M1 - Renal, Fall 2007

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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.
Folic acid

\[
\text{Folic acid} \quad \xrightarrow{\text{NADPH} + \text{H}^+} \quad \text{Dihydrofolate} \quad \xrightarrow{\text{NADP}^+} \quad \text{Tetrahydrofolate} \quad \xrightarrow{\text{NADPH} + \text{H}^+} \quad \text{Dihydrofolate} \quad \xrightarrow{\text{NADP}^+} \quad \text{Folic acid}
\]
Inhibitors of DHFR are important therapeutics:

- Methotrexate - chemotherapy
- Trimethoprim - inhibits bacterial DHFR
- Pyrimethamine - inhibits malarial DHFR
Methionine Cycle
And Biological Methyl Groups
Homocysteine $\rightarrow$ Methionine

Homocysteine $\rightarrow$ N$^\delta$-methyl THF $\rightarrow$ Methionine

Homocysteine $\rightarrow$ Vitamin B$_{12}$ $\rightarrow$ Methionine
Carbon donor
(e.g. serine or glycine)

Tetrahydrofolate

N°, N° methylène tetrahydrofolate

N° methyl tetrahydrofolate

methionine

homocysteine

NADH + H⁺

NAD⁺
Other methyl acceptors:
DNA ("CpG Islands")
RNA

\[
\begin{align*}
\text{Methionine} & \xrightarrow{\text{ATP, PP}_i + P_i} \text{S-Adenosyl methionine} \\
\text{Norepinephrine} & \xrightarrow{\text{SAM, SAH}} \text{Epinephrine}
\end{align*}
\]
**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.