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M1 - Renal, Fall 2007

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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

oxaloacetate

fumarate

TCA Cycle

Folate metabolism

Methylene THF

Met Cycle

Purines

DNA

RNA

Pyrimidines

Uric Acid

(energy)

Nucleic Acid metabolism
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 $+ N^6, N^{10}$ methylene tetrahydrofolate

Tetrahydrofolate $+ NH_2C(-)H \rightarrow N^6, N^{10}$ methylene tetrahydrofolate
Methionine Cycle And Biological Methyl Groups
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

N^6, N^4 methylene tetrahydrofolate

methionine

homocysteine

NADH + H^+

NAD^+

N^4 methyl tetrahydrofolate
Other methyl acceptors:
DNA ("CpG Islands")
RNA
The image depicts a metabolic pathway involving the conversion of homocysteine to methionine. The process involves several key steps:

1. **Homocysteine** is converted to **S-adenosyl homocysteine** by the enzyme adenosyltransferase.
2. **S-adenosyl homocysteine** is then converted to **S-adenosyl methionine** by the enzyme adenosyltransferase, with the methyl group being donated to biological substrate.
3. **S-adenosyl methionine** can be reconverted to **homocysteine** and **adenosine** through the action of adenosyltransferase.
4. **Adenosine** is then deaminated to form **NH₃** and **adenosine**.
5. **Methionine** is converted to **S-adenosyl methionine** by the enzyme adenosyltransferase, with the methyl group being transferred to a biological substrate.
6. **Methyl group donation** occurs through the transfer of **N⁵-methyl THF** to the biological substrate, facilitated by **NAD⁺**.

The pathway is driven by enzymes and co-factors such as **NAD⁺**, **NADH**, and **vitamin B₁₂**. The final product is **methionine**, which can be further metabolized or used for biosynthesis.
**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.