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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 $\rightarrow$ glycine + $\text{N}^6,\text{N}^{10}$-methylene tetrahydrofolate

Tetrahydrofolate + glycine $\rightarrow$ $\text{N}^6,\text{N}^{10}$-methylene tetrahydrofolate
\[
\text{Gly} \quad \text{Ser} \quad \rightarrow \quad \text{N}^4, \text{N}^6 \text{methylene tetrahydrofolate} \quad \rightarrow \quad \text{Biosynthesis of thymidylate}
\]

\[
\text{N}^4, \text{N}^6 \text{methylene tetrahydrofolate} \quad \rightarrow \quad \text{Biosynthesis of purines}
\]

\[
\text{N}^4 \text{ methyl tetrahydrofolate} \quad \rightarrow \quad \text{Biosynthesis of methionine}
\]

\[
\text{N}^4 \text{ formyl tetrahydrofolate}
\]
Methionine Cycle
And Biological Methyl Groups
Homocysteine → \( N^\epsilon \)-methyl THF → Vitamin \( B_12 \) → Methionine.
Carbon donor (e.g., serine or glycine)

Tetrahydrofolate

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

NADH + H^+

methionine

homocysteine

\[ \text{N}^\ddagger \text{ methyl tetrahydrofolate} \]
Other methyl acceptors:

DNA ("CpG Islands")
RNA

Methionine

\[
\begin{align*}
\text{OOC} & \quad \text{C} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{SCH}_3 \\
\text{H} & \quad \text{H}
\end{align*}
\]

ATP \rightarrow PP_i + P_i

S-Adenosyl methionine

\[
\begin{align*}
\text{OOC} & \quad \text{C} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{SCH}_3 \\
\text{H} & \quad \text{CH}_2
\end{align*}
\]

Norepinephrine

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

SAM \rightarrow SAH

Epinephrine

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{HO} & \quad \text{C} \quad \text{CH}_2 \quad \text{N} \quad \text{CH}_3 \\
\text{H} & \quad \text{H}
\end{align*}
\]
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.