SEM- II

MBIO CC 203. BIOCHEMISTRY

VITAMIN B9 & B12

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VITAMIN B9

Common name : liver Lactobacillus casei factor

Chemical name : folic acid or folacin ($C_{19}H_{19}O_6N_7$)

History :Folic acid and related compounds, which is one of the B vitamins, was discovered in **1941**, as a growth factor for bacteria. It was found to be essential for all vertebrates including man. **Its name was derived from the Latin word *folium,* which means leaf, because it was first isolated from spinach leaves** and is widely distributed in green, leafy plants. Folic acid is pteroyl-mono-glutamic acid. It is quite soluble in slightly alkaline or acid solution; but is reasonably stable in neutral or alkaline solutions, especially in the absence of air.

Sources **:** It is widely distributed in foods. Green leafy vegetables, liver, kidney, legumes and yeast are rich sources of folic acid. It is a relatively stable vitamin but storage and cooking losses can be as high as 50 per cent, especially if cooking water is discarded.

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Structure **:** A folic acid molecule consists of 3 units viz., glutamic acid, p-aminobenzoic acid and a derivative of the heterocyclic fused-ring compound pterin.

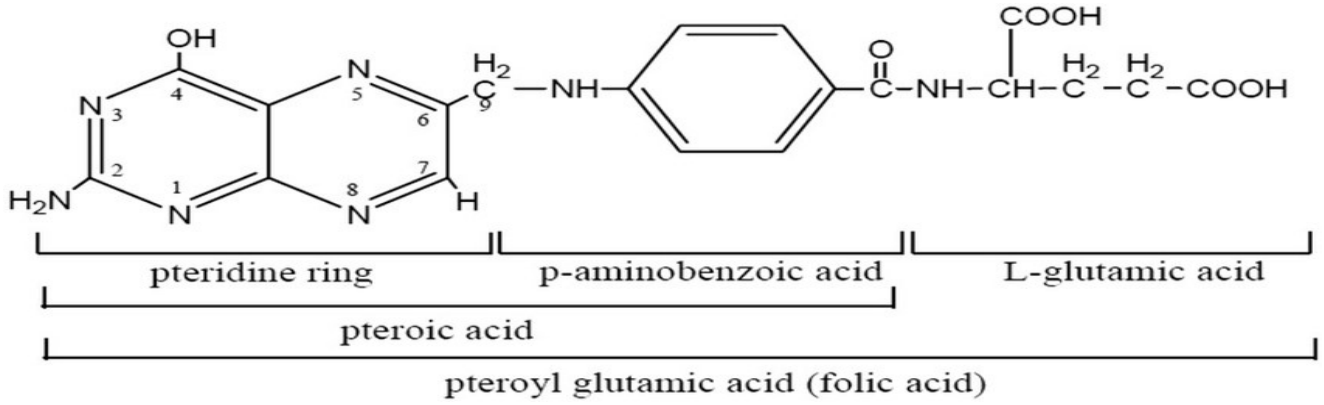

Fig1. Structure of Vit B9/ folic acid/ pteroyl-L-glutamic acid (PGA)

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Biological active form: Folic acid undergoes a series of metabolic conversions to its various coenzyme forms after it is absorbed. Its biologically active form is **tetrahydrofolate.** Latter is formed in two step reaction as follow:

Folic acid (FA) is first reduced to dihydrofolic acid (DHFA or FH_2) by enzyme **folic reductase.**

DHFA is finally reduced to 5,6,7,8-tetrahydrofolic acid (THFA or FH_4) by enzyme **dihydrofolic reductase**.

Note : above reaction is associated with **oxidation of NADPH/NADH** and requires ascorbic acid (Vit C).

Functions

- THF plays a key role in one carbon metabolism essential for biosynthesis of purine pyrimidine and amino acids.
- In One carbon metabolism, THF acts as carrier of one carbon group in form of methyl –CH3, methylene =CH2, formyl -HCO, etc), thus mediating several one-carbon transfer reaction.
- In this metabolism, a carbon unit from serine or glycine is transferred to tetrahydrofolate (THF) to form methylene-THF.
- Fate of methylene-THF

1. This is either used as such for the **synthesis of thymidine**, which is incorporated into DNA

2. oxidized to formyl-THF which is used for the synthesis of purines, which are building blocks of RNA and DNA, or

3. it is reduced to methyl-THF which used to methylate **homocysteine to form methionine**, a reaction which is catalyzed by a B12-containing methyltransferase.

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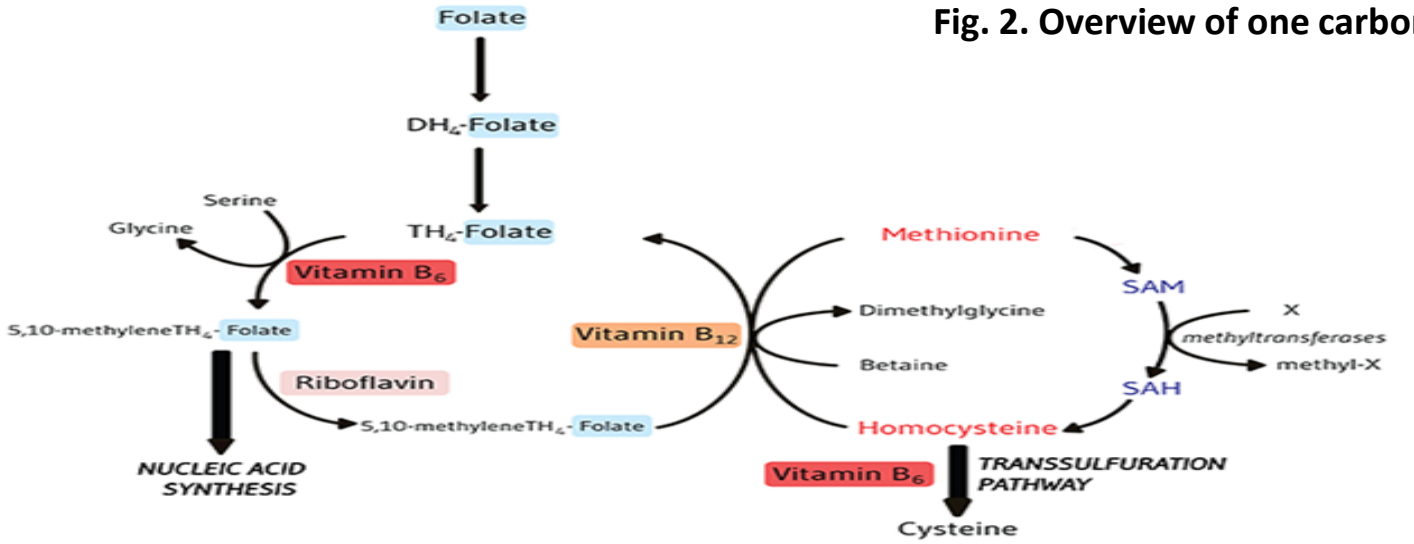
Fig. 2. Overview of one carbon metabolism



5,10-methylenetetrahydrofolate is required for the synthesis of nucleic acids, and 5-methyltetrahydrofolate is required for the formation of methionine from homocysteine. Methionine, in the form of methyl donor S-adenosylmethionine (SAM), is essential to many biological methylation reactions, including DNA methylation. Methylenetetrahydrofolate reductase (MTHFR) is a riboflavin (FAD)-dependent enzyme that catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. *SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; TH_4-Folate, Tetrahydrofolate.*

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Human requirements: 0.1mg for infants, 0.2 mg for children, 0.4 mg for adult and women. Pregnant women may require upto 0.8 mg per day.

Deficiency:

- In human prolonged and severe folic acid deficiency leads to **megaloblastic anaemia (abnormal large RBCs), glossitis** (swollen and inflamed tongue), **gingivitis** (inflammation of gums) and gastro intestinal disorders.
- Also causes elevated level of homocystein.
- Pregnant women need more folic acid to lower the risk of neural tube birth defects, including cleft palate, spina bifida, and brain damage. Neural tube defects are birth defects caused by abnormal development of the neural tube, a structure that eventually gives rise to the brain and spinal cord.
- In chicks, lack of this factor causes anemia, rats develop achromotrichia (failure in normal pigmentation of hair), while in monkeys show macrocytic anemia (anemia characterized by the presence of giant RBCs), leukopenia and edema (retention of water by skin tissues).

Vitamin B12

Common name : Anti-pernicious anemia (APA) factor

Chemical name : Cyanocobalamin

History :

- It was discovered through studies of **pernicious anemia**, a condition that begins with a megaloblastic anaemia and leads to an irreversible degeneration of the central nervous system. **George Minot and George William Murphy** discovered that that the condition could be reversed by feeding afflicted patients with about half a pound of liver a day. This land mark in medicine brought them **Nobel Prize in 1934**.
- It was the last member of the B vitamins was isolated in crystalline form in **1948** independently by **E. Lester Smith in England** and by **Edward Rickes and Karl Folkers** in the United States.

Sources:

The richest sources are liver, meats, milk, eggs, fish, meat, cheese and other dairy products are good sources. Produced by microorganisms may inhabit in gut.

Plants are not sources of Vit B12 except *Spirulina* a blue green algae.

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Structure :

Cyanocobalamin ($C_{63}H_{88}O_{14}N_{14}PCo$) contains a **tetrapyrrole ring system**, which is chemically very similar to the porphyrin ring system of the haeme compounds.

A unique feature is presence of an atom of heavy metal **cobalt in trivalent state**.

Co atom is **centrally located** and is surrounded by a macrocyclic structure of **4 reduced pyrrole rings** (A, B, C, D) **collectively called as corrin**.

2 pyrrole rings **(A & D)** of 4 are directly attached to each other rather than **methylene bridge between B & C**.

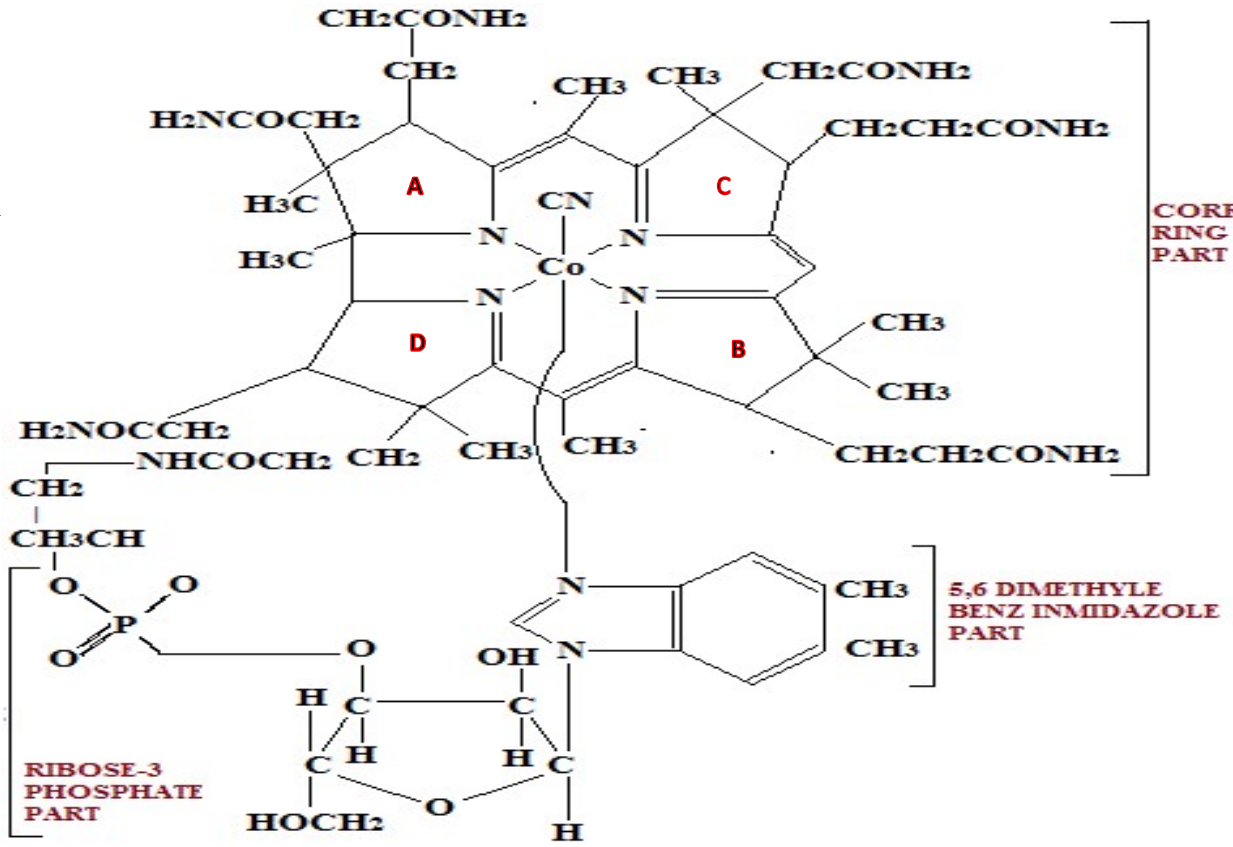
Another distinct feature is presence of **isopropanol, phosphate and ribose and 5,6-dimethyl- benzimidazole** in that order, the end of the loop being attached to the central cobalt atom.

Vitamin B12 forms – Cyanide (CN) group is replaced by other ions

Vit B12a Cyanocobalamin

Vit B12b- Hydroxocobalamin (CN replaced by hydroxyl grp) ,

Vit B12c nitrocobalamin (replaced by Nitrite).



VITAMIN B12 (CYANOCOBALAMIN)

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Biochemical functions

Coenzyme B12 is associated with following biochemical reaction:

1. 1,2 shift of hydrogen atom. eg. **Methylmalonyl-CoA mutase**: – Isomerization of methyl malonyl CoA to succinyl CoA.
2. Carrier of methyl group**. eg. Methionine synthase**: –methylation of homocysteine to methionine.
3. Isomerization of carboxylic acids. eg. Glutamic acid into β-methyl-aspartic acid.
4. Dismutation of vicinal diols to corresponding aldehydes. eg. Propane-1,2-diol to propionaldehyde.

Deficiency:

Deficiency disease caused is **pernicious anaemia** (anemia caused by failure of erythrocyte formation. It is characterized by RBCs becoming abnormally large and fewer in number. Major systems affected by this disease are **hematopoietic and central nervous system**.

Human requirements: Recommended daily allowance 2-4µg for children, 5 µg for men & women.

THANK YOU