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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

Folate metabolism

Methylene THF

Met Cycle

oxaloacetate

fumarate

TCA Cycle

Nucleic Acid metabolism

Purines DNA RNA Pyrimidines

Uric Acid (energy)
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
$N^\prime$-methyl tetrahydrofolate

Biosynthesis of methionine

$N^\prime, N^\prime$-methylenetetrahydrofolate

Biosynthesis of thymidylate

$N^\prime$-formyl tetrahydrofolate

Biosyntheses of purines

$N^\prime$-methyl tetrahydrofolate

$N^\prime\prime$-formyl tetrahydrofolate
Methionine Cycle
And Biological Methyl Groups
Carbon donor (e.g., serine or glycine)

Tetrahydrofolate

Carbon donor (e.g., serine or glycine)

N^6, N^5 methylmethylenetetrahydrofolate

NADH + H^+

methionine

homocysteine

N^5 methyl tetrahydrofolate

NAD^+
Other methyl acceptors:
DNA ("CpG Islands")
RNA

- Methionine
- S-Adenosyl methionine
- Norepinephrine
- Epinephrine
The diagram illustrates the methylation cycle, showing the conversion of homocysteine to methionine, and the reverse reaction. Key steps include:

1. Homocysteine is converted to S-adenosyl homocysteine (SAH) using ATP and PPi.
2. SAH donates a methyl group to S-adenosyl methionine (SAM) to form homocysteine and methylated SAM.
3. SAM is used in various biological reactions, including protein modification.
4. The cycle is fueled by NADH and vitamin B12.

Key molecules and reactions:
- Homocysteine
- Adenosine
- S-adenosyl homocysteine
- S-adenosyl methionine
- NADH
- Vitamin B12
- ATP
- PPi
**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.