2007-09

M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

<http://hdl.handle.net/2027.42/64946>
http://hdl.handle.net/2027.42/64946
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.
Inhibitors of DHFR are important therapeutics:
Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
The image represents a biochemical reaction involving tetrahydrofolate, serine, glycine, and their respective derivatives.

The chemical equations show the following reactions:

1. Tetrahydrofolate + serine + H₂O → glycine + tetrahydrofolate
2. Tetrahydrofolate + glycine + NAD⁺ → N⁶, N¹⁰ methylene tetrahydrofolate + NADH + CO₂
Methionine Cycle
And Biological Methyl Groups

Methionine

S-Adenosyl Methionine

S-Adenosyl Homocysteine

Homocysteine

Serine

Cysteine

(remainder of homocysteine degraded for energy)

tetrahydrofolate

NS methyl tetrahydrofolate

Methyl acceptor

see examples

Methylated acceptor

ATP + H₂O

PPi + Pi
Homocysteine in vitamin B_{12} catalyzed reaction with N\textsuperscript{6} -methyl THF to form methionine.
Carbon donor (e.g., serine or glycine)

Tetrahydrofolate

$N^\alpha, N^\alpha$ methylene tetrahydrofolate

NADH + H$^+$

NAD$^+$

methionine

homocysteine

$N^\alpha$ 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.