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

Dihydrofolate

Tetrahydrofolate

NADPH + H⁺ → NADP⁺

NADP⁺ → NADPH + H⁺
Inhibitors of DHFR are important therapeutics:
Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
Tetrahydrofolate + Serine → Water + Glycine

Tetrahydrofolate + Glycine → N^6, N^14 methylene tetrahydrofolate

NAD^+ + Glycine → NADH + N^6, N^14 methylene tetrahydrofolate
Methionine Cycle
And Biological Methyl Groups
$\text{N}^\text{6} - \text{methyl THF}$

$\text{THF}$

$\text{vitamin B}_12$

$\text{homocysteine}$

$\text{methionine}$
Carbon donor (e.g., serine or glycine)

\[ \text{Tetrahydrofolate} \]

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

\[ \text{methionine} \]

\[ \text{NADH} + \text{H}^+ \]

\[ \text{homocysteine} \]

\[ \text{NAD}^+ \]

\[ \text{N}^\circ \text{ methyl tetrahydrofolate} \]
Other methyl acceptors:
DNA ("CpG Islands")
RNA

Methionine → S-Adenosyl methionine

Norepinephrine → Epinephrine

ATP, PP_i + P_i
SAM, SAH
The diagram illustrates the metabolic pathway involving the interconversion of homocysteine and methionine. The cycle includes the following steps:

1. Homocysteine is converted to S-adenosyl homocysteine (SAH) by adenosine in the presence of ATP and PPi.
2. SAH donates a methyl group to an acceptor, leading to the formation of methionine.
3. Methionine is converted back to homocysteine via a series of reactions involving NADH, NAD+, THF, and vitamin B₁₂.

The cycle is catalyzed by various enzymes, indicating the dynamic interplay between these molecules in cellular metabolism.
**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.