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)
Folic Acid is Synthesized By Bacteria

Dietary folate: folic acid (meats, green veggies) *requires* the intestinal enzyme ‘Conjugase’ for absorption.
Folic acid

Dihydrofolate

Tetrahydrofolate
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
Methionine Cycle
And Biological Methyl Groups
Homocysteine is converted to methionine through a process involving vitamin B₁₂ and N⁶-methyl THF.
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

N^\circ, N^\circ \text{ methylene}

methylene
tetrahydrofolate

methionine

NADH + H^+

homocysteine

NAD^+

N^\circ \text{ methyl}
tetrahydrofolate
Other methyl acceptors:
DNA (“CpG Islands”)
RNA

Methionine

S-Adenosyl methionine

Norepinephrine

Epinephrine

SAM

SAH
The diagram illustrates the metabolic pathway involving homocysteine and methionine.

1. **Homocysteine** is converted to **S-adenosylhomocysteine** via Adenosine.
2. **NADH** and **NAD** participate as coenzymes in the reaction.
3. **N^5^-methyl THF** is the methyl donor.
4. Vitamin B₁₂ is required for the conversion of homocysteine to methionine.
5. **Methyl group** is transferred from **S-adenosylmethionine** to biological substrates.
6. **ATP** and **PP_i** are involved in the energy metabolism of the pathway.

The process includes the conversion of homocysteine to methionine, which is then methylated to form S-adenosylmethionine, supporting various cellular functions.
**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.