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
Tetrahydrofolate + serine → H₂O + glycine

Tetrahydrofolate + glycine → N^6, N^14 methylene tetrahydrofolate
$N^\prime$-methyl tetrahydrofolate → Biosynthesis of methionine

Gly

$N^\prime_1$, $N^\prime_2$-methylene tetrahydrofolate → Biosynthesis of thymidylate

Ser

$N^\prime$-formyl tetrahydrofolate → Biosynthesis of purines

IUPAC structures of $N^\prime$-methyl tetrahydrofolate and $N^\prime_1$-formyl tetrahydrofolate.
Methionine Cycle
And Biological Methyl Groups
homocysteine \[\text{N}^\text{6} -\text{methyl THF} \rightarrow \text{THF} \rightarrow \text{methionine}\]
Carbon donor (e.g., serine or glycine)

Tetrahydrofolate

\[ \text{Tetrahydrofolate} \xrightarrow{\text{Carbon donor}} \text{N}^\circ, \text{N}^\circ \text{methylene tetrahydrofolate} \]

\[ \text{N}^\circ \text{methyl tetrahydrofolate} \]
Other methyl acceptors:
DNA ("CpG Islands")
RNA

- Methionine
  - ATP
  - PP<sub>i</sub> + P<sub>i</sub>
  - S-Adenosyl methionine

- Norepinephrine
  - SAM
  - SAH
  - 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.