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.

Para-aminobenzoic acid (PA.BA)
sulfanilamide
Folic acid

Dihydrofolate

Tetrahydrofolate

NADPH + H⁺

NADP⁺
Inhibitors of DHFR are important therapeutics:
Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
\[ \text{Gly} \rightarrow \text{Ser} \]

\[ \text{N}^1\text{-methyl tetrahydrofolate} \]

\[ \text{N}^1, \text{N}^5\text{ methylene tetrahydrofolate} \]

\[ \text{N}^1, \text{N}^5\text{ formyl tetrahydrofolate} \]

\[ \text{Biosynthesis of methionine} \]

\[ \text{NAD}^+ \]

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

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

\[ \text{H}_2\text{O} \]

\[ \text{Biosynthesis of thymidylate} \]

\[ \text{Biosynthesis of purines} \]
Methionine Cycle

And Biological Methyl Groups
\[
\text{homocysteine} \xrightarrow{\text{vitamin } B_{12}} \text{methionine}
\]
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

N\textsuperscript{5}, N\textsuperscript{10} methylene tetrahydrofolate

methionine

homocysteine

N\textsuperscript{5} methyl tetrahydrofolate

NADH + H\textsuperscript{+}

NAD\textsuperscript{+}
Other methyl acceptors:
- DNA ("CpG Islands")
- RNA

Methionine

S-Adenosyl methionine

Norepinephrine

Epinephrine

SAM

SAH
The diagram illustrates the metabolic pathway for the conversion of homocysteine to methionine. Key components include:

- **Homocysteine**
- **Methionine**
- **Adenosine**
- **NADH**
- **NAD<sup>+</sup>**
- **N<sup>5</sup>-methyl THF**
- **THF**
- **Vitamin B<sub>12**

The pathway involves the following steps:

1. **Homocysteine** is converted to **Methionine** by transferring a methyl group from **N<sup>5</sup>-methyl THF** to **THF** using **Vitamin B<sub>12**

2. **Adenosine** is used to activate the **methyl group** donated to **biological substrate**.

3. **ATP** and **PP<sub>i** are involved in the energy transduction steps.

The cycle is completed by the regeneration of **NADH** and **NAD<sup>+</sup>**.
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.