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

\[
\text{NADPH} + \text{H}^+ \quad \rightarrow \quad \text{NADP}^+ 
\]

Dihydrofolate

\[
\text{NADPH} + \text{H}^+ \quad \rightarrow \quad \text{NADP}^+ 
\]

Tetrahydrofolate
Inhibitors of DHFR are important therapeutics:

Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
Tetrahydrofolate + serine $\rightarrow$ H$_2$O $\rightarrow$ glycine $\rightarrow$ N$^6$, N$^{10}$ methylene tetrahydrofolate

Tetrahydrofolate + glycine $\rightarrow$ N$^6$, N$^{10}$ methylene tetrahydrofolate
Methionine Cycle
And Biological Methyl Groups

- Methionine
  - $\text{CH}_3 - S - \text{CH}_3 - \text{CH}_3 - \text{C} - \text{COO}^-$
  - ATP + $\text{H}_2\text{O}$
  - S-Adenosyl Methionine
    - $\text{CH}_3 - (\text{S} - \text{C} - \text{CH}_3 - \text{C} - \text{C} - \text{COO}^-)$
  - Biogenic Methylation reaction
    - Methyl acceptor
    - Methylated acceptor

- Homocysteine
  - $\text{CH}_3 - S - \text{CH}_3 - \text{CH}_3 - \text{C} - \text{COO}^-$
  - NS methyl tetrahydrofolate

- S-Adenosyl Homocysteine
  - $\text{CH}_3 - (\text{S} - \text{C} - \text{CH}_3 - \text{C} - \text{C} - \text{COO}^-)$

- Serine
  - $\text{CH}_3 - S - \text{CH}_3 - \text{CH}_3 - \text{C} - \text{COO}^-$

- Cysteine
  - $\text{CH}_3 - S - \text{CH}_3 - \text{CH}_3 - \text{C} - \text{COO}^-$

(remainder of homocysteine degraded for energy)
Tetrahydrofolate

Carbon donor (e.g. serine or glycine)

N\text{\textdegree}, N\text{\textdegree} methylene tetrahydrofolate

methionine

decarboxylation

homocysteine

NADH + H\textsuperscript{+}

NAD\textsuperscript{+}

N\text{\textdegree} methyl tetrahydrofolate
Other methyl acceptors:
DNA ("CpG Islands")
RNA

Methionine

S-Adenosyl methionine

Norepinephrine

Epinephrine
Adenosine

\[ \text{Adenosine} \rightarrow \text{Homocysteine} \]

\[ \text{Homocysteine} \rightarrow \text{S-Adenosyl Homocysteine} \]

\[ \text{S-Adenosyl Homocysteine} \rightarrow \text{Methionine} \]

\[ \text{Methionine} \rightarrow \text{S-Adenosyl Methionine} \]

\[ \text{S-Adenosyl Methionine} \rightarrow \text{Adenosine} \]

\[ \text{Adenosine} \rightarrow \text{Homocysteine} \]

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**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.