M1 - Renal, Fall 2007

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Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
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)

- Methyl-THF
- Methylene-THF
- THF Cycle
- Methionine Cycle

Diet:
- THF
- DHF
- Folate

Connects to Amino Acids

Connects to Nucleic Acids

Donation of one carbon (from Ser, Gly)

Formyl-THF

Purine biosynthesis

Thymidylate synthetase
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
Methionine Cycle
And Biological Methyl Groups
Homocysteine → N^6-methyl THF → THF → Vitamin B₁₂ → Methionine
Carbon donor (e.g., serine or glycine)

Tetrahydrofolate

methionine

homocysteine

$\text{N}^6$, $\text{N}^8$ methylene tetrahydrofolate

$\text{N}^6$ methyl tetrahydrofolate

$\text{NAD}^+$

$\text{NADH} + \text{H}^+$
Other methyl acceptors:
  DNA ("CpG Islands")
  RNA

Methionine → S-Adenosyl methionine

Norepinephrine → Epinephrine

SAM → SAH
The figure illustrates the metabolic pathway involving the conversion of homocysteine to methionine.

- **Homocysteine** is converted to **S-adenosyl homocysteine**.
- **S-adenosyl homocysteine** donates its methyl group to **S-adenosyl methionine**.
- **S-adenosyl methionine** is then converted back to **homocysteine**.

The pathway involves several key components, including ATP, PPi, and NADH. The methyl group is donated to biological substrates as part of the 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.