M1 - Renal, Fall 2007

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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

Dihydrofolate

Tetrahydrofolate
Inhibitors of DHFR are important therapeutics:
Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
Methionine Cycle
And Biological Methyl Groups

Methionine

\[
\text{CH}_3-S-C\text{H}_2-C\text{H}_2-C\text{O}^\bullet
\]

\[
\text{ATP} + H_2O \rightarrow \text{PPi} + \text{Pi}
\]

S-Adenosyl Methionine

\[
\text{CH}_3-S-C\text{H}_2-C\text{H}_2-C\text{O}^\bullet
\]

NS methyl tetrahydrofolate

tetrahydrofolate

Homocysteine

\[
\text{HS-C}\text{H}_2-C\text{H}_2-C\text{O}^\bullet
\]

\[
\text{H}_2O \rightarrow \text{CO}_2
\]

S-Adenosyl Homocysteine

\[
\text{CH}_3-S-C\text{H}_2-C\text{H}_2-C\text{O}^\bullet
\]

Methyl acceptor

Biogenic Methyl transfer
Methylated acceptor

Serine

\[
\text{HS-C}\text{H}_2-C\text{H}_2-C\text{O}^\bullet
\]

Cysteine

(remainder of homocysteine degraded for energy)
Homocysteine is converted to methionine through a process involving THF and vitamin B_12.

\[ \text{Homocysteine} \rightarrow \text{N}^\circ\text{-methyl THF} \rightarrow \text{THF} \rightarrow \text{Methionine} \]
Carbon donor (e.g., serine or glycine)

Tetrahydrofolate

N\textsuperscript{5}, N\textsuperscript{10} methyl tetrahydrofolate

NADH + H\textsuperscript{+}

NAD\textsuperscript{+}

methionine

homocysteine
Other methyl acceptors:
DNA ("CpG Islands")
RNA

Methionine $\rightarrow$ S-Adenosyl methionine

Norepinephrine $\rightarrow$ Epinephrine

\[ \text{SAM} \rightarrow \text{SAH} \]
**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.