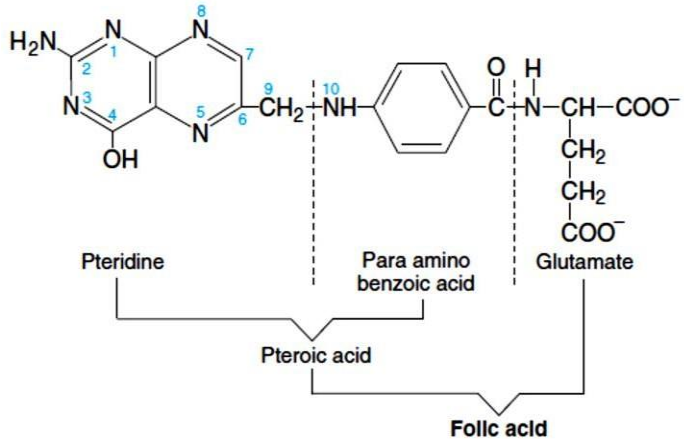
ONE-CARBON METABOLISM and METABOLIC DISEASES

The degradation pathways for several amino acids produce one-carbon units that are transferred to tetrahydrofolate (H_4folate or THF) as an **intermediate carrier**. Tetrahydrofolate, in turn, donates the single carbons to various biosynthetic intermediates.

The following **one-carbon units** are encountered in the biological reactions, which constitute one-carbon pool

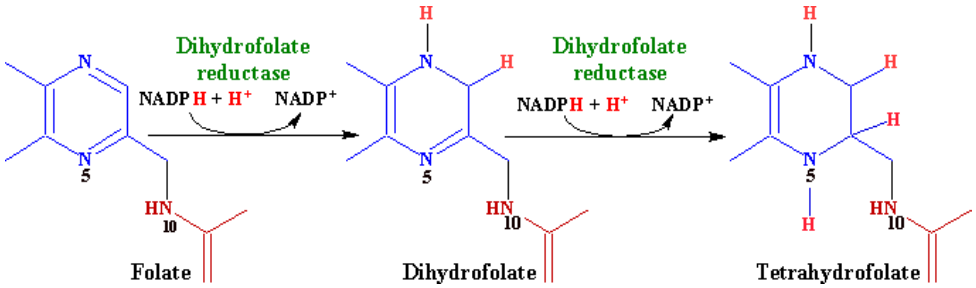
Methyl ($-CH_3$)
Methylene ($=CH_2$)
Methenyl ($-CH=$)
Hydroxymethyl ($-CH_2OH$)
Formyl ($-CH=O$)
Formimino ($-CH=NH$)

Folic acid is the vitamin as it is found in the diet. It consists of three distinct moieties: a **pteridine** moiety, a ***p*-aminobenzoate (PABA)** moiety, and one or several **glutamate residues**. Mammals can synthesize these components, but lack the enzymes necessary for their conjugation. The number of **glutamate residues** containedin folic acid or THF **changes** at various stages of transport and utilization. Intestinal uptake and transport through the blood occur with only one glutamate attached. After uptake into liver cells, several more glutamate residues are added.



The metabolically active form of folate is THF, which is formed from folate in two successive NADPH-dependent reductions, both catalyzed by the same enzyme, namely, **dihydrofolate reductase**. The hydrogen atoms are present at positions 5, 6, 7 and 8 of THF.

The one-carbon unit covalently binds with THF at position N^5 or N^{10} or on both N^5 and N^{10} of pteroyl structure of folate.

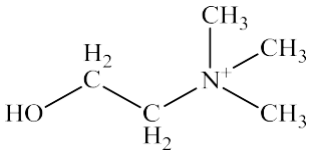


The one-carbon metabolism is rather complex, involving many reactions. For the sake of better understanding, it is divided into generation and utilization of one-carbon units, and the role of methionine and vitamin B_{12}.

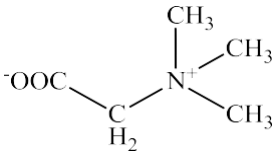
I. Generation of one-carbon units

Many compounds (**particularly amino acids**) act as donors of one-carbon fragments:

1. When serine is converted to glycine, N^5, N^{10}-methylene THF is formed. This is the most predominant entry of one-carbon units into one-carbon pool.
2. The formate released from tryptophan metabolism combines with THF to form N^{10}-formyl THF.
3. Histidine contributes formimino fragment to produce N^5-formimino THF.
4. Choline and betaine contribute to the formation of N^5-methyl THF.



Choline



Betaine

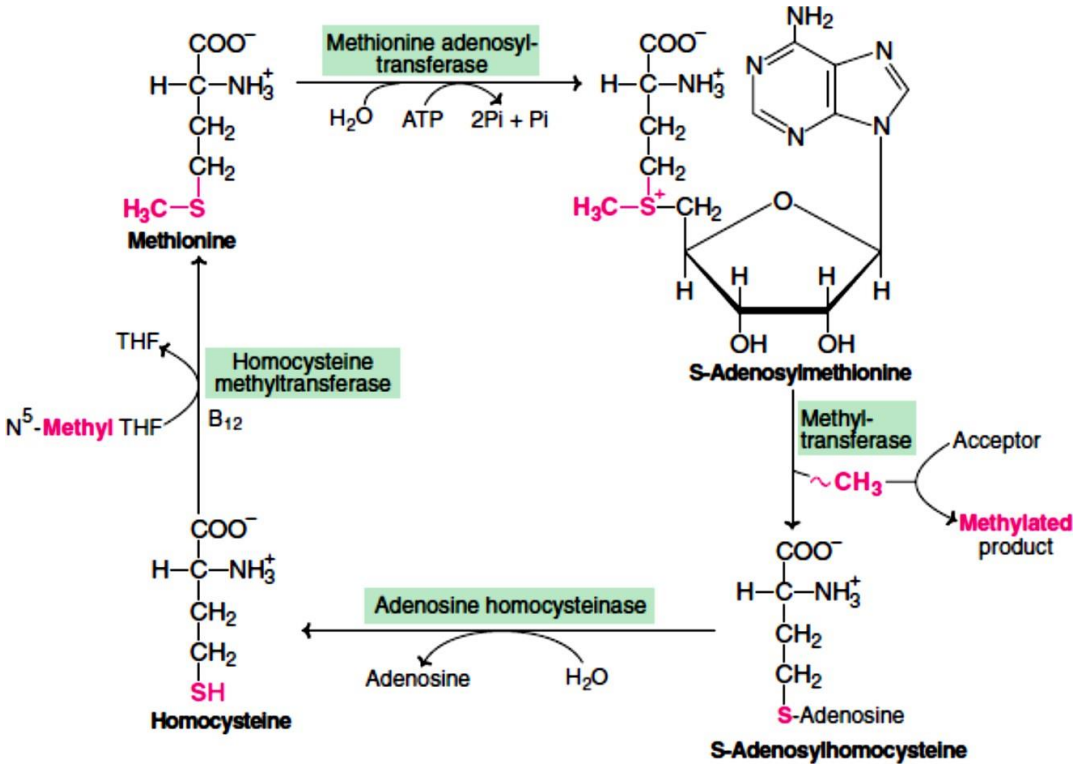
The different derivatives of THF carrying one-carbon units are interconvertible, and this is metabolically significant for the continuity of one-carbon pool.

II. Utilization of one-carbon moieties

One-carbon fragments from THF are used for the **synthesis** of a wide variety of compounds. These include purines and pyrimidine nucleotide (thymidylate), formylmethionine (required for initiation of protein synthesis in bacteria), glycine, etc.

III. Role of methionine and B_{12} in one-carbon metabolism

Methyl ($-CH_3$) group is an important one-carbon unit in many biosynthetic reactions. The role of active methionine as methyl donor in transmethylation reactions is good example. Although *tetrahydrofolate* can carry a *methyl group* at N-5, the methyl group's *transfer potential is insufficient* for most biosynthetic reactions. **S-Adenosylmethionine** is more commonly used for methyl group transfers. It is synthesized from ATP and methionine by the action of **methionine adenosyl-transferase**. This reaction is unusual in that the nucleophilic sulfur atom of methionine attacks at the 5' carbon of the ribose moiety of ATP, releasing triphosphate, rather than attacking at one of the phosphorus atoms. S-Adenosylmethionine is a potent alkylating agent by virtue of its destabilizing sulfonium ion. The methyl group is subject to attack by nucleophiles and is about 1,000 times more reactive than the methyl group of N^5-methyltetrahydrofolate.



After the **release of methyl group**, methionine is converted to homocysteine. For the regeneration of methionine, free homocysteine and N^5-methyl THF are required and this reaction is dependent on methylcobalamin (vitamin B_{12}). The one-carbon pool, under the control of THF, is linked with methionine metabolism (transmethylation) through vitamin B_{12}. Hence, vitamin B_{12} is also involved in one-carbon metabolism.

- ✓ Folate deficiency impairs DNA synthesis and cell division resulting in many clinical conditions such as macrocytic anemia and neural tube defects in pregnancy (spina bifida or anencephaly).

- ✓ Folic acid antagonists:

Methotrexate (structural analogue of folic acid), competitively inhibits dihydrofolate reductase, is used in the treatment of leukemia.

Sulfonamides (structural analogues of PABA), competitively inhibit the enzyme responsible for the conjugation of PABA in folic acid molecule, are antibacterial agents.

Note:

Some authors consider **CO_2 as a one-carbon unit**, others do not agree. Carbon dioxide is involved in many biochemical reactions (**carboxylation**); **biotin** serves as a carrier of CO_2 in these reactions. For instance, **conversion of pyruvate to oxaloacetate in gluconeogenesis**.

Metabolic Diseases of Amino Acid Catabolism

Defective synthesis or decreased activity of enzymes involved in amino acid catabolism is associated with many metabolic diseases.
Metabolic defects in transaminases, which fulfill central metabolic functions, may be incompatible with life.

Proline

There are two metabolic disorders of proline catabolism.
The metabolic block in **type I hyperprolinemia** is at **proline dehydrogenase**.
The metabolic block in **type II hyperprolinemia** is at **Δ^1-pyrroline-5-carboxylate dehydrogenase**, which also participates in the catabolism of arginine, and ornithine. Since proline and hydroxyproline catabolism are affected, both *Δ^1-pyrroline-5-carboxylate* and *Δ^1-pyrroline-3-hydroxy-5-carboxylate* are excreted.
Hyperpolinemia is associated with seizures, intellectual disability, or other neurological problems.

Arginine and Ornithine

Mutations in **ornithine transaminase** elevate **plasma** and **urinary ornithine** and are associated with **gyrate atrophy of the choroid and retina.** Treatment involves restricting dietary arginine.

Note:
Defective arginase is associated with hyperargininemia
In the **hyperornithinemia–hyperhomocitrulinuria-hyperammonemia syndrome,** a defective mitochondrial **ornithine permease** impairs transport of ornithine into mitochondria where it participates as an intermediate in urea synthesis.

Histidine

Benign disorders of histidine catabolism include **histidinemia** and **urocanic aciduria** associated with impaired **histidase and urocanase,** respectively.
In **folic acid deficiency,** transfer of the formimino group is impaired, and formiminoglutamate (Figlu) is excreted.

Note:
Excretion of Figlu following a dose of histidine thus can be used to detect folic acid deficiency.

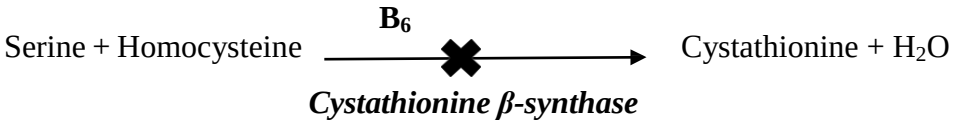
Glycine

Nonketotic hyperglycinemia or **Glycine encephalopathy,** is a rare inborn error of glycine degradation, due to defective **glycine cleavage complex**. Glycine accumulates in all body tissues including the central nervous system.
The defect in **primary hyperoxaluria** is the failure to catabolize **glyoxylate** formed

by the deamination of glycine. Subsequent oxidation of glyoxylate to **oxalate** results in urolithiasis, nephrocalcinosis, and early mortality from renal failure or hypertension.

Cystine and Cysteine

Homocystinurias (vitamin B_6-responsive or vitamin B_6-unresponsive) result from a deficiency in the reaction catalyzed by **cystathionine β-synthase**:



Consequences include osteoporosis and mental retardation.

Note:
Epidemiologic and other data link **plasma homocysteine levels** to cardiovascular diseases risk, but the role of homocysteine as a causal cardiovascular risk factor remains controversial.

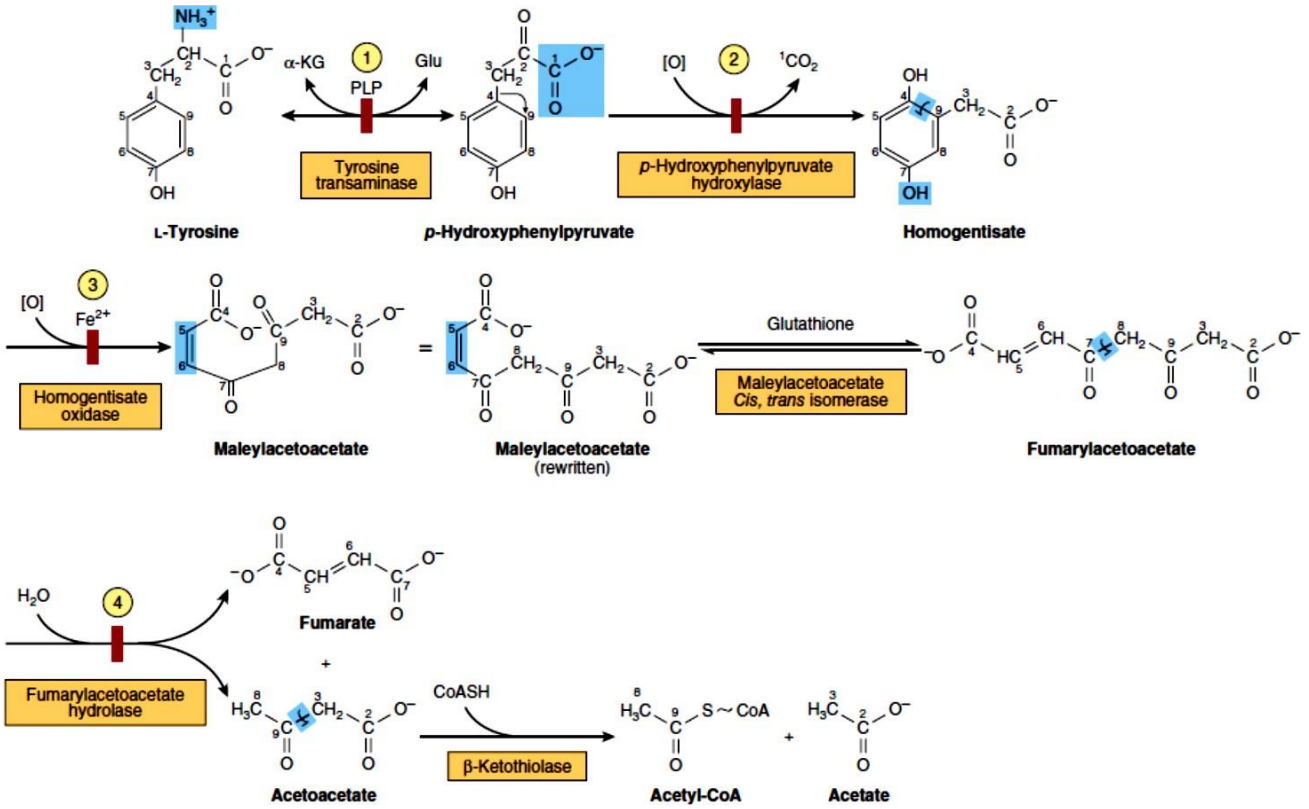
Tyrosine

Several metabolic disorders are associated with the tyrosine catabolic pathway:

- ✓ **Type I tyrosinemia (tyrosinosis)** results from defective **fumarylacetoacetate hydrolase**.
- ✓ **Type II tyrosinemia (Richner-Hanhart syndrome),** a defect in **tyrosine aminotransferase**.
- ✓ **Neonatal tyrosinemia,** due to lowered activity of ***p*-hydroxyphenylpyruvate hydroxylase**.
- ✓ **Alkaptonuria** is a defective **homogentisate oxidase**. The urine darkens on exposure to air due to oxidation of excreted homogentisate. Late in the disease, there is arthritis and connective tissue pigmentation (ochronosis) due to oxidation of homogentisate to benzoquinone acetate, which polymerizes and binds to connective tissue.

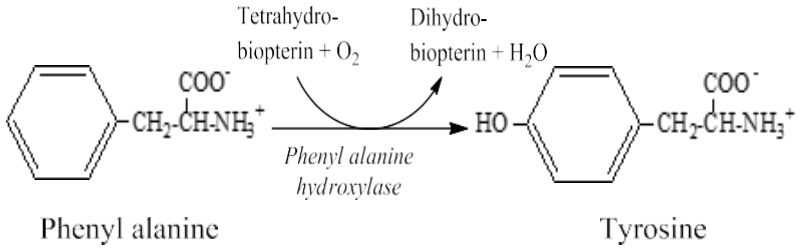
Except for alkaptonuria, these disorders result in elevated blood tyrosine levels.

Hypertyrosinemia results in liver disease or neurologic abnormalities, such as seizures or developmental delay. Therapy employs a diet low in tyrosine and phenylalanine.

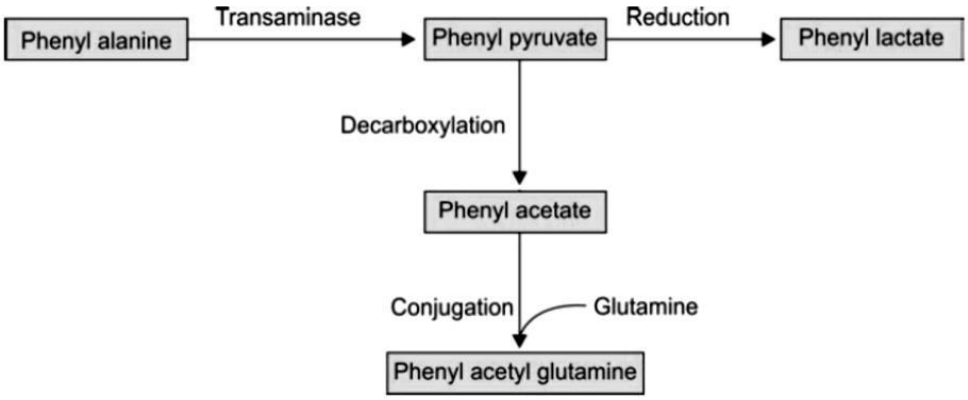


Phenylalanine

Hyperphenylalaninemias arise from defects in **phenylalanine hydroxylase** (**type I, classic phenylketonuria (PKU)**), in **dihydrobiopterin reductase** **(types II and III),** or in dihydrobiopterin biosynthesis **(types IV and V)**.



There are two routes by which the excess phenylalanine can be metabolized: oxidation to tyrosine (the normal and main route for degradation of phenylalanine, and the normal route for biosynthesis of tyrosine), and transamination to phenylpyruvate and subsequent further metabolism to phenyl lactate, phenylacetate, and phenylacetyl glutamine (a minor route, which comes to the fore when the main route is blocked).



- ✓ A diet low in phenylalanine can prevent the mental retardation of PKU.
- ✓ Elevated blood phenylalanine may not be detectable until 3 to 4 days postpartum.
- ✓ False-positives in premature infants may reflect delayed maturation of enzymes of phenylalanine catabolism.

Branched chain amino acids

Defect in the **α-keto acid dehydrogenase complex** results in **maple syrup urine disease (MSUD)** or **branched-chain ketonuria**. As the name implies, the odor of urine in suggests maple syrup, or burnt sugar.
Plasma and urinary levels of leucine, isoleucine, valine, and their α-keto acids and α-hydroxy acids (reduced α-keto acids) are elevated, but the urinary keto acids derive principally from leucine.

Signs and symptoms of MSUD include often, fatal ketoacidosis, neurological derangements, mental retardation, and a maple syrup odor of urine.

In **intermittent branched-chain ketonuria,** the α-keto acid dehydrogenase retains some activity, and symptoms occur later in life.