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.
Inhibitors of DHFR are important therapeutics:
Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
\[ \text{N}^\text{a}-\text{methyl tetrahydrofolate} \rightarrow \text{Biosynthesis of methionine} \]

\[ \text{N}^\text{a}, \text{N}^\text{b} \text{ methylene tetrahydrofolate} \rightarrow \text{Biosynthesis of thymidylate} \]

\[ \text{Gly} \quad \text{Ser} \]

\[ \text{N}^\text{a}, \text{N}^\text{b} \text{ methenyl tetrahydrofolate} \]

\[ \text{H}_2\text{O} \rightarrow \text{Biosyntheses of purines} \]

\[ \text{N}^\text{a} \text{ formyl tetrahydrofolate} \]

\[ \text{N}^\text{a} 	ext{ methyl tetrahydrofolate} \]

\[ \text{N}^\text{a} 	ext{ formyl tetrahydrofolate} \]
Methionine Cycle
And Biological Methyl Groups
homocysteine $\xrightarrow{\text{N}^6\text{-methyl THF}}$ vitamin $B_12$ $\xrightarrow{\text{THF}}$ methionine
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate → $N^\circ, N^\circ$ methylene tetrahydrofolate

methionine → homocysteine

$N^\circ$ methyl tetrahydrofolate

NADH + H$^+$ → NAD$^+$
Other methyl acceptors:
DNA ("CpG Islands")
RNA
The diagram illustrates the conversion of homocysteine to methionine. The process involves the following steps:

1. Homocysteine is converted to S-adenosyl homocysteine with the donation of a methyl group from S-adenosyl methionine.
2. The methyl group is transferred to the biological substrate, forming methionine.
3. S-adenosyl homocysteine is regenerated.

The reaction also involves the consumption of NADH and the production of NAD⁺. The diagram highlights the roles of certain vitamins and coenzymes, such as vitamin B₁₂, in the reaction.
**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.