M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

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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
Tetrahydrofolate + serine $\rightarrow$ water + glycine

N$^\delta$, N$^{1\alpha}$ methylene tetrahydrofolate

N$^\delta$, N$^{1\alpha}$ methylene tetrahydrofolate + glycine $\rightarrow$ NAD$^+$ + CO$_2$ + NADH

Tetrahydrofolate

N$^\delta$, N$^{1\alpha}$ methylene tetrahydrofolate
Methionine Cycle
And Biological Methyl Groups
\[
\text{homocysteine} \rightarrow \text{N}^\text{6} \text{-methyl THF} \rightarrow \text{THF} \rightarrow \text{methionine}
\]
Carbon donor (e.g., serine or glycine)

Tetrahydrofolate

\[ \text{N}^\text{v}, \text{N}^\text{v} \text{ methylene tetrahydrofolate} \]

NADH + H^+

methionine

homocysteine

NAD^+

N^v methyl tetrahydrofolate
Other methyl acceptors:
DNA ("CpG Islands")
RNA

\[
\text{Methionine} \xrightarrow{ATP, PP_i + P_i} \text{S-Adenosyl methionine}
\]

\[
\text{Norepinephrine} \xrightarrow{\text{SAM}} \text{Epinephrine}
\]
The diagram illustrates the metabolic pathway involving Adenosine, homocysteine, methionine, NADH, NAD⁺, and vitamin B₁₂. The cycle starts with Adenosine and proceeds through the conversion of homocysteine to methionine, facilitated by the addition of a methyl group. The methyl group donor is N⁵-methyl THF, which is later regenerated through the involvement of NAD⁺ and vitamin B₁₂. The metabolic cycle also requires ATP and PP₃ as energy sources, with P_i being released as a waste product. The methyl group is ultimately transferred to biological substrates, illustrating the importance of this metabolic pathway in cellular processes.
**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.