M1 - Renal, Fall 2007

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

- Amino acids
- Glu, Gln, Asp, NH₃
- Urea

Folate metabolism

- Methylene THF
- Met Cycle

TCA Cycle

- Oxaloacetate
- Fumarate

Nucleic Acid metabolism

- Purines
- DNA
- RNA
- Pyrimidines
- Uric Acid
- (energy)
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)

Diet:
- THF
- DHF
- Folate

Connects to
- Amino Acids
- Nucleic Acids

Donation of one carbon
(from Ser, Gly)

Connects to
Methylene-THF

Methyl-THF

THF Cycle

Formyl-THF

Purine biosynthesis

Thymidylate synthetase

Methionine Cycle
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
\[ \text{Gly} \quad \text{Ser} \]

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

\[ \text{N}^4, \text{N}^5 \text{ methylene tetrahydrofolate} \]

\[ \text{N}^4, \text{N}^5 \text{ formyl tetrahydrofolate} \]

\[ \text{Biosynthesis of methionine} \]

\[ \text{Biosynthesis of thymidylate} \]

\[ \text{Biosynthesis of purines} \]
Methionine Cycle
And Biological Methyl Groups
$\text{N}^6\text{-methyl THF}$

$\text{THF}$

$\text{vitamin B}_12$

$\text{Homocysteine}$

$\text{Methionine}$
Tetrahydrofolate

Carbon donor (e.g. serine or glycine)

N^6, N^4 methylene tetrahydrofolate

methionine

homocysteine

NAD^+ + H^+

NADH + H^+

N^6 methyl tetrahydrofolate
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.