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M1 - Renal, Fall 2007

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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
\[
\begin{align*}
\text{Gly} & \quad \text{Ser} \\
N^\prime \text{ methyl tetrahydrofolate} & \quad \text{NAD}^+ \quad \text{Biosynthesis of methionine} \\
& \quad \text{NADH} + \text{H} \\
& \quad \text{NADPH} + \text{H} \\
N^\prime, N^\circ \text{ methylene tetrahydrofolate} & \quad \text{NADPH} \\
& \quad \text{H}_2\text{O} \quad \text{Biosyntheses of purines} \\
N^\prime \text{ formyl tetrahydrofolate} & \quad \text{Biosynthesis of thymidylate} \\
\end{align*}
\]
Methionine Cycle
And Biological Methyl Groups
\[
\text{homocysteine} \xrightarrow{\text{vitamin B}_12} \text{methionine}
\]
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

methionine

NADH + H+

NAD+

homocysteine

N^\circ \text{ methyl tetrahydrofolate}

N^\circ, N^\circ \text{ methylene tetrahydrofolate}
Other methyl acceptors:

DNA ("CpG Islands")

RNA
**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.