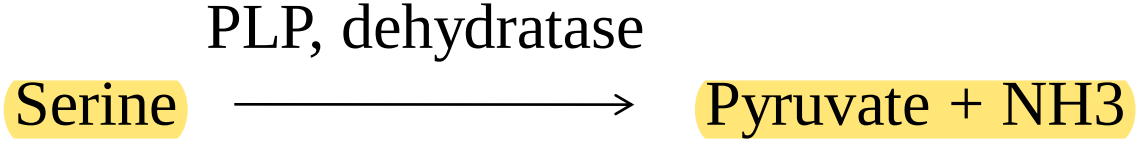
- It stimulates gastric HCl secretion and is involved in inflammation and allergic reactions

3- Glutamate on decarboxylation gives GABA which inhibits transmission of nerve impulses



the arrow is wrong, it must be reversed toward histamine

- 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



- 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

daily requirements

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

when B6 is deficient it will affect :

- 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 microytic 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)

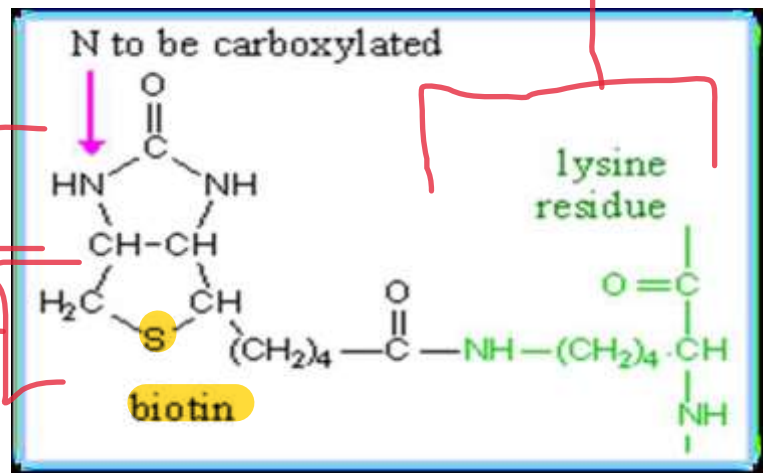
- It is formerly known as anti-egg white injury factor or vitamin H
- It is water soluble sulfur containing B-complex vitamin
- Biotin mainly participates in the carboxylation reactions

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

$$\text{Pyruvate} \xrightarrow[\text{ADP+Pi Biotin, Mg++/Mn}]{\text{CO2, ATP, pyruvate carboxylase}} \text{Oxaloacetate}$$

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

$$\text{Acetyl CoA} \xrightarrow[\text{ADP+Pi Biotin, Mg++/Mn}]{\text{CO2, ATP, Acetyl CoA carboxylase}} \text{Malonyl CoA}$$

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

$$\text{Propionyl CoA} \xrightarrow[\text{ADP+Pi Biotin, Mg++/Mn}]{\text{CO2, ATP, propionyl CoA carboxylase}} \text{D – Methyl malonyl CoA}$$

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

$$\text{β - Methyl crotonyl CoA} \xrightarrow[\text{ADP+Pi Biotin, Mg++/Mn}]{\text{CO2, ATP, β - Methyl crotonyl CoA carboxylase}} \text{β – Methylglutaconyl CoA}$$

- 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