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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)

Methyl-THF

THF Cycle

Methionine Cycle

Connects to Amino Acids

Donation of one carbon (from Ser, Gly)

THF

DHF

Folate

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.
Folic acid

Dihydrofolate

Tetrahydrofolate

\[ \text{Folic acid} \quad \xrightarrow{\text{NADPH} + H^+} \quad \text{Dihydrofolate} \]

\[ \text{Dihydrofolate} \quad \xrightarrow{\text{NADP}^+} \quad \text{Tetrahydrofolate} \]

\[ \text{Tetrahydrofolate} \quad \xrightarrow{\text{NADPH} + H^+} \quad \text{Dihydrofolate} \]

\[ \text{Dihydrofolate} \quad \xrightarrow{\text{NADP}^+} \quad \text{Folic acid} \]
Inhibitors of DHFR are important therapeutics:

- Methotrexate - chemotherapy
- Trimethoprim - inhibits bacterial DHFR
- Pyrimethamine - inhibits malarial DHFR
Methionine Cycle and Biological Methyl Groups
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

$N^\circ, N^\circ$ methylene tetrahydrofolate

NADH + H$^+$

NAD$^+$

methionine

homocysteine

$N^\circ$ methyl tetrahydrofolate
Other methyl acceptors:
DNA ("CpG Islands")
RNA

- Methionine
- S-Adenosyl methionine
- Norepinephrine
- Epinephrine

Reactions:
- Methionine + ATP → S-Adenosyl methionine + PP$_i$ + P$_i$
- Norepinephrine + SAM → Epinephrine + SAH

Chemical structures for Methionine, S-Adenosyl methionine, Norepinephrine, and Epinephrine are shown.
**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.