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 + H₂O → glycine + N⁺, N⁴⁺ methylene tetrahydrofolate

Tetrahydrofolate + glycine + NAD⁺ → N⁺, N⁴⁺ methylene tetrahydrofolate + NADH
Methionine Cycle
And Biological Methyl Groups
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

N\textsuperscript{6}, N\textsuperscript{5} methylene tetrahydrofolate

methionine

homocysteine

N\textsuperscript{5} methyl tetrahydrofolate

NAD\textsuperscript{+} + H\textsuperscript{+}

NADH
Other methyl acceptors:
  DNA ("CpG Islands")
  RNA

Methionine

S-Adenosyl methionine

Norepinephrine

Epinephrine
The diagram illustrates the metabolism of homocysteine and methionine. Homocysteine undergoes a series of reactions involving NADH and NAD+ to form methionine.

1. Homocysteine is converted to S-adenosyl homocysteine (SAH) through an adenosyl transferase reaction.
2. SAH donates a methyl group to form methionine, which is then activated by adenosine to form S-adenosyl methionine (SAM).
3. SAM is a key methyl donor in various biochemical pathways.

The process is driven by the conversion of NADH to NAD+, which serves as an electron donor in the reaction. Vitamin B12 is also essential for this process.
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.