FOLIC ACID

History

- 1941: Investigations at University of Wisconsin revealed – factor was required for the growth of certain micro-organisms
- 1941: Factor was prepared in a concentrated form of spinach by Mitchell, Snell & Williams
- They named the factor as ‘Folic acid’, derived from Latin word ‘Folium’ means ‘Leaf’
- 1945: Angier gave its chemical structure & synthesised it
Chemistry

- Folic acid is composed of 3 components –
  - ‘Pteridine’ nucleus – composed of fused pyrimidine & pyrazine rings
  - Para-aminobenzoic acid (PABA)
  - Glutamic acid

- Pteridine group is linked with PABA by methylene bridge → ‘Pteroic acid’

- Glutamic acid is attached to PABA by peptide linkage
  - Polyglutamates may be attached – up to 7 glutamic acid residues to the pteroyl group
Chemistry

- Folic acid is thus chemically ‘Pteroyl glutamic acid’
- Folic acid related compounds containing polyglutamates are grouped under the generic name ‘Folacin’
- Folic acid is a water soluble, heat stable compound, destroyed by light & acid medium
**Sources**

- **Rich Sources**: Yeast, liver, green leafy vegetables, cereals, pulses, oil seeds
- **Good Sources**: Roots, tubers, meat, fish & fruits
- **Poor Source**: Milk
- Intestinal bacteria also provides certain amount of the vitamin
Recommended Dietary Allowance

- Adults: 100 to 200 μg/day
- Infants & Children: 50 to 100 μg/day
- Pregnancy, Lactation: 200 to 400 μg/day
Absorption, Storage, Transport & Excretion

- Folic acid is absorbed from upper part of **jejenum**
- Polyglutamate forms are first cleaved into monoglutamate form by the intestinal enzymes before absorption
- It is transported in blood bound to β - globulins
- It is found relatively in higher concentrations in the liver
- Specific tissue transporters bind to the plasma membrane, and is internalised by non-clathrin mediated endocytosis
- It is not stored in the body & excess is excreted in urine
- Normal serum levels of folic acid is : 3 to 21 ng / ml
Functions

 Biography enzyme forms of folic acid is:
- Tetrahydrofolic acid (THFA)

In the liver, folic acid is first reduced to 7,8-dihydrofolic acid, which is further reduced to 5,6,7,8 tetrahydrofolate

Both the reactions are catalysed by the enzyme ‘Folate reductase’ requires NADPH & Vitamin C
Functions (Contd)

Tetrahydrofolate is a carrier of one-carbon groups.

- One carbon compound is an organic molecule that contains single carbon atom
- One carbon compounds occurring in human metabolism includes:
  - Formyl ( - CHO)
  - Formimino ( -CH = NH)
  - Methenyl ( - CH =)
  - Methylene ( - CH₂ -)
  - Hydroxymethyl ( - CH₂OH)
  - Methyl ( - CH₃)
These one carbon compounds are attached either to 5\textsuperscript{th} OR 10\textsuperscript{th} OR to both 5\textsuperscript{th} & 10\textsuperscript{th} positions of THFA

Thus active forms (carriers) of one carbon compounds includes:
- $N^5$ – formyl tetrahydrofolic acid (Folinic acid)
- $N^5$ – forimino tetrahydrofolic acid
- $N^5, N^{10}$ – methenyl tetrahydrofolic acid
- $N^5, N^{10}$ – methylene tetrahydrofolic acid
- $N^{10}$ hydroxymethyl tetrahydrofolic acid
- $N^5$ – methyl tetrahydrofolic acid
Folic acid is involved in ‘One carbon’ metabolism
- accepting & transfer of one carbon moiety

ONE CARBON MOIETY DONORS
- Formimino glutamic acid – Formimino group
- Methionine, Choline, Thymine & Betaine – Methyl group
- Serine - β - carbon
Functions (Contd)

ONE CARBON MOIETY ACCEPTORS

- Position 2 & 8 of purine ring
- N-formyl methionine of t-RNA
- Interconversion of Glycine to serine
- Interconversion of Homocystine to methionine
- Synthesis of Thymine from uracil
- Formation of ethanolamine from choline
- Synthesis of histidine
Deficiency Manifestations

- Folate deficiency is the most common of all the water soluble vitamins, particularly in **INDIA**

- Deficiency is caused due to –
  - Pregnancy & lactation – daily requirement is increased
  - Defective absorption due to intestinal diseases
  - Drugs like anticonvulsants, sulphonamides, trimethoprim – FOLATE ANTAGONISTS
  - Folate reductase enzyme deficiency
  - Hemolytic anaemia of any cause due to increased requirement
Deficiency Manifestations

Pathogenesis

- Folate deficiency causes ↓ intracellular concentration of THFA
- ↓ synthesis of nuclear materials like purine & thymidilate → ↓ in DNA synthesis
- Arrest of cell division
- Seriously affects rapidly dividing cells in bone marrow & intestinal mucosa
Deficiency Manifestations

- Hematologic manifestation ‘Macrocytic anaemia’ – Most characteristic feature of folate deficiency
- During RBC formation, ‘S’ phase of cell cycle is prolonged & cell division is delayed
- DNA synthesis is delayed, but protein synthesis in RBCs is continued normally
- Hemoglobin thus accumulates in RBC precursors & RBCs becomes macrocytic
- Nuclear remnants such as Howell-Jolly bodies & Cabot rings are commonly seen
Deficiency Manifestations

- In severe folate deficiency, reticulocytes & nucleated RBCs are seen in circulation
- RBC life span is decreased due to their rapid destruction in the spleen
- Anaemia results due to hemolysis, reduced RBC formation & decreased oxygen carrying capacity of blood
- Similar defects in granulocytes & megakaryocytes results in leukopenia & thrombocytopenia
- GI manifestation includes vomiting, abdominal pain & diarrhoea
Deficiency Manifestations

- Assessment of Folate deficiency
  - Measurement of folate levels in serum
  - Histidine load test (FIGLU excretion test)
    - 5 grams of histidine is given orally in 3 divided doses at 4 hourly intervals & urine is collected after 24 hours
    - In normal persons, <35 mgs of FIGLU is excreted in urine
- Peripheral blood smear
- Prompt administration of 1mg of folic acid per day along with combination of Vitamin B\textsubscript{12}