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

\[
\text{NADPH} + \text{H}^+ \rightleftharpoons \text{NADP}^+ \\
\text{NADPH} + \text{H}^+ \rightleftharpoons \text{NADP}^+ \\
\text{NADPH} + \text{H}^+ \rightleftharpoons \text{NADP}^+ \\
\]
Inhibitors of DHFR are important therapeutics:

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

Tetrahydrofolate + glycine $\rightarrow$ N^6, N^10 methylene tetrahydrofolate
\[ \text{Gly, Ser} \rightarrow \text{N}^\prime, \text{N}^\circ \text{methylenetetrahydrofolate} \]

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

\[ \text{N}^\prime, \text{N}^\circ \text{methylenetetrahydrofolate} \rightarrow \text{Biosynthesis of thymidylate} \]

\[ \text{N}^\prime \text{formyltetrahydrofolate} \rightarrow \text{Biosynthesis of purines} \]

\[ \text{N}^\prime \text{methyl tetrahydrofolate} \]

\[ \text{N}^\prime \text{formyl tetrahydrofolate} \]
Methionine Cycle
And Biological Methyl Groups
Homocysteine  \xrightarrow{\text{N}^6-\text{methyl THF}} \text{THF} \xrightarrow{\text{vitamin B}_12} \text{methionine}
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

N°, N° methylene tetrahydrofolate

N° methyl tetrahydrofolate

methionine

homocysteine

NADH + H⁺

NAD⁺
Other methyl acceptors:
- DNA ("CpG Islands")
- RNA

Methionine

\[
\text{OOC-C-CH}_2\text{CH}_2\text{SH} \quad \text{ATP} \quad \text{PP}_i + P_i \quad \text{NH}_3^+ \quad \text{OOC-C-CH}_2\text{CH}_2\text{SH} \quad \text{adenosine}
\]

S-Adenosyl methionine

Norepinephrine

\[
\text{HO-OC-CH}_2\text{NH}_3^+ \quad \text{SAM} \quad \text{SAM} \quad \text{SAH} \quad \text{HO-OC-CH}_2\text{NH}_3^+ \quad \text{HO-OC-CH}_2\text{N-CH}_3
\]

Epinephrine
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.