2007-09

M1 - Renal, Fall 2007

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<http://hdl.handle.net/2027.42/64946>
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Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
Folate ("One-Carbon") Pathways
Click on any blue box to see details
(Start with the section with ‘Diet’ and follow the paths with red arrows)
Folic Acid is Synthesized By Bacteria

Dietary folate: folic acid (meats, green veggies)
*requires* the intestinal enzyme ‘Conjugase’ for absorption.
Inhibitors of DHFR are important therapeutics:
Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
The diagram illustrates the biosynthesis pathways involving folate coenzymes. The reactions include:

- **Biosynthesis of methionine**:
  - $N^\text{5}$-methyl tetrahydrofolate
  - NAD$^+$

- **Biosynthesis of thymidylate**:
  - $N^\text{5}, N^\text{10}$-methylene tetrahydrofolate
  - NADPH + H$^+$

- **Biosynthesis of purines**:
  - $N^\text{10}$-formyl tetrahydrofolate
  - $N^\text{5}$-formyl tetrahydrofolate
  - $H_2O$

The structures of $N^\text{5}$-methyl tetrahydrofolate and $N^\text{10}$-formyl tetrahydrofolate are also depicted in the diagram.
Methionine Cycle
And Biological Methyl Groups
\[
\text{homocysteine} \xrightarrow{\text{vitamin B}} \text{methionine}
\]
Carbon donor (e.g., serine or glycine)

Tetrahydrofolate

$N^\delta, N^\delta$-methylene tetrahydrofolate

NADH + H^+ → NAD^+

methionine

homocysteine

$N^\delta$ methyl tetrahydrofolate
Other methyl acceptors:
DNA ("CpG Islands")
RNA

Methionine

S-Adenosyl methionine

Norepinephrine

Epinephrine
Folate Deficiencies: Symptom: megaloblastic anemia

Dietary deficiency:
Common especially in developing countries, lower socioeconomic classes
Folate deficiency secondary to bowel irritation:

• Conjugase is essential for adequate absorption of dietary folates

• Conjugase production may be compromised by bowel irritation:

  ‘Tropical Sprue’ - bowel irritation probably arising from bacterial origin, causes intestinal inflammation and malabsorption.

  ‘Celiac Sprue’ - similar outcome, but the original irritation is due to an allergic response, for example to gliaden (a component in gluten)
Folate Deficiency Secondary to B12 deficiency: the ‘methyl trap’ hypothesis

B12 is also critical in other reactions, ones for which the deficiency has serious neurological consequences.