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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 $\xrightarrow{\text{H}_2\text{O}}$ glycine + $\text{N}^\delta$, $\text{N}^{\delta'}$ methylene tetrahydrofolate

Tetrahydrofolate + glycine $\xrightarrow{\text{NAD}^+}$ $\text{N}^\delta$, $\text{N}^{\delta'}$ methylene tetrahydrofolate
The diagram illustrates the biosynthesis pathways involving tetrahydrofolate derivatives. Key compounds and reactions include:

- **N^1-methyl tetrahydrofolate**
- **N^1, N^4-methylene tetrahydrofolate**
- **N^1-formyl tetrahydrofolate**

The biosynthesis of methionine involves the conversion of NAD and NADH to NAD^+ and NADPH. Similarly, the biosynthesis of thymidylate involves the conversion of NADP and NADPH to NADP^+ and NADP^H.

For purines, the process involves the conversion of NAD^+ and NADPH to NADP^+ and NADP^H, respectively.

Additionally, the diagram features structural representations of N^1-methyl tetrahydrofolate and N^1-formyl tetrahydrofolate, with specific functional groups highlighted.
Methionine Cycle
And Biological Methyl Groups
\[
\text{homocysteine} \xrightarrow{\text{vitamin B}_12} \text{methionine}
\]
Tetrahydrofolate

Carbon donor (e.g. serine or glycine)

N^6, N^4 methylene tetrahydrofolate

methionine

homocysteine

N^4 methyl tetrahydrofolate

NADH + H^+

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

\[
\text{Methionine} \rightarrow \text{S-Adenosyl methionine}
\]

\[
\text{Norepinephrine} \rightarrow \text{Epinephrine}
\]
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.