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
Tetrahydrofolate

serine + glycine

$\text{NH}_2\text{C}(-\text{H})\text{CH}_2\text{OH}$

$\text{H}_2\text{O}$

$\text{NH}_3\text{C}(-\text{H})\text{H}$

$\text{N}^6, \text{N}^{10}$ methylene tetrahydrofolate

Tetrahydrofolate

Glycine

$\text{NAD}^+$

$\text{NH}_4^+$

$\text{CO}_3^-$

$\text{NADH}$

$\text{N}^6, \text{N}^{10}$ methylene tetrahydrofolate
Methionine Cycle
And Biological Methyl Groups

- Methionine
- S-Adenosyl Methionine
- Homocysteine
- S-Adenosyl Homocysteine
- Serine
- Cysteine

- Tetrahydrofolate
- N5 methyl tetrahydrofolate

- Methyl acceptor
- Biogenic Methylation reaction
- Methylated acceptor

- ATP + H2O
- PPi + Pi

(remainder of homocysteine degraded for energy)
Homocysteine

\[
\text{H} \quad \text{OOC} \quad \text{C} \quad \text{CH}_2 \text{CH}_2 \text{SH}
\]

\[\text{N}^6\text{—methyl THF}\]

\[\text{THF}\]

\[\text{vitamin B}_12\]

\[
\text{H} \quad \text{OOC} \quad \text{C} \quad \text{CH}_2 \text{CH}_2 \text{SCH}_3
\]

Methionine
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

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

N\textsuperscript{5} methyl tetrahydrofolate

methionine

homocysteine

NADH + H\textsuperscript{+}

NAD\textsuperscript{+}
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.