L

Water soluble Vitamin

Niacin

Niacin, or nicotinic acid, is a substituted pyridine derivative. The biologically active coenzyme forms are nicotinamide adenine dinucleotide (NAD+) and its phosphory-lated derivative, nicotinamide adenine dinucleotide phosphate (NADP+).

Synonyms:- nicotinic acid – pellagra preventing factor .

Sources:-

a- Animal source: Liver, meat, fish.

b- Vegetable source : legumes (peas, beans, lentils), nuts, certain green vegetables.

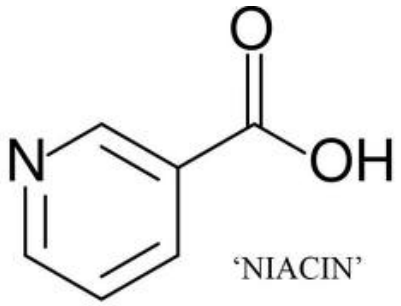
Chemistry

Nicotinic acid (niacin) is chemically pyridine-3-carboxylic.It derives its name from the fact that it can be prepared by oxidation of nicotine.

Biologic (active) forms:-

In tissues, nicotinamide is present largely as a dinucleotide, the pyridine 'N' being linked to a D-ribose residue.

Two such nucleotide active forms are known.



'NIACIN'

1- Nicotinamide adenine dinucleotide (NAD)

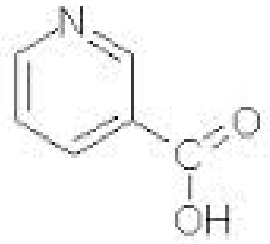
The compound contains:

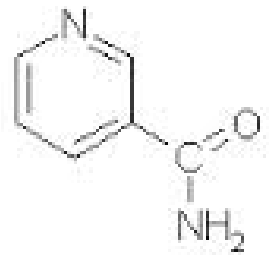
a- One molecule of nicotinamide.

b- Two molecules of D- ribose .

c- Two molecules of phosphoric acid.

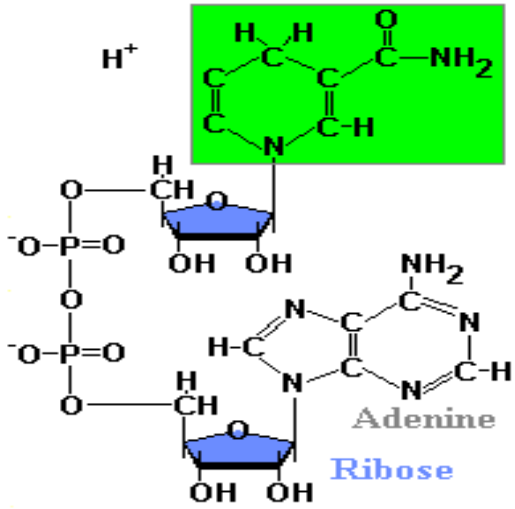
d- One molecule of adenine.





2-Nicotinamide adenine dinucleotide phosphate (NADP+).

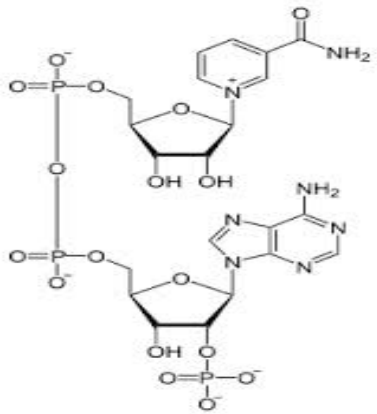
This compound differs from NAD+ in that it contains an additional molecule of phosphoric acid attached to2- position of D- ribose attached to N-9 of adenine.



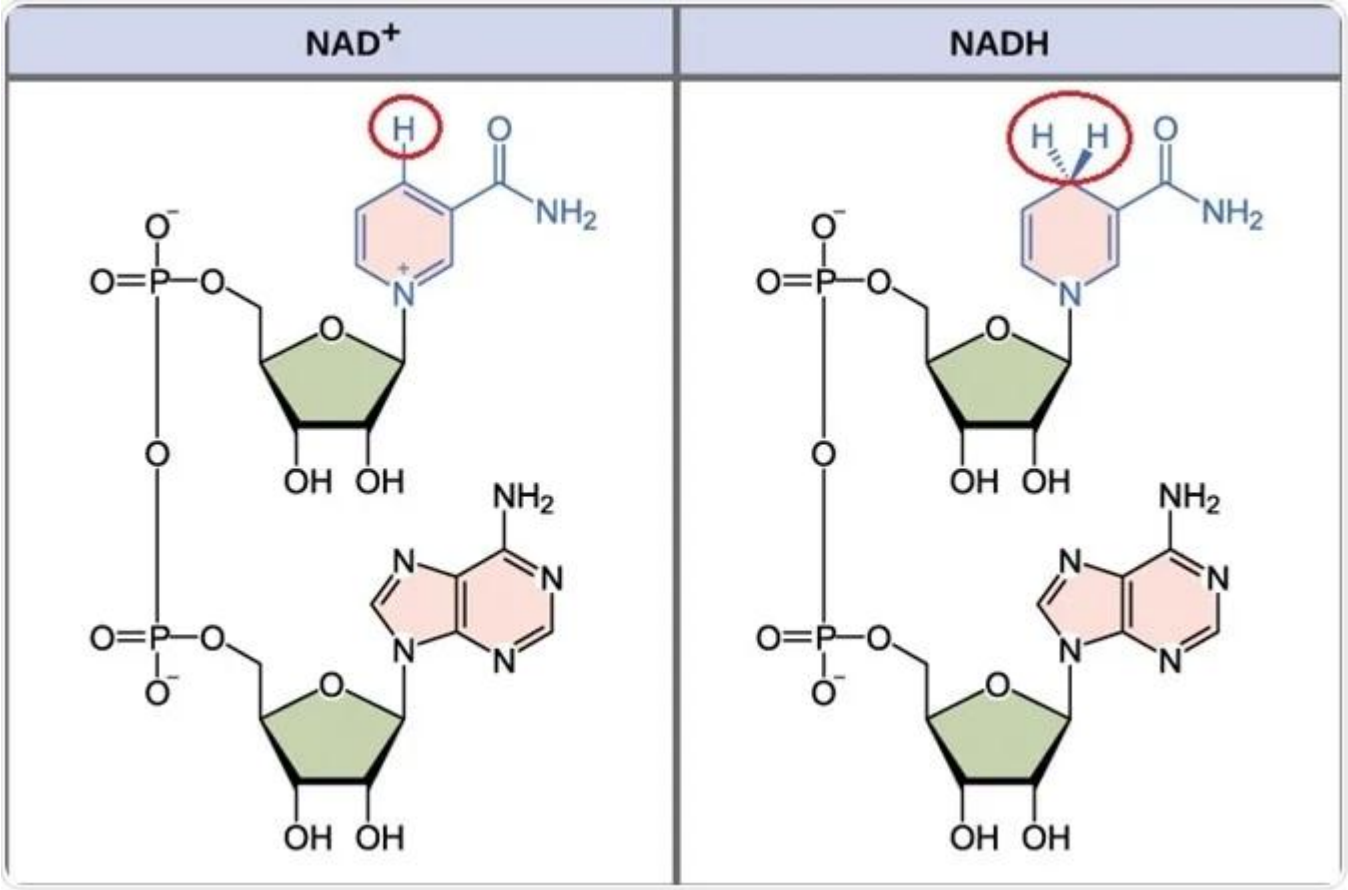
NADH + H+

Stability

Stable in acid medium but not in alkaline medium.



NADPH


NAD+
NADH
H
O
NH2
O⁻
O=P–O
O
N
OH OH
NH2
N
N
N
N
O=P–O
O⁻
H H

Metabolism :-

Nicotinic acid and its amide are readily absorbed by the intestine . The largest portion of nicotinic acid excreted in urine after methylation of the N of the pyridine ring . Traces of nicotinamide are also eliminated in sweat.

Metabolic role

1-Both NAD and NADP are co-enzymes of several dehydrogenases which catalyzes oxidation reduction reactions. NAD and NADP act as carriers of hydrogen groups in such reactions.The pyridine ring participates in oxidation reduction of substrates.

2- Some NAD requiring enzymes are (a) Glyceraldehyde-3-phosphate dehydrogenase (b) Malate dehydrogenase (c) β-hydroxy acyl-CoA dehydrogenase.

3- Function of NADP+ is similar to that of NAD in hydrogen and electron transport. Some NADP requiring enzymes are (a) glucose-6-phosphate dehydrogenase (b) Glutathione reductase (c) Malic enzyme.

Deficiency manifestation

Nicotinic acid deficiency in the diet as well as tryptophan produces a disease called pellagera (pell= skin , agra = rough) .

Cardinal features described as are dermatitis , diarrhea, and dementia (if not treated , the 4^{th} D (Death) follows.

Clinical features

A- Skin lesions: involves areas of skin exposed to sunlight, heat and subjected to pressure . The skin become reddened, later brown, thickened and scaly.

B- GIT manifestation:

1-Incluede anorexia, nausea ,vomiting, abdominal pain ,with alternating constipation and diarrhea. Diarrhea becomes intractable later.

2-Gingivitis and stomatitis with reddening of the lip.

3-Achlorhydria present in about 40%.

4-Thickening and inflammation of the colon with cystic lesions of the mucosa, which later becomes atrophic and ulcerated.

C- Cerebral manifestation: include headache, depression, insomnia, and other mental symptoms.

D-General effects: these include:

a –Inadequate growth.

b – Loss of weight and strength.

c – Anemia.

d – Dehydration.

Daily requirement

In adults 17-21 mg daily

In infants 6 mg

Pyridoxine (vit .B6)

Synonyms:- anti dermatitis factor, vit B6

Sources :- The vit is distributed widely in animal and plant tissues-rich sources of the vit are yeast ,rice, various seeds and cereal grains and egg- yolk. Moderate a mounts are present in liver, kidney, muscle, fish.

Chemistry

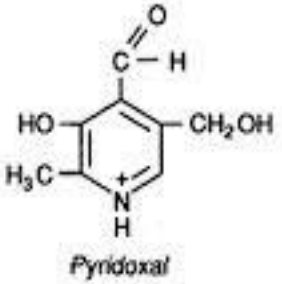
Vitamin B6 is a collective term for pyridoxine, pyridoxal, and pyridoxamine, all derivatives of pyridine. They differ only in the nature of the functional group attached to the ring

1- Pyridoxol (pyridoxine) is chemically (4,5-hydroxymethyl-2 methyl -3-ol pyridin

2- It occurs in association, perhaps in equilibrium , with an aldehyde Pyridoxal

3- pyridoxamine form. All three forms exhibited vit B6 activity.

Pyridoxine



Pyridoxal

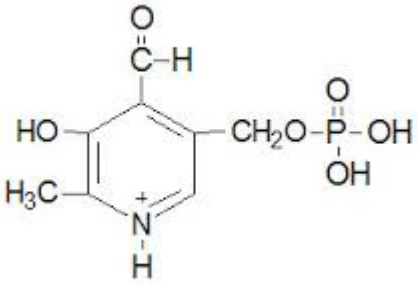
Stability

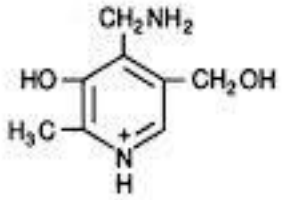
Pyridoxine is stable to heat and alkali but is unstable to UV light. Pyridoxal and pyridoxamine are labile compounds, readily destroyed by exposure to air, light and heat in dilute solutions .

Biological (active) forms :-

Biological active forms of the vitamin :-

1- Pyridoxal – PO4

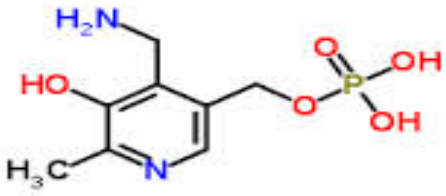


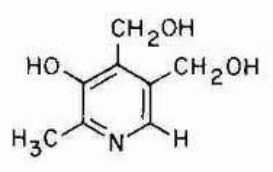


Pyridoxamine

2-pyridoxamine – PO4

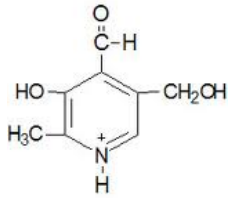
The active forms are the phosphorylated derivatives .
Phosphorylation involves the hydroxymethyl group ,CH2OH at position 5 in the pyridine ring.





Pyridoxine

Dehydrogenase



pyridoxal

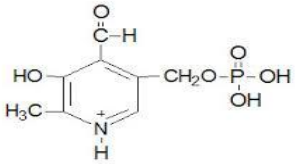
pyridoxamine phosphate

pyridoxal kinase

ATP

ADP

pyridoxial phosphate



Metabolism:-

Absorption :- Dietary vit B6 is readily absorbed by the intestine.

Excretion

1-Pyridoxal and pyridoxamine are excreted in urine in small amounts 0.5-0.7 mg /day.
Most of pyridpxal is excreted in urine after oxidation of CHO in postion 4 to COOH to form pyridoxic acid which biologically inactive

Metabolic role

Pyridoxal phosphate is active form. It is formed from pyridoxal by phosphorylation catalyzed by pyridoxal kinase

1- Co-transaminase :- acts as co enzyme for the enzymes transaminases (aminotransferases) in transamination reaction.

Transamination: Transaminase enzymes needed to break down amino acids are dependent on the presence of pyridoxal phosphate. The proper activity of these enzymes is crucial for the process of moving amine groups from one amino acid to another.

2-Co-decarboxylase :- acts as coenzyme for the enzyme decarboxylase in decarboxylation reaction. glutamate decarboxylase which converts glutamate to γ-aminobutyrate (GABA)..

3-Transulfuration :- it takes part in transulfuration reactions involving transfer of SH group .

4-Acts in inter conversion of glycine and serine by serine hydroxy methyl transferase.

5- Pyridoxal – P is required as a coenzyme in the biosynthesis of arachidonic acid from linoleic acid .

6-Required for synthesis of sphingomyelin from serine.

7- Required as a coenzyme for amino acid racemases :-

D-Glutamic acid ⟶ L- Glutamic acid .

8- Required for intramitochondrial fatty acids synthesis (chain elongation of fatty acids).

9- Required for active transport of amino acid through cell membrane and intestinal absorption of amino acids.

10- Constituent of muscle phosphorylase .
11- Promotes the transport of K+ across the membrane.
12- Vit B6 is involved in synthesis of coenzyme A from pantothenic acid.

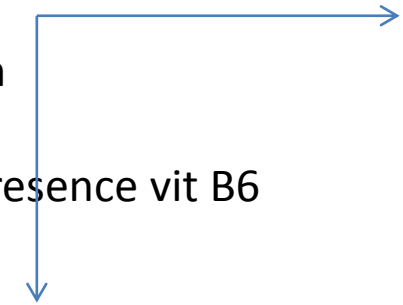
Deficiency manifestation :-

1- It is rare in human adults. However microcytic hypochromic anemia due to decreased heme synthesis, skin lesions that resemble those occur in niacin deficiency, depression and mental disturbances are observed in experimentally induced vitamin B6 deficiency in humans.
2. In children vitamin B6 deficiency causes epileptic form convulsions (seizures) due to decreased formation of neuro transmitters like GABA, serotonin and catecholamines.
3. In experimental animals vitamin B6 deficiency causes growth retardation, skin lesions, convulsions etc.
4. Pyridoxine deficiency alters immune response.
3- Neuritis and neuropathy develop in patients suffering from tuberculosis and on treatment with high doses of isonicotinic acid hydrazide (INH)which has anti vitamin activity.

INH + Pyridxal $\longrightarrow$ Pyridoxal – hydrazone
(complex that is excreted in urine).
INH- pyridoxal will block normal function of pyridoxal.

4- Reduces the coenzyme A level in liver.

5- Tryptophan metabolism is also altered , there is increased xanthurenic acid excretion in urine of pregnant women in pregnancy , deficiency of B6 is due to increased demand by the fetus.



Nicotinic acid (minor pathway)

7- In B6 deficiency immune response is impaired.

8- Roughening of the skin .

Daily requirement

For adult 2 mg /day for infant 0.3-0.4 mg /day for pregnancy 2.5 mg /day

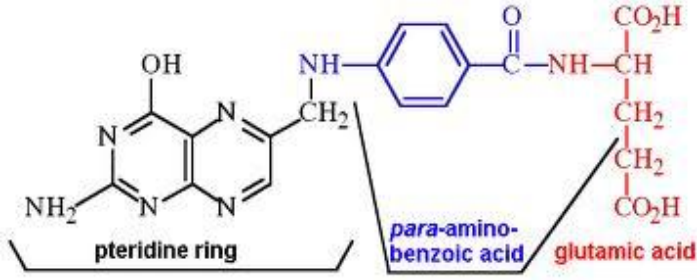
Folic acid

Synonyms :- vit M, pteroylglutamic acid, B9

Sources :-

1- Widely distributed in nature being present in many animal and plant tissues and in microorganisms.

2- Particularly abundant in liver, yeast, kidney and green leafy vegetables . Spinach and cauliflower are also good source other good sources are ; meat, fish wheat, milk, fruits.



Chemistry:-

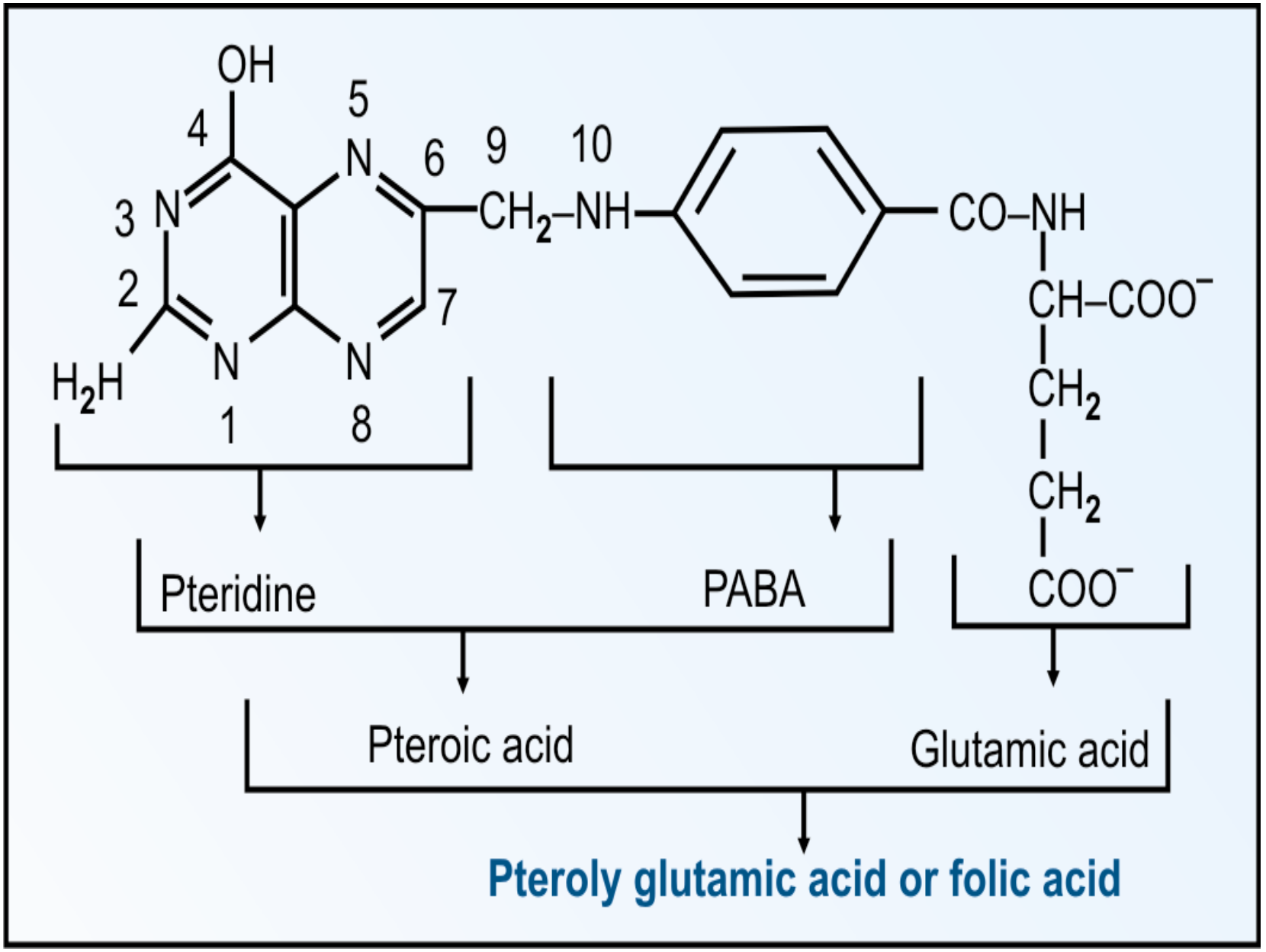
The term folic acid derived from Latin folium(leaf) . Chemically folic acid or folate consists of:-

1- A pteridine nucleus consists pyrimidine and pyrazine rings.

2- Para- aminobenzoic acid (PABA) .

3- Glutamic acid.

The pteridine group linked with para-aminobenzoic acid (PABA) is called pteroic acid. It is then attached to glutamic acid to form pteroylglutamic acid or folic acid


OH
4
5
N
6
9
10
3
N
2
7
CH_2–NH
CO–NH
CH–COO^-
H_2H
N
N
1
8
CH_2
CH_2
Pteridine
PABA
COO^-
Pteroic acid
Glutamic acid
Pteroly glutamic acid or folic acid

Biological active form :-

Active form (coenzyme) of the vitamin is the reduced tetrahydrofolate FH4 obtained by addition of four hydrogen to the pteridine moiety at 5,6,7 and 8 position.

Clinical importance :-

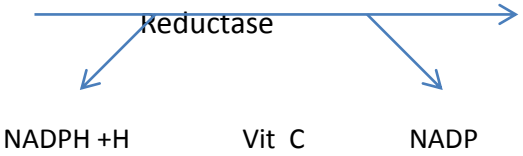
Some of clinically described cases of folic acid deficiency anemia may actually be due to inherited deficiency of folic acid reductase .

Folinic acid :- This is another one of the active forms of folic acid a 'formyl' derivative . It is reduced tetrahydrofolate (FH4) with a formyl group on position 5 .

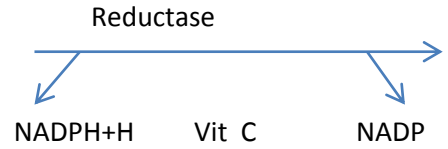
Formation of FH4:-

Folic acid before functioning as a coenzyme, must be reduced first to 7,8- dihydrofolic acid (FH2) and then to 5,6,7,8-tetrahyrofolate(F.H4).

The steps of the reactions are as follows:-

1- Folate 

FH2

2- FH2 

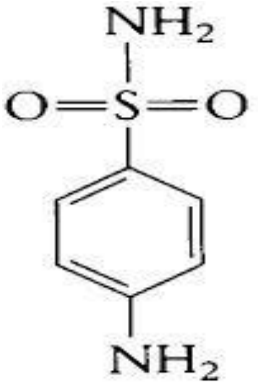
FH4

Biosynthesis and metabolism

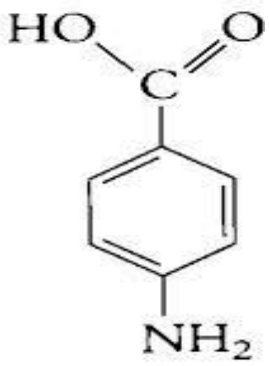
1- many microorganisms including those inhabiting the intestinal tract can synthesis folic acid . Bacterial can synthesis folic acid from the components, pteridine, PABA and glutamate. When sulphonmides are given, such micro-orgtanisms cannot synthesis folic acid and so their growth is inhibited.

Effect of drugs:- Sulphonamide drugs and antibiotics they have structural similarity with PABA inhibit their growth and by blocking the incorporation of PABA the synthetic pathway So, they competitively inhibit the enzyme responsible for the incorporation of PABA into dihydropteroic acid, the immediate precursor of folic acid.

2-Higher animals including human beings cannot synthesize folic acid and it has to be supplied in diet in human beings, intestinal bacteria can synthesize it and is a good source.



Sulfanilamide



PABA

Absorption :-

Folic acid is readily absorbed by the upper part of jejunum. In the blood, it is transported by beta globulins. It is taken up by the liver where the co-enzymes are produced. Folic acid is not stored in tissues.

Excretion :-

2-5 mg/day excrete in urine. 20% of ingested folate that remains unabsorbed and large amounts of unabsorbed folic acid which synthesized by intestinal flora are excreted in feces. Folate is incorporated into the RB cells during erythropoiesis and is retained there. Red cell folate is are liable indicator of the folate status of the body.

Deficiency :-

With normal intestinal flora and in the absence of gastro-intestinal absorption defects, a deficiency is rare . But under conditions of sulfonamide or antibiotic therapy or in case of malabsorption, deficiency symptoms occur.

Deficiency signs and symptoms :-

1- affects cell multiplication, RNA and DNA synthesis.

2- Morphologic changes occur in nucleated RBC and bone marrow , megaloblastic anemia (macrocytic anemia) .

3- Also neurological symptoms may appear in advanced stage .

4- Gastrointestinal symptoms may occur (glossitis).

5- Elevated blood homocysteine which is associated with atherosclerotic, heart disease, with folate and vit B6 deficiency in some case.

Birth Defects

Folic acid deficiency during pregnancy may lead to neural tube defects in the fetus. Folic acid prevents birth defects (fetal malformations such as spina bifida). So, intake of folic acid is a must from early pregnancy.

Cancer

Folic acid is beneficial in prevention of cancer. Folate deficiency contributes to the etiology of bronchial carcinoma and cervical carcinoma.

Requirements

For adult 400-500 mg/day
For children 100-300 mg/day
For pregnant women 800- mg /day