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.

**Formulae:**
- Folic Acid
- Para-aminobenzoic acid (PAABA)
- Sulfanilamide
Inhibitors of DHFR are important therapeutics:

Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
Tetrahydrofolate + \( \text{COO}^- \text{NH}_2 - \text{CH} - \text{H} \text{CH}_2 - \text{OH} \) (serine) \( \rightleftharpoons \text{H}_2\text{O} \) \( \text{COO}^- \text{NH}_3 - \text{C} - \text{H} \text{H} \) (glycine) + \( \text{NH}_3 - \text{N} - \text{H} \text{CH}_2 - \text{N} \) (et al) \( \text{N}^\text{\textdegree} \text{N}^\text{\textdegree} \) methylene tetrahydrofolate

Tetrahydrofolate + \( \text{NH}_2 - \text{N} - \text{H} \text{CH}_2 - \text{NH} \) (et al) \( \rightleftharpoons \text{NAD}^+ \text{NH}_3^+ \text{CO}_3^- \text{NADH} \) \( \text{NH}_3 - \text{C} - \text{H} \text{H} \) (glycine) + \( \text{NH}_3 - \text{N} - \text{H} \text{CH}_2 - \text{N} \) (et al) \( \text{N}^\text{\textdegree} \text{N}^\text{\textdegree} \) methylene tetrahydrofolate
Methionine Cycle And Biological Methyl Groups
Homocysteine \[ \text{NH}_3^+ \overset{-\text{OOC}}{\longrightarrow} \overset{\text{C}}{\longrightarrow} \overset{\text{CH}_2 \text{CH}_2 \text{SH}}{\rightarrow} \] reacts with \( \text{N}^\delta \text{-methyl THF} \) to form THF, which is then converted to Methionine \[ \text{NH}_3^+ \overset{-\text{OOC}}{\longrightarrow} \overset{\text{C}}{\longrightarrow} \overset{\text{CH}_2 \text{CH}_2 \text{SCH}_3}{\rightarrow} \] by vitamin B\(_2\).
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

N\(^\circ\), N\(^\circ\) methylene tetrahydrofolate

methionine

homocysteine

NADH + H\(^+\)

NAD\(^+\)

N\(^\circ\) methyl tetrahydrofolate
Other methyl acceptors:
DNA ("CpG Islands")
RNA
The diagram illustrates the metabolism of homocysteine to methionine. The process involves the donation of a methyl group from S-adenosylmethionine to homocysteine, catalyzed by the enzyme methionine adenosyltransferase. NADH and NAD+ act as electron carriers, and vitamin B12 is involved in the reaction. The reaction also involves the hydrolysis of ATP to PPi, providing energy for the reaction. The methyl group is donated to a biological substrate, which is not explicitly named in the diagram.
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.