M1 - Renal, Fall 2007

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Folic Acid is Synthesized By Bacteria

Dietary folate: folic acid (meats, green veggies) *requires* the intestinal enzyme ‘Conjugase’ for absorption.
Folic acid

\[
\text{NADPH} + \text{H}^+ \rightarrow \text{NADP}^+ 
\]

Dihydrofolate

\[
\text{NADPH} + \text{H}^+ \rightarrow \text{NADP}^+ 
\]

Tetrahydrofolate

\[
\text{NADPH} + \text{H}^+ \rightarrow \text{NADP}^+ 
\]
Inhibitors of DHFR are important therapeutics:

- Methotrexate - chemotherapy
- Trimethoprim - inhibits bacterial DHFR
- Pyrimethamine - inhibits malarial DHFR
Tetrahydrofolate + serine $\rightarrow$ glycine + N$^6$, N$^{10}$ methylene tetrahydrofolate

Tetrahydrofolate + glycine $\rightarrow$ N$^6$, N$^{10}$ methylene tetrahydrofolate
$N^\text{f}$ methyl tetrahydrofolate $\xrightarrow{\text{NAD}^+}$ Biosynthesis of methionine

Gly $\leftarrow$ NADH $+ \text{H}^+$

Ser $\leftarrow$ NADPH $+ \text{H}^+$

$N^\text{f}, N^\text{p}$ methylene tetrahydrofolate $\xrightarrow{\text{NADP}^+}$ Biosynthesis of thymidylate

$N^\text{f}, N^\text{p}$ methenyl tetrahydrofolate $\xrightarrow{\text{H}_2 \text{O}}$

$N^\text{fL}$ formyl tetrahydrofolate $\xrightarrow{\text{Biosyntheses of purines}}$

$N^\text{f}$-methyl tetrahydrofolate

$N^\text{fL}$ formyl tetrahydrofolate
Methionine Cycle
And Biological Methyl Groups
\[
\begin{align*}
\text{homocysteine} & \xrightarrow{\text{vitamin } B_12} \text{methionine} \\
\end{align*}
\]
Tetrahydrofolate

Carbon donor (e.g., serine or glycine)

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

NADH + H$^+$

NAD$^+$

$\text{N}^\text{v}$ methyl tetrahydrofolate

methionine

homocysteine
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.