M1 - Renal, Fall 2007

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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)

- Connects to Amino Acids
- Donation of one carbon (from Ser, Gly)
- THF
- DHF
- Folate
- Folate
- THF Cycle
- Formyl-THF
- Methylene-THF
- Methyl-THF
- THF Cycle
- Methionine Cycle
- Connects to Nucleic Acids lectures
- 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
Tetrahydrofolate + serine $\rightarrow$ glycine $\rightarrow$ N$^\delta$, N$^{\delta^\prime}$ methylene tetrahydrofolate

Tetrahydrofolate + glycine $\rightarrow$ N$^\delta$, N$^{\delta^\prime}$ methylene tetrahydrofolate
Methionine Cycle
And Biological Methyl Groups

\[ \text{CH}_2 - \text{S} - \text{CH} - \text{CH} - \text{C} - \text{COO}^- \]
\[ \text{ATP} + \text{H}_2\text{O} \rightarrow \text{PPi} + \text{Pi} \]

\[ \text{CH}_3 \]
\[ \text{S} - \text{CH} - \text{CH} - \text{C} - \text{COO}^- \]

S-Adenosyl Methionine

\[ \text{tetrahydrofolate} \rightarrow \text{NS methyl tetrahydrofolate} \]

\[ \text{CH} - \text{S} - \text{CH} - \text{CH} - \text{C} - \text{COO}^- \]

Homocysteine

\[ \text{Bioplastic Methylation reaction} \]
\[ \text{Methyl acceptor} \rightarrow \text{Methylated acceptor} \]

\[ \text{CH}_3 \]
\[ \text{S} - \text{CH} - \text{CH} - \text{C} - \text{COO}^- \]

S-Adenosyl Homocysteine

\[ \text{X} - \text{CH} - \text{C} - \text{COO}^- \]
\[ \text{Serine} \]

\[ \text{X} - \text{CH} - \text{C} - \text{COO}^- \]
\[ \text{Cysteine} \]

(remainder of homocysteine degraded for energy)
\[ \text{homocysteine} \xrightarrow{\text{vitamin B}_12} \text{methionine} \]
Tetrahydrofolate

Carbon donor (e.g. serine or glycine)

N\text{\textsuperscript{5}}, N\text{\textsuperscript{10}} methylene tetrahydrofolate

N\text{\textsuperscript{5}} methyl tetrahydrofolate

methionine

homocysteine

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

NADH + H\text{\textsuperscript{+}}
Other methyl acceptors:

DNA ("CpG Islands")
RNA

Methionine

\[
\text{ATP} \rightarrow_{PP_i + P_i} ^{\text{S-Adenosyl methionine}}
\]

Norepinephrine

\[
\text{SAM} \rightarrow_{\text{SAH}} ^{\text{Epinephrine}}
\]
**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.