2007-09

M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

<http://hdl.handle.net/2027.42/64946>
http://hdl.handle.net/2027.42/64946
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.
Folic acid

\[
\text{NH}_2-\text{N} \begin{array}{c} \text{CH}_2-\text{N} \\
\text{CH}_2-\text{N} \end{array} \text{O} \begin{array}{c} \text{COO}^- \text{O} \\
\text{N} \begin{array}{c} \text{CHCH}_2\text{C} \\
\text{C} \end{array} \text{OH} 
\end{array}
\]

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

Dihydrofolate

\[
\text{NH}_2-\text{N} \begin{array}{c} \text{CH}_2-\text{N} \\
\text{CH}_2-\text{N} \end{array} \text{O} \begin{array}{c} \text{COO}^- \text{O} \\
\text{N} \begin{array}{c} \text{CHCH}_2\text{C} \\
\text{C} \end{array} \text{OH} 
\end{array}
\]

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

Tetrahydrofolate

\[
\text{NH}_2-\text{N} \begin{array}{c} \text{CH}_2-\text{N} \\
\text{CH}_2-\text{N} \end{array} \text{O} \begin{array}{c} \text{COO}^- \text{O} \\
\text{N} \begin{array}{c} \text{CHCH}_2\text{C} \\
\text{C} \end{array} \text{OH} 
\end{array}
\]
Inhibitors of DHFR are important therapeutics:
Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
\[ \text{Gly, Ser} \rightarrow \text{N}^4, \text{N}^8 \text{ methylene tetrahydrofolate} \rightarrow \text{Biosynthesis of thymidylate} \]

\[ \text{N}^4 \text{ methylenetetrahydrofolate} \rightarrow \text{NAD}^+ \rightarrow \text{NADH + H}^+ \]

\[ \text{N}^4, \text{N}^8 \text{ methenyl tetrahydrofolate} \rightarrow \text{NADP}^+ \rightarrow \text{NADPH + H}^+ \]

\[ \text{N}^4 \text{ formyl tetrahydrofolate} \rightarrow \text{Biosyntheses of purines} \]

\[ \text{N}^4 \text{- methyl tetrahydrofolate} \]

\[ \text{N}^{14} \text{ formyl tetrahydrofolate} \]
Methionine Cycle And Biological Methyl Groups
\[
\text{homocysteine} \xrightarrow{\text{vitamin B}_12} \text{methionine}
\]
Other methyl acceptors:
DNA ("CpG Islands")
RNA

Methionine

\[
\begin{align*}
&\text{NH}_3^+ \\
&-\text{OOC} - \text{C} - \text{CH}_2 \text{CH}_2 \text{SC} \text{H}_3 \\
&\text{H}
\end{align*}
\]

\[\text{Methionine} \rightarrow \text{ATP} \rightarrow \text{PP}_i + \text{P}_i \rightarrow \text{S-Adenosyl methionine}\]

Norepinephrine

\[
\begin{align*}
&\text{OH} \\
&\text{OH} - \text{C} - \text{CH}_2 - \text{NH}_3^+ \\
&\text{H}
\end{align*}
\]

\[\text{Norepinephrine} \rightarrow \text{SAM} \rightarrow \text{SAH} \rightarrow \text{Epinephrine}\]

Epinephrine
**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.