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
Tetrahydrofolate + serine \rightarrow H_2O + glycine + N^6, N^10 methylene tetrahydrofolate

Tetrahydrofolate + glycine \rightarrow NAD^+ + CO_3^{2-} + NADH + N^6, N^10 methylene tetrahydrofolate
\[ \text{N}^\text{v} \text{ methyl tetrahydrofolate} \rightarrow \text{Biosynthesis of methionine} \]

\[ \text{Gly} \rightarrow \text{N}^\text{v}, \text{N}^\text{o} \text{ methylene tetrahydrofolate} \rightarrow \text{Biosynthesis of thymidylate} \]

\[ \text{N}^\text{v}, \text{N}^\text{o} \text{ methenyl tetrahydrofolate} \rightarrow \text{N}^\text{v} \text{ formyl tetrahydrofolate} \rightarrow \text{Biosyntheses of purines} \]

\[ \text{N}^\text{v} \text{ - methyl tetrahydrofolate} \]
\[ \text{N}^\text{v} \text{L formyl tetrahydrofolate} \]
Methionine Cycle
And Biological Methyl Groups
\[
\text{homocysteine} \xrightarrow{N^\epsilon \text{-methyl THF}} \text{vitamin B}_12 \xrightarrow{\text{THF}} \text{methionine}
\]
Other methyl acceptors:
DNA ("CpG Islands")
RNA

\[
\begin{align*}
\text{Methionine} & \quad \text{S-Adenosyl methionine} \\
\text{Norepinephrine} & \quad \text{Epinephrine}
\end{align*}
\]
The diagram illustrates the metabolic pathway involving NADH, NAD+, N5-methyl THF, vitamin B12, and the conversion of homocysteine to methionine.

1. **NADH** and **NAD+** are involved in redox reactions.
2. **N5-methyl THF** acts as a methyl donor.
3. Vitamin **B12** is required for the conversion of homocysteine to methionine.
4. **Homocysteine** is converted to **methionine**.
5. **Adenosine** and **S-adenosyl homocysteine** are also part of the pathway.
6. **Methyl group** is donated to biological substrate.
7. ATP and **PPi** are used in the reaction.

The pathway is regulated and essential for various biological 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.