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428 ECA
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Biochemistry-141

Water-Soluble Vitamins

BIOCHEMICALS TEAM

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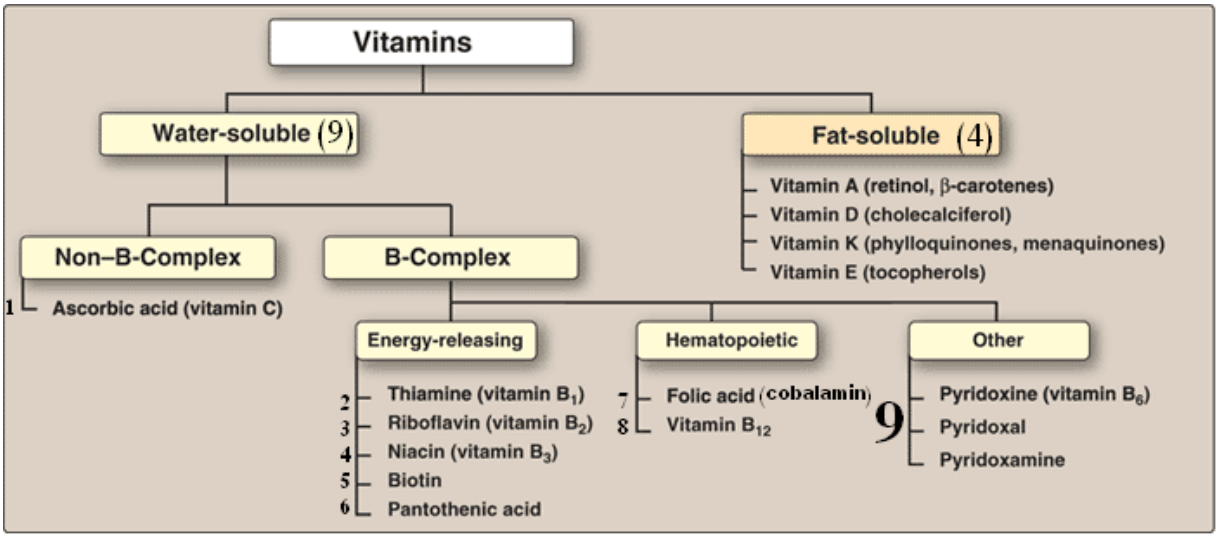
428
biochemicals

WATER-SOLUBLE VITAMINS

I. OVERVIEW

Vitamins: a variety of organic compounds that are needed in small amount for healthy body function.

- Must be supplied by diet as the're not synthesized in adequate quantities by the body
- 9 vitamins are water-soluble and 4 are fat-soluble:

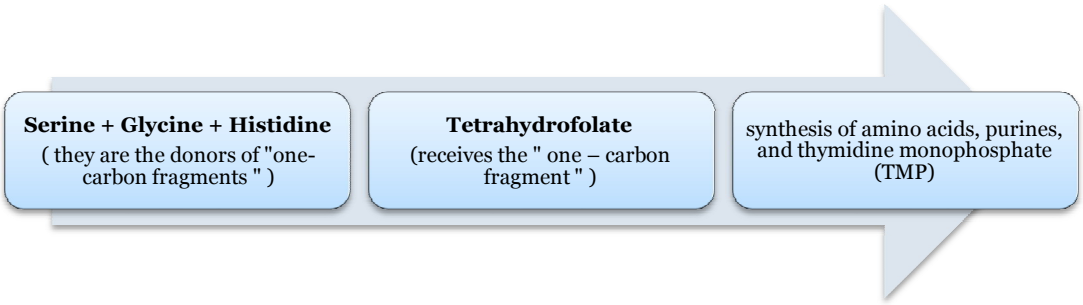


- **Function:** required for specific cellular functions, for example:
  - **Water-soluble:** many act as precursors of coenzymes
    - *(but only one fat-soluble vitamin (vit. K) has a coenzyme function)*
  - **Fat-soluble:**
    - released, absorbed and transported with the dietary fat
    - not readily excreted in urine
    - some is stored in the liver and adipose tissue
    - in case of excess intake of vit. A & D → risk of accumulation of toxic quantities

II. FOLIC ACID (FOLATE)

- **Function:** plays a key role in one-carbon metabolism, essential for biosynthesis of several compounds.
- **Deficiency:** probably the most common vitamin deficiency in the U.S., particularly among *pregnant* women and *alcoholics*.

A. FUNCTION OF FOLIC ACID



B. NUTRIONAL ANEMIAS

- **Anemia:** a condition of low heamoglobin concentration in blood resulting in reduced ability to transport oxygen
  - **Nutritional anemia:** anemia caused by inadequate intake of one or more essential nutrients
    - Can be classified according to the size of the RBCs or mean corpuscular volume (MCV) observed in the individual
    - **Microcytic anemia:** caused by lack of iron
      - most common form of nutritional anemia.
    - **Macrocytic anemia:** results from folic acid or vitamine B_{12} deficiency
      - Second major category.

      NOTE: Macrocytic Anemia is commonly called megaloblastic because, as the folic acid and vitamine B_{12} deficiency causes accumulation of large immature RBC precursors (megaloblasts) in blood and bone marrow

1. FOLATE AND ANEMIA

- Low serum folate can be caused by :
  - Increased demand (Lactation - Prgnancy)
  - Poor absorption (pathology of small intestine)
  - treatment with drugs that are dihydrofolate reductase inhibitors (e.g. methotrexate)
  - alcoholism
- a deficiency develops within a few weeks of a folate-free diet
- **Result:** Megaloblastic anemia
  - Megaloblastic anemia here is caused by the stop of synthesis of purines and TMP, leading to an inability of cells to make DNA and divide

  NOTE: Before starting therapy, it is important to evaluate the cause of megaloblastic anemia, because vitamine B_{12} deficiency indirectly causes symptoms of this disorder.

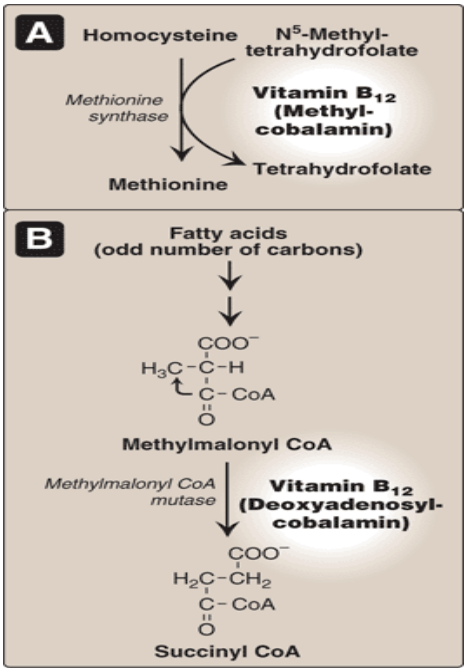
2. FOLATE AND NEURAL TUBE DEFECTS IN THE FETUS

- Most common neural tube defects: spina bifida and anencephaly.
  - These defects are reduced by folic acid supplementation
    - All women of childbearing age (even before pregnancy) are advised to consume 0.4 mg/day of folate
    - Adequate folate nutrition must occur at conception time , because in the 1st weeks of fetal life, critical development occurring needs folate. (before the woman is aware of her pregnancy)
    - folate is added to grain products, so 0.1 mg/day of folate is supplemented, this will allow approximately 50% of reproductive-aged women to receive 0.4 mg/day of folate from all sources.
  - Folate intake should NOT exceed 1 mg/day to avoid complicating the diagnosis of vitamin B_{12} deficiency

III. COBALAMIN (VITAMIN B_{12})

- in humans two essential enzymatic reactions require Vitamin B12:

1) *remethylation* of homocysteine to methionine (fig .A)
2) *isomerization* of methylmalonyl coenzyme A (CoA)
   - **methylmalonyl Coenzyme A.:**
     - produced During degradation of :
       - ✓ some Amino Acids and
       - ✓ Fatty acids with odd numbers of carbon atoms , (fig.B)



- neurologic manifestations of vitamin B12 deficiency .

abnormal fatty acids accumulate and become incorporated into cell membranes,

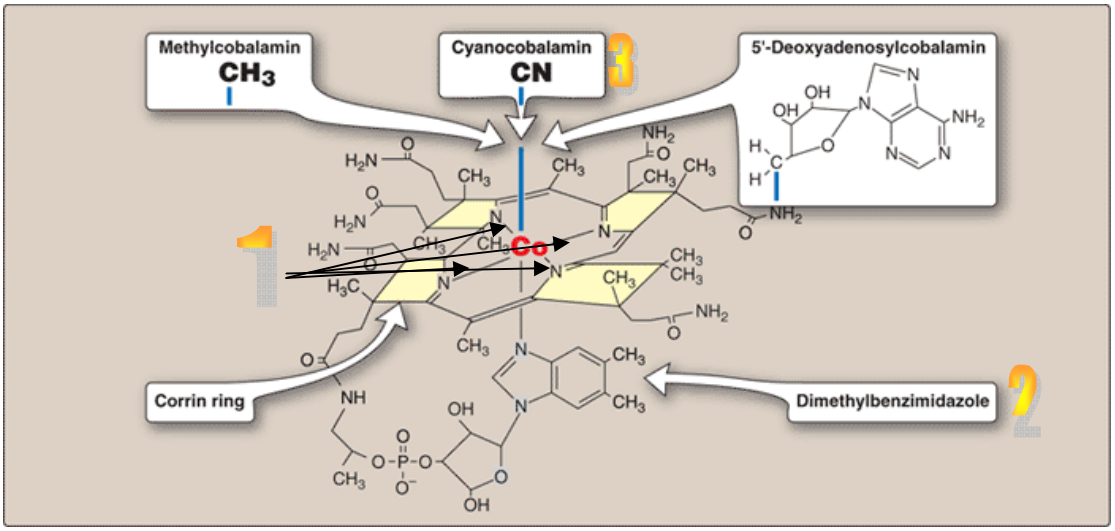
↓

including cells those of the nervous system

A. STRUCTURE OF COBALAMIN AND ITS COENZYME FORMS:

- Contains a corrin ring system having 4 pyrrole rings (like prophyrins) but, in cobalamin two of the rings are linked directly (without a methene bridge)

- **Cobalt is held in the center of the Corrin ring by (see figure 28.6 below)**
  1- four bonds with nitrogen , coordination from the four pyrrole groups.
  2- Bond with the nitrogen of 5,6-dimethylbenzimidazole .
  3- Bond with cyanide (in commercial preparations of the vitamin as *cyanocoblamine*)



- the cyanide (CN) group in cyanocobalamin is replaced to form coenzymes as follows:
  - CN replaced with **5′-deoxyadenosine** to form 5′-deoxyadenosylcobalamin (forming an unusual carbon-cobalt fond)
  - with **methyl** to form **methylcobalamin**

To sum up: The coenzyme forms of cobalamin are:

5′-deoxyadenosylcobalamin → in which cyanide is replaced **with 5′-deoxyadenosine** (forming an unusual carbon–cobalt bond),

methylcobalamin → in which cyanide is replaced by **a methyl group**

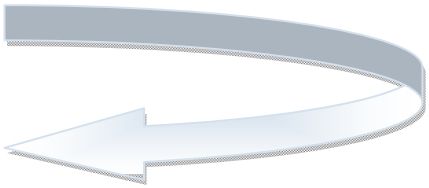
B. DISTRIBUTION OF COBALAMIN:

- Vitamin B12 is synthesized only by microorganisms ; it is NOT present in plants.
- We mentioned that plants do not synthesize B_{12} , but what about animals ? from where do they maintain their B_{12} ?!
  1- from their natural bacterial flora
  2- by eating foods derived from other animals (and not plants)
- **Cobalamin is present in appreciable amounts in :**
  - Liver, whole milk, Eggs, Oysters, Fresh Shrimp, chicken, Pork

C. FOLATE TRAP HYPOTHESIS:

- The effects of cobalamin deficiency are most pronounced in *rapidly dividing* cells, such as:
  - the erythropoietic tissue of bone marrow
  - the mucosal cells of the intestine
- **Tetrahydrofolate has two forms :**
  1. N^5-N^{10}-methylene tetrahydrofolate.
  2. N^{10} –formyl tetrahydrofolate.

Erythropoietic tissue & mucosal cells need them(1 & 2) Because they are important for synthesis of nucleotides required for DNA replication .



- cobalamin deficiency is hypothesized to lead to a deficiency of the tetrahydrofolates forms needed in purine and TMP synthesis :

In vitamin B12 deficiency,there is impaired utilization of the N^5-methyl form of tetrahydrofolate

↓

N^5- methyl tetrahydrofolate cannot convert directly to other forms of tetrahydrofolate

↓

Folate is trapped in the N^5 - methyl form(N^5-methyl tetrahydrofolate)

↓

Increase levels of N5-methyl tetrahydrofolate →decrease levels of the other forms of tetrahydrofolate needed in purine and TMP synthesis .

↓

resulting in the symptoms of megaloblastic anemia.

D. CLINICAL INDICATIONS FOR VITAMIN B12:

- Vitamin B12 is **stored** in the body in significant amounts (4-5 mg), in contrast of other water-soluble vitamins
- As a result, it may take several years for the clinical symptoms of B12 deficiency to develop in individuals who have had a partial or total gastrectomy.
  - (who, therefore, become intrinsic factor-deficient, and can no longer absorb the vitamin.

PERNICIOUS ANEMIA:

- **causes of pernicious anemia :**
  1. Absence of vitamin B12 in the diet. (**RARE**)
  2. Failure of absorption of vitamin B12 from intestine . (more much **COMMON**)
  3. autoimmune destruction of the gastric parietal cells.(the MOST **common**)
     - Gastric parietal cells → synthesis of intrinsic factor (glycoprotein)
- Lack of intrinsic factor prevents the absorption of vitamin B12 , resulting in pernicious anemia .

Normally, vitamin B12 (from diet) binds to intrinsic factor (in the intestine)

↓

The cobalamin–intrinsic factor complex travels through the gut

↓

This complex eventually binds to specific receptors on the surface of mucosal cells of the ileum.

↓

The bound cobalamin is transported into the mucosal cell and, subsequently, into the general circulation,

↓

In the general circulation it is carried by B12-binding proteins.

- If there is lack of intrinsic factor → prevents the absorption of vitamin B12 → vitamin B12 deficiency .
- **patients with Cobalamine (B12) deficiency:**
  - Usually anemic
  - Neuropsychiatric symptoms → later in the development of the disease
  - CNS symptoms may occur in the absence of anemia
  - The CNS effects are irreversible

- **treatment**
  1. giving high-dose B12 orally
  2. intramuscular injection of cyanocobalamin.
- **When to stop therapy ?**
  Therapy must be continued throughout the lives of patients with pernicious anemia

Folic acid can partially reverse the hematologic abnormalities of B12 deficiency and, therefore, can mask a cobalamin deficiency. Thus, therapy of megaloblastic anemia is often initiated with folic acid and vitamin B12 until the cause of the anemia can be determined.

EXPLANATION

when megaloblastic anemia is maiy1nly caused by deficiency of cobalamine , and treated with folic acid only , this may mask the main cause , which is the deficiency of cobalamine .. , that's why when we treat megaloblastic anemic patient , we start with both folic acid and cobalamine , until we can determine the main cause ☺

عشان ما نكون بنعالج العرض(نقص حمض الفوليك) و نترك المسبب الرئيسي للأنيميا (نقص B_{12})

IV. ASCORBIC ACID (VITAMIN C)

Active form: ascorbate acid

- **Functions:**
  - **Main function:** reducing agent in several different reactions
  - Has a role as a coenzyme in hydroxylation reactions.
    - (e.g. hydroxylation of prolyl and lysyl residues of collagen)
    - So, required for maintining normal C.T., as well as for wound healing.
  - Also facilitates the absorbtion of dietary iron from the intestine

A. DEFICIENCY OF ASCORBIC ACID

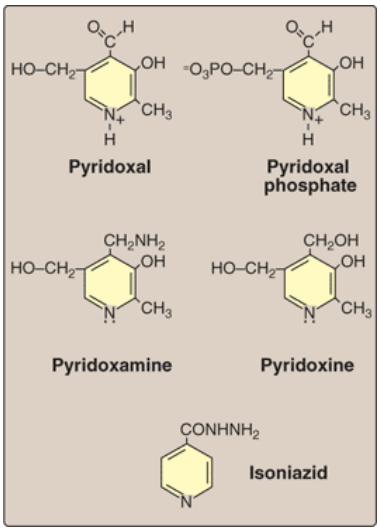
- Results in ***Scurvy***: characters:
  - Sore and spongy gums
  - Loose teeth
  - Fragile blood vessels
  - Swollen joints
  - Anemia
- Many symptoms can be explained by a deficiency in the hydroxylation of collagen (defective C.T.)

B. PREVENTION OF CHRONIC DISEASE

- **Antioxidants:** a group of nutrients including **vitamin C** as well as vitamin E and β-carotene
- Diets rich in antioxidants decreases incidence of some chronic diseases such as coronary heart disease and certain cancers.
  - However, antioxidants alone don't cause any benefit clinically here.

V. PYRIDOXINE (VITAMIN B6)

- **Vitamin B_6:** 3 pyridine derivatives: *Pyridoxine*, *pyridoxal* and pyridoxamine.
  - They differ only by the *functional group* attached to the ring
- **Sources:**
  - **Pyridoxine:** primarily in plants
  - **Pyridoxal** and **Pyridoxamine:** animal
- **Biologically active coenzyme:** *pyridoxal phosphate*.
  - All 3 compounds can be its precursors.
  - **Function:** as a coenzyme for many enzymes, especially those catalyzing amino acid reactions.



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

A. CLINICAL INDICATIONS FOR PYRIDOXINE:

1. ISONAZID

- **Isonazid:** (isonicotinic acid hydrazide) a drug frequently used to treat tubercolosis
- It can cause a vitamin B6 deficiency by forming an inactive derivative with *pyridoxal phosphate*.
- That's why a dietary supplementation of B6 is an adjunct to the *isoniazid* treatment.

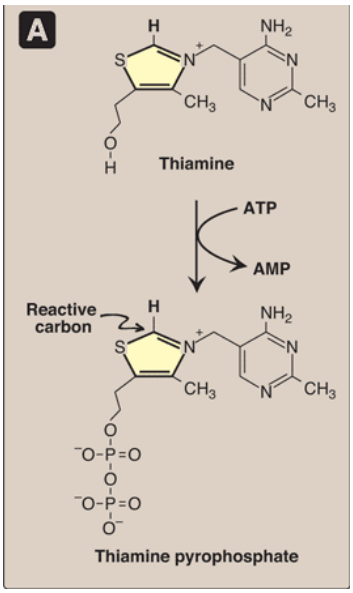
2. DIETARY DEFICIENCIES IN PYRIDOXINE: extremely **rare** but can been seen in:

1- Newborn infants fed formulas low in B6.
2- In women taking oral contraceptives.(ادوية منع الحمل)
3- In alcoholics.

B. TOXICITY OF PYRIDOXINE

- An intake greater than 2 g/day of pyriodoxine can cause Neurologic symptoms.
- **Treatment:** stop the intake of pyridoxine. We will see a Substantial improvement (huge improvement) However, there won't be a complete recovery.

VI. THIAMINE (VITAMIN B_1)



- **Its active form:** *Thiamine Pyrophosphate*
  - **Formation:** ATP gives a pyrophosphate (PP_i) to thyamine.
  - **Function**: coenzyme for:-
    - *transketolase* for the formation or degradation of α-ketols
    - in the oxidative decarboxylation of α-keto acid .

A. CLINICAL INDICATIONS FOR THIAMINE :

- Oxidative decarboxylation of pyruvate and α- ketoglutrate
  - plays key role in energy metabolism of most cells.
  - particularly important in nervous system tissues .

THIAMINE DEFICIENCY :

decrease activity of these dehydrogenase (pyruvate & α-ketoglutarate .) ➔
➔ decrease production of ATP ➔ impaired cellular functions .

DIAGNOSIS OF THIAMINE DEFICIENCY :

- on when there is addition of thiamine pyrophosphate , we will observe increase in erythrocyte transketolase .. this elevation is considered with the deficiency of thiamine .

DISORDERS CAUSED BY DEFICIENCY OF THIAMINE :

BERIBERI :

- severe thiamine deficiency syndrome .
- found in areas where diet include polished rice as major component .

infantile Beriberi (in children) :

- signs :
  - tachycardia
  - vomiting
  - convulsions
  - death → if not treated
- if mothers are deficient in thiamine : nursing infants can have a rapid onset at this deficiency syndrome.

Adult beriberi :

- **Characterized by :**
  - Dry skin .
  - Irritability .
  - Disorderly thinking .
  - Progressive paralysis .

Wernicke-korsakoff syndrome :

- In USA , thiamine deficiency which primarily seen in chronic alcoholism is due to :
  - Dietary insufficiency
  - Impaired intestinal absorption of the vitamin B1 (thiamine)
- Characterized by :
  - Apathy
    - Loss of memory
      - Rhythmical to - and – fro motion of the eyeballs (nystagmus).
- Treatment of Neurologic consequences of wernicke's syndrome :
  - Treatable (can be treated)
  - Thiamine supplementation is used .
  - Intravenous thiamine administration :
    - Typically initiated at 50 mg/day until the same dose is tolerated orally.

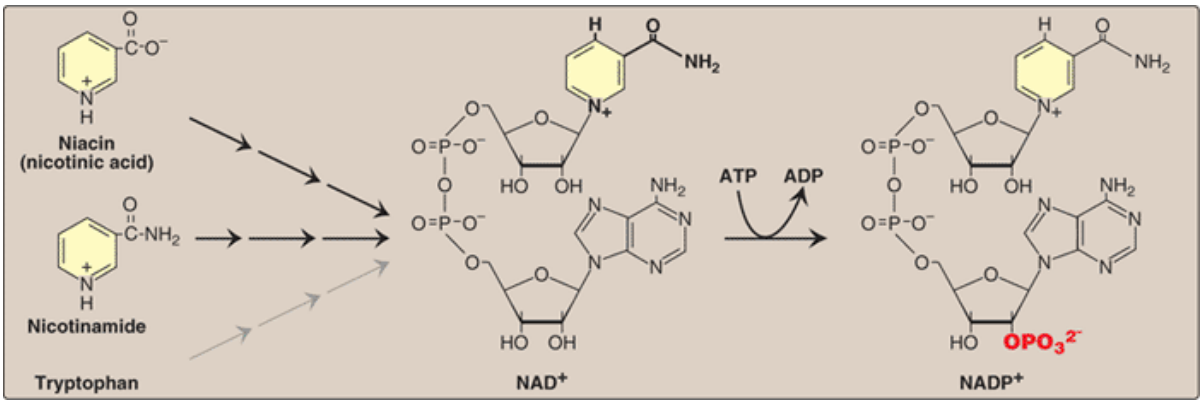
VII. NIACIN

- **Niacin** (or **nicotinic acid**): a substituted pyridine derivative .
- **Biologically active forms**: NAD^+ & $NADP^+$
  - They serve as Coenzymes in oxidation-reduction reactions .

What happen in oxidation-reduction reactions ?

- Reduction of pyridine ring of NAD^+ & $NADP^+$, by accepting a hydride ion " H^- " to form NADH & NADPH .

$$NAD^+, NADP^+ \xrightarrow{Reduction\ of\ pyridine\ ring,accepting\ H-ion} NADH , NADPH$$



NICOTINAMIDE :

- **Nicotinamide:** a derivative of **nicotinic acid** (niacin) that contains an amide group (instead of carboxyl group in niacin)
- Occurs in diet as well.
- Inside the body, Nicotinamide is readily deaminated to nicotinic acid.
  - So, nictonaminde is nutritionally equal to nicotinic acid (niacin)

Nicotinamide ——deamination——→ Nicotinic Acid "niacin"

DISTRIBUTION OF NIACIN :

- Unrefined and enriched grains and cereals , Milk, Lean meat " specially liver "

CLINICAL INDICATIONS FOR NIACIN :

- **Pellegra**: disease in skin , GIT , CNS.
  - **Symptoms**: three 'D's → +/- 'D'

3Ds { **D**ermatitis → skin; **D**iarrhea → GIT; **D**ementia → CNS } +/- D { + → Death → if not treated; - → No Death → if treated. }

TREATMENT OF HYPERLIPIDEMIA USING NIACI

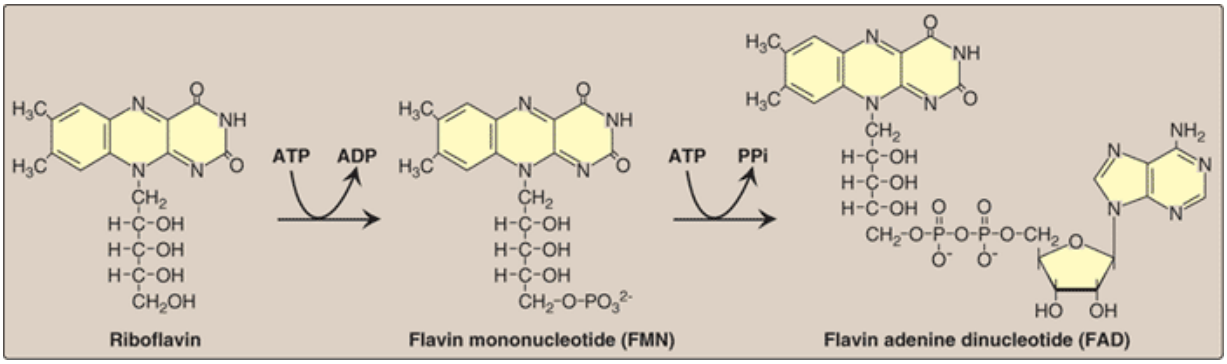
Niacin strongly inhibits lipolysis in adipose tissue (given at doses 100 times RDA) → *Decreases* circulating Fatty Acids (from adipose tissue) → *Decrease* synthesis of TAG in the liver (from FA) → *Decrease* production of VLDL & therefore LDL (which are cholesterol rich) → *Decrease* cholesterol level in plasma.

Why do we use Niacin in order to treat **type "2b" hyperlipoproteinemia** particularly?

- Because in this condition, both VLDL & LDL are high, and niacin works to lower them

VIII. RIBOFLAVIN (VITAMIN B_2)

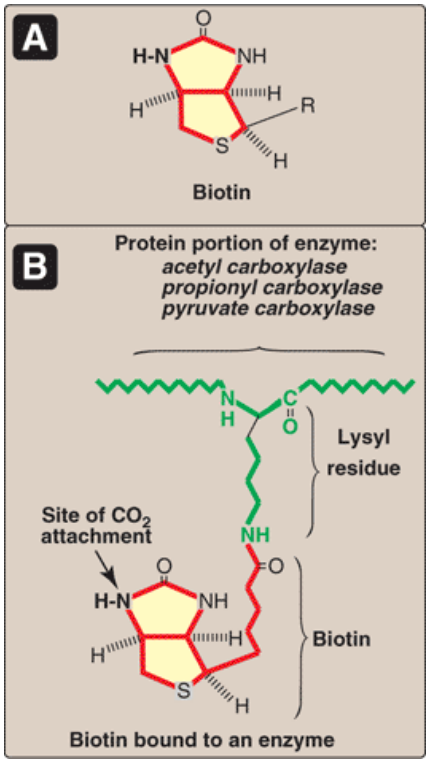
- **Biologically active forms:**
  1. **FMN** (Flavin Mononucleotide)
     - **Formation:** ATP gives a Phosphate group to riboflavin to form FMN
  2. **FAD** (Flavin Adenine Dinucleotide)
     - **Formatoin:** ATP gives an AMP moiety from ATP to FMN



- **Reduction Capability:** FMN and FADeach can accept reversibly 2 hydrogen atoms, to form $FMNH_2$ and $FADH_2$.
- **Flavoenzymes:** catalyze the oxidation or reduction of a substrate
  - FMN and FAD are bound tightly to them (sometimes covalently)
- **Riboflavin Deficiency:** not associated with a major human disease
  - It frequently accompanies other vitamin deficiencies *(especially vitamin B's)*

- **Dificeincy symptoms:**
  - Dermatitis
  - Cheilosis (clefting *(cracking)* at the corners of the mouth)
  - Glossitis (smooth and purplish tongue)

IX. BIOTIN



- **Biotin:** a coenzyme in carboxylation reactions.
- **Function:** serves as a carrier of activated carbon dioxide.
- Biotin is covalently bound to the ε-amino groups of lysine residues of biotin-dependent enzymes.

BIOTIN DEFICIENCY:

- Does not occur frequently because it is found widely in food.
  - Also, intestinal bacteria supply a large percentage of the biotin required in humans.
- The deficiency only occurs in the addition of raw egg white to the diet.
  - Raw egg white contains a glycoprotein named **avidin** which tightly binds biotin and prevent its absorption in the intestine.
- **Symptoms:** dermatitis, glossitis, loss of appetite, and nausea.
- However, it has been estimated that 20 eggs/ day have to be in the diet to cause the deficiency. Thus, eating occasional raw egg in the diet does not lead to Biotin deficiency.

NOTE: Eating raw eggs is generally not recommended due to the possibility of *salmonella infection*.

Multiple carboxylase deficiency results from a defect in the ability to link biotin to carboxylases or to remove it from carboxylases during their degradation. Treatment is biotin supplementation.

X. PANTOTHENIC ACID

1- Component of Coenzyme A (see below)
2- Component of Fatty acid synthase.

- **Sources :** widely distributed , but the most important sources are eggs , liver , and yeast
- **Deficiency of pantethonic acid :**
  - Not well characterized in humans
  - No RDA* has been established. **RDA : Recommended Dietary Allowance.*

COENZYME A

- **Function:** transfer of acyl groups .
- Contains ***thiol*** group , which carries acyl compounds as activated thiol esters.
- e.g: Succinyl CoA , Fatty acyl CoA , Acetyl CoA.