M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

http://hdl.handle.net/2027.42/64946
Unless otherwise noted, the content of this course material is licensed under a Creative Commons Attribution – Share Alike 3.0 License.

Copyright 2007, Robert Lyons.

The following information is intended to inform and educate and is not a tool for self-diagnosis or a replacement for medical evaluation, advice, diagnosis or treatment by a healthcare professional. You should speak to your physician or make an appointment to be seen if you have questions or concerns about this information or your medical condition. You assume all responsibility for use and potential liability associated with any use of the material.

Material contains copyrighted content, used in accordance with U.S. law. Copyright holders of content included in this material should contact open.michigan@umich.edu with any questions, corrections, or clarifications regarding the use of content. The Regents of the University of Michigan do not license the use of third party content posted to this site unless such a license is specifically granted in connection with particular content objects. Users of content are responsible for their compliance with applicable law. Mention of specific products in this recording solely represents the opinion of the speaker and does not represent an endorsement by the University of Michigan.

Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
Amino Acid metabolism

Amino acids

Glu, Gln, Asp, NH₃

Urea

Folate metabolism

Methylene THF

Methyl Cycle

Nucleic Acid metabolism

Purines

DNA

RNA

Pyrimidines

Uric Acid

(energy)
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 $\xrightleftharpoons{}$ H$_2$O + glycine

$\text{NH}_2\text{N}^-\text{C}^-\text{H} \quad \text{NH}_3^+\text{C}^-\text{H} + \text{N}^\delta, \text{N}^{\delta'} \text{methylene tetrahydrofolate}$

Tetrahydrofolate + glycine $\xrightleftharpoons{}$ NAD$^+$ + NADH

$\text{NH}_2\text{N}^-\text{C}^-\text{H} \quad \text{NH}_3^+\text{C}^-\text{H} + \text{N}^\delta, \text{N}^{\delta'} \text{methylene tetrahydrofolate}$
N\textsuperscript{5} methyl tetrahydrofolate $\rightarrow$ Biosynthesis of methionine

Gly, Ser $\leftarrow$ N\textsuperscript{5}, N\textsuperscript{10} methylene tetrahydrofolate $\rightarrow$ Biosynthesis of thymidylate

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

N\textsuperscript{10} formyl tetrahydrofolate $\rightarrow$ Biosyntheses of purines

\[\text{N}\textsuperscript{5}\text{-methyl tetrahydrofolate}\]

\[\text{N}\textsuperscript{10}\text{formyl tetrahydrofolate}\]
Methionine Cycle
And Biological Methyl Groups
homocysteine → \textit{N}^\text{6} -\text{methyl} \text{ THF} \rightarrow \text{THF} \rightarrow \text{methionine}
Carbon donor (e.g., serine or glycine)

Tetrahydrofolate

N^6, N^6 methylene tetrahydrofolate

NADH + H^+

NAD^+

Methionine

Homocysteine

N^6 methyl tetrahydrofolate
Other methyl acceptors:
DNA ("CpG Islands")
RNA

Methionine

S-Adenosyl methionine

Norepinephrine

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.