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

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

Dihydrofolate

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

Tetrahydrofolate
Inhibitors of DHFR are important therapeutics:
- Methotrexate - chemotherapy
- Trimethoprim - inhibits bacterial DHFR
- Pyrimethamine - inhibits malarial DHFR
Tetrahydrofolate + serine \xrightarrow{H_2O} COO^- + NH_3 - C - H + glycine

N^6, N^{10} methylene tetrahydrofolate

Tetrahydrofolate + glycine \xrightarrow{NAD^+} NH_4^+ + CO_3^{2-} + NADH

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

\[
\text{CH}_3 - \text{S} - \text{CH}_2 - \text{CH}_3 - \text{CH} = \text{CO}^\text{-}\]

Methionine

\[
\text{CH}_3 - \text{S} - \text{CH}_2 - \text{CH}_3 - \text{CH} = \text{CO}^\text{-}\]

S-Adenosyl Methionine

\[
\text{CH}_3 - \text{S} - \text{CH}_2 - \text{CH}_3 - \text{CH} = \text{CO}^\text{-}\]

S-Adenosyl Homocysteine

\[
\text{CH}_3 - \text{S} - \text{CH}_2 - \text{CH}_3 - \text{CH} = \text{CO}^\text{-}\]

Homocysteine

\[
\text{CH}_3 - \text{S} - \text{CH}_2 - \text{CH}_3 - \text{CH} = \text{CO}^\text{-}\]

Serine

\[
\text{CH}_3 - \text{S} - \text{CH}_2 - \text{CH}_3 - \text{CH} = \text{CO}^\text{-}\]

Cysteine

(remnant of homocysteine degraded for energy)
\[ \text{homocysteine} \rightarrow \text{N}^\text{6}-\text{methyl THF} \rightarrow \text{THF} \rightarrow \text{methionine} \]
Tetrahydrofolate

Carbon donor (e.g. serine or glycine)

\[ \text{N}^\text{4}, \text{N}^\text{4} \text{ methylene tetrahydrofolate} \]

methionine

\[ \text{N}^\text{4} \text{ methyl tetrahydrofolate} \]

homocysteine

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

\[ \text{NAD}^+ \]
Other methyl acceptors:
DNA ("CpG Islands")
RNA

Methionine

S-Adenosyl methionine

Norepinephrine

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.