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

\[ \text{NADPH} + \text{H}^+ \]

\[ \text{NADP}^+ \]

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\[ \text{NADP}^+ \]
Inhibitors of DHFR are important therapeutics:
Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
\[ \text{Gly} \rightarrow \text{N}^\text{t}, \text{N}^\text{o} \text{methylene tetrahydrofolate} \rightarrow \text{N}^\text{t} \text{formyl tetrahydrofolate} \rightarrow \text{Biosyntheses of purines} \]

\[ \text{N}^\text{t} \text{ methyl tetrahydrofolate} \rightarrow \text{Biosynthesis of methionine} \]

\[ \text{N}^\text{t}, \text{N}^\text{o} \text{ methenyl tetrahydrofolate} \rightarrow \text{Biosynthesis of thymidylate} \]

\[ \text{H}_2\text{O} \]
Methionine Cycle
And Biological Methyl Groups
\[
\text{homocysteine} \xrightarrow{\text{vitamin B}_12} \text{N}^6\text{-methyl THF} \xrightarrow{\text{THF}} \text{methionine}
\]
Tetrahydrofolate

Carbon donor (e.g. serine or glycine)

N^6, N^6 methylene tetrahydrofolate

methionine

NADH + H^+

homocysteine

NAD^+

N^6 methyl tetrahydrofolate
Other methyl acceptors:
DNA ("CpG Islands")
RNA
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.