M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

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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)
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 + $\text{N}^\text{v}, \text{N}^{\text{v}}$ methylene tetrahydrofolate

Tetrahydrofolate + glycine $\rightarrow$ $\text{N}^\text{v}, \text{N}^{\text{v}}$ methylene tetrahydrofolate
$N^4$-methyl tetrahydrofolate $\rightarrow$ Biosynthesis of methionine

$N^4$, $N^6$-methylene tetrahydrofolate $\rightarrow$ Biosynthesis of thymidylate

$N^4$, $N^6$-methenyl tetrahydrofolate

$N^4$-formyl tetrahydrofolate $\rightarrow$ Biosyntheses of purines

$N^4$-methyl tetrahydrofolate

$N^{14}$-formyl tetrahydrofolate
Methionine Cycle
And Biological Methyl Groups
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

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

NAD\textsuperscript{+}

methionine

homocysteine

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

- Methionine
- S-Adenosyl methionine
- Norepinephrine
- Epinephrine

Reactions:
- Methionine + ATP → S-Adenosyl methionine
- Norepinephrine + SAM → Epinephrine

SAM: S-Adenosylmethionine
SAH: S-Adenosylhomocysteine
**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.