Aromatic amino acids AND Sulfur containing amino acids

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I) Catabolic pathways Aromatic amino acids

Aromatic Amino Acids

Aromatic amino acids **phenylalanine & tyrosine** are catabolized to **fumarate** and **acetoacetate**.

Hydroxylation of **phenylalanine** to form tyrosine involves the reductant **tetrahydrobiopterin**. Biopterin, like folate, has a pteridine ring.

Dihydrobiopterin is reduced to tetrahydrobiopterin by electron transfer from **NADH**.

Thus NADH is secondarily the e^- donor for conversion of phenylalanine to tyrosine.

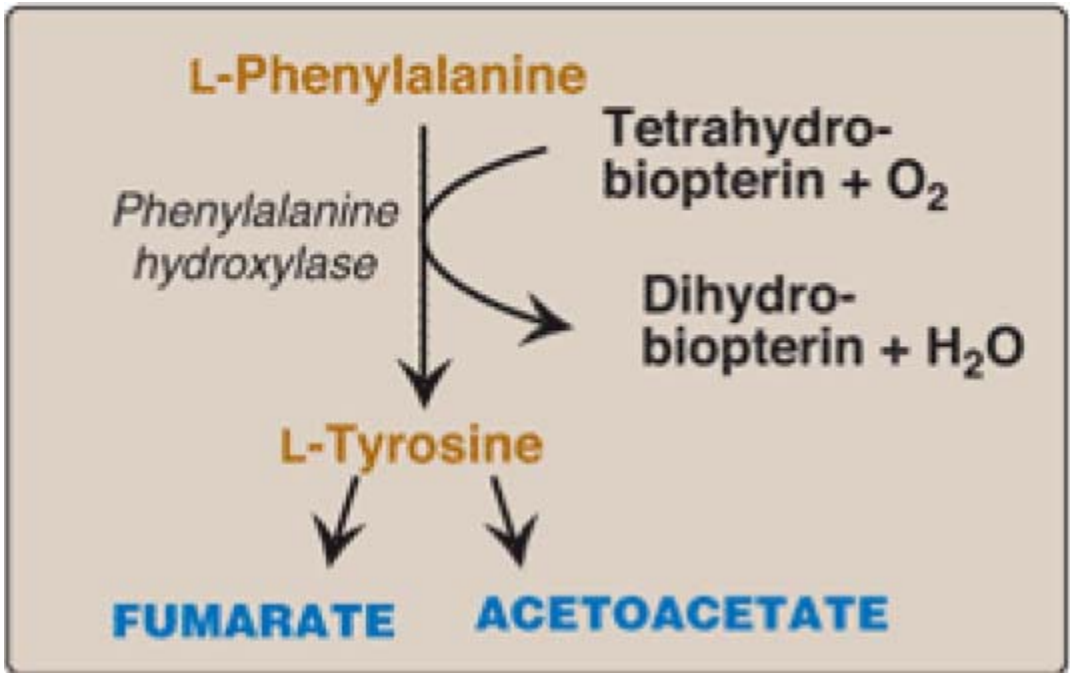
Phe and Tyr are degraded to fumarate and acetoacetate

- The first step in Phe degradation is conversion to Tyr so both amino acids are degraded by the same pathway.

- Total=6 reactions to form fumarate and acetoacetate.

Amino Acids that enter metabolism as fumarate

Phenylalanine and Tyrosine



Phenylalanine —hydroxylated→ Tyrosine → Fumarate
Tyrosine → Acetoacetate

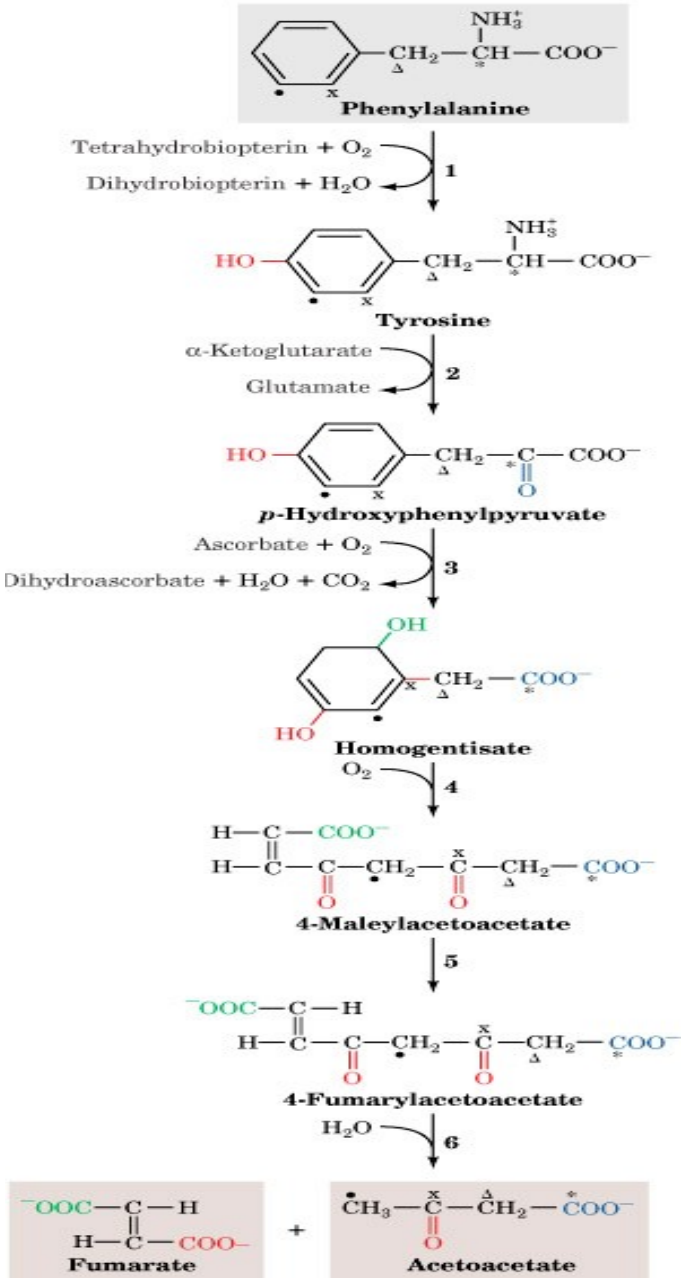
Hence these two aa are both glucogenic and ketogenic

Phe and Tyr are degraded to fumarate and acetoacetate

- The first step in Phe degradation is conversion to Tyr so both amino acids are degraded by the same pathway.
- 6 reactions

Phe and Tyr are degraded to fumarate and acetoacetate in 6 step reactions

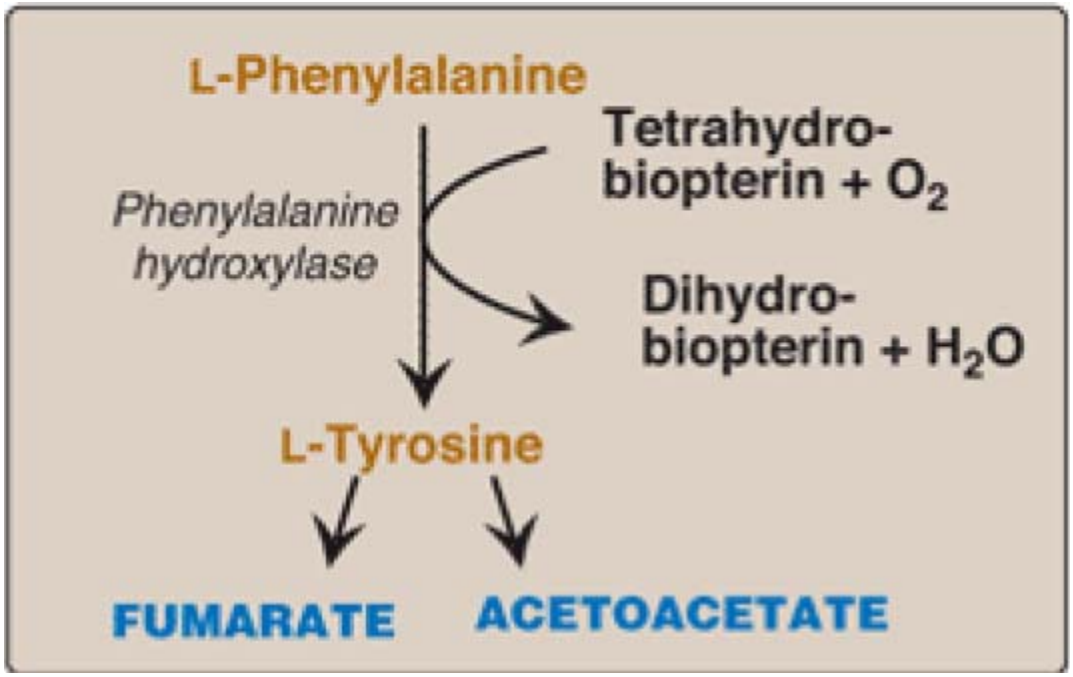
1. Phenylanalnine hydroxylase
2. Aminotransferase
3. p-hydroxyphenylpyruvate dioxygenase
4. Homogentisate dioxygenase
5. Maleylacetoacetate isomerase
6. Fumarylacetoacetase



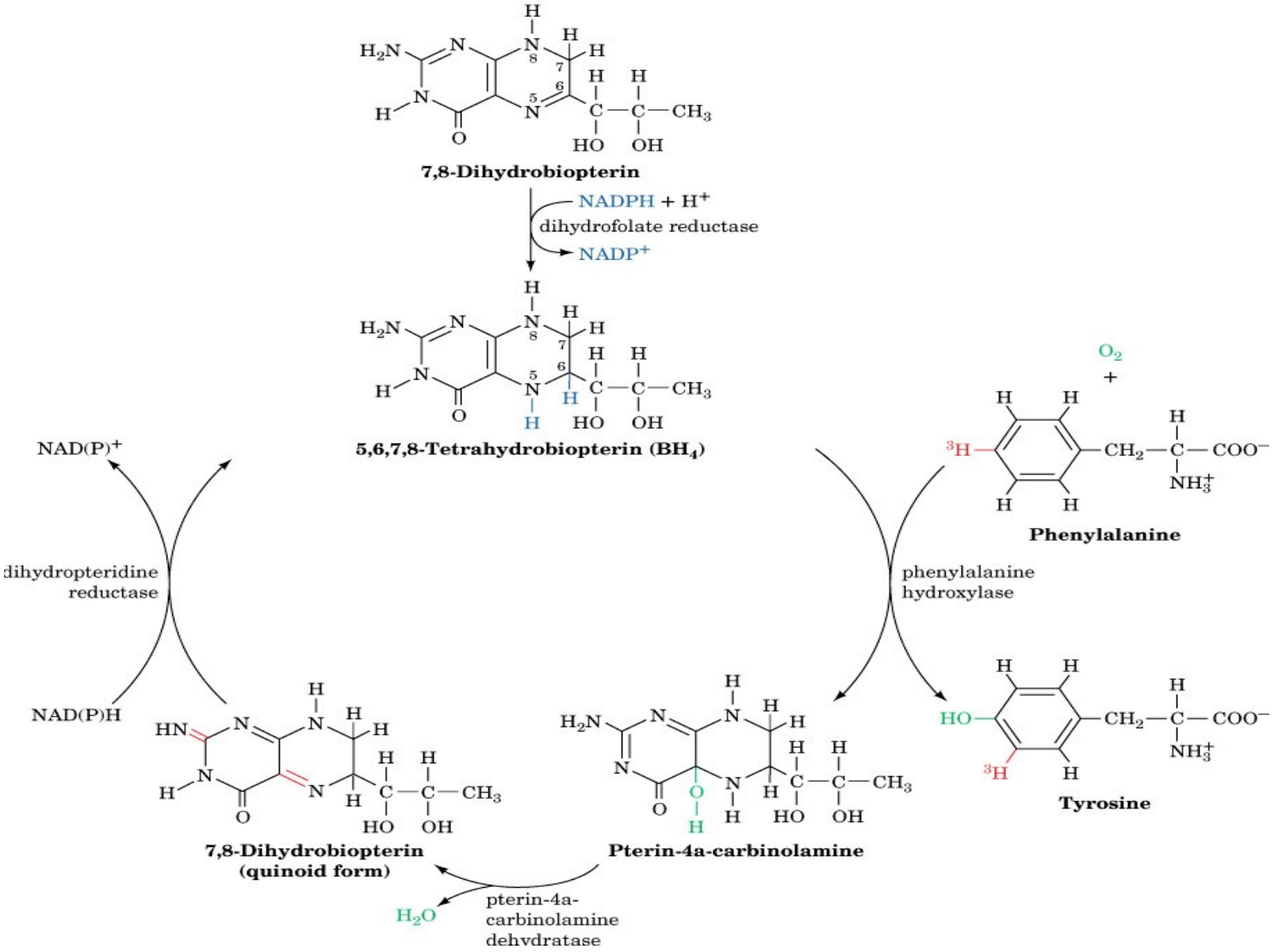
Phenylalanine hydroxylase has biopterin cofactor

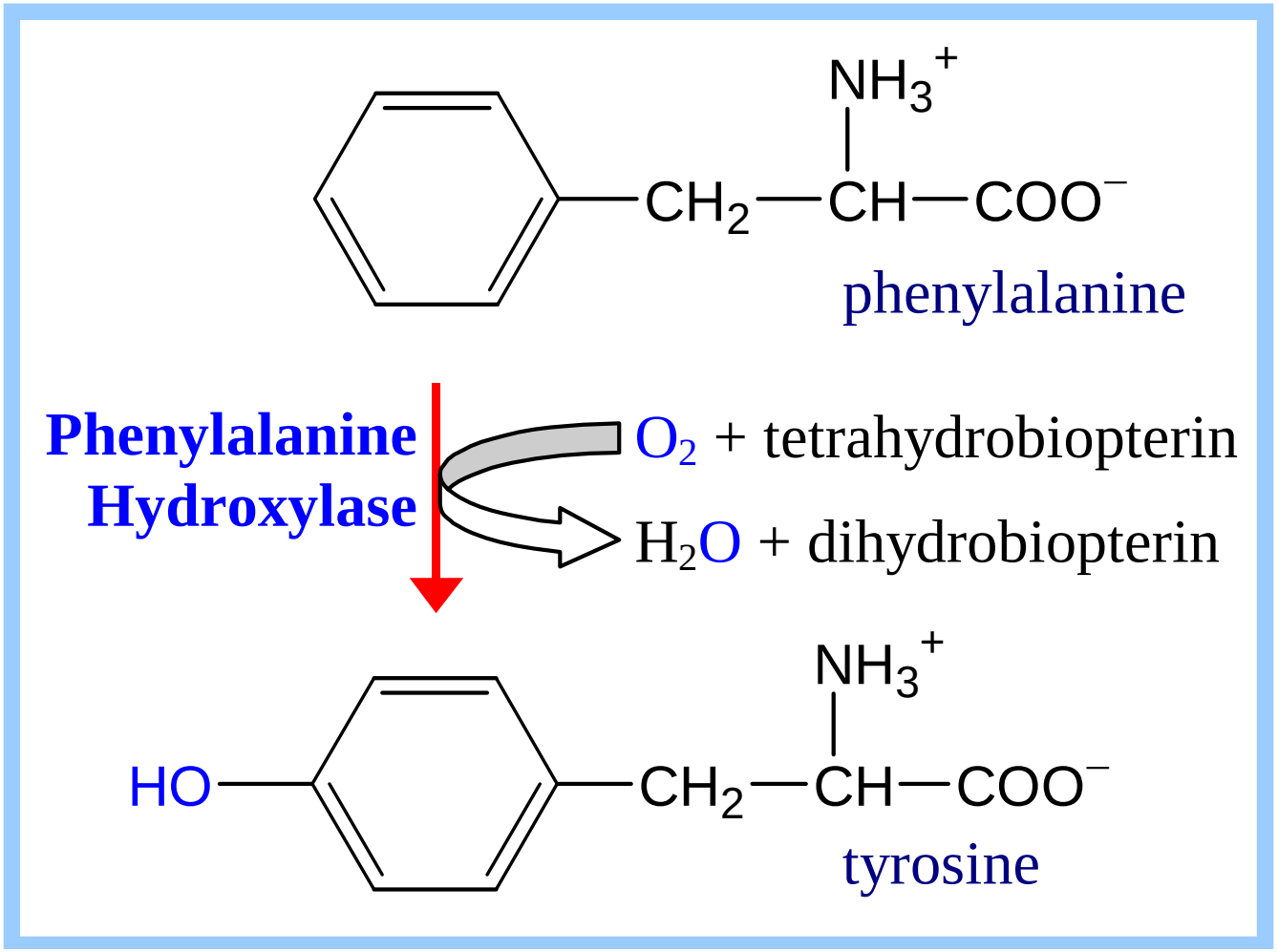
- 1st reaction is a hydroxylation reaction by **phenylalanine hydroxylase (PAH)**, a non-heme-iron containing homotetrameric enzyme.
- Requires O2, FeII, and **biopterin** a **pterin derivative.**
- **Pterins have a pteridine ring (similar to flavins)**
- **Folate derivatives (THF) also contain pterin rings.**

Active Tetrahydrobiopterin (BH_4) must be regenerated



Active BH_4 must be regenerated



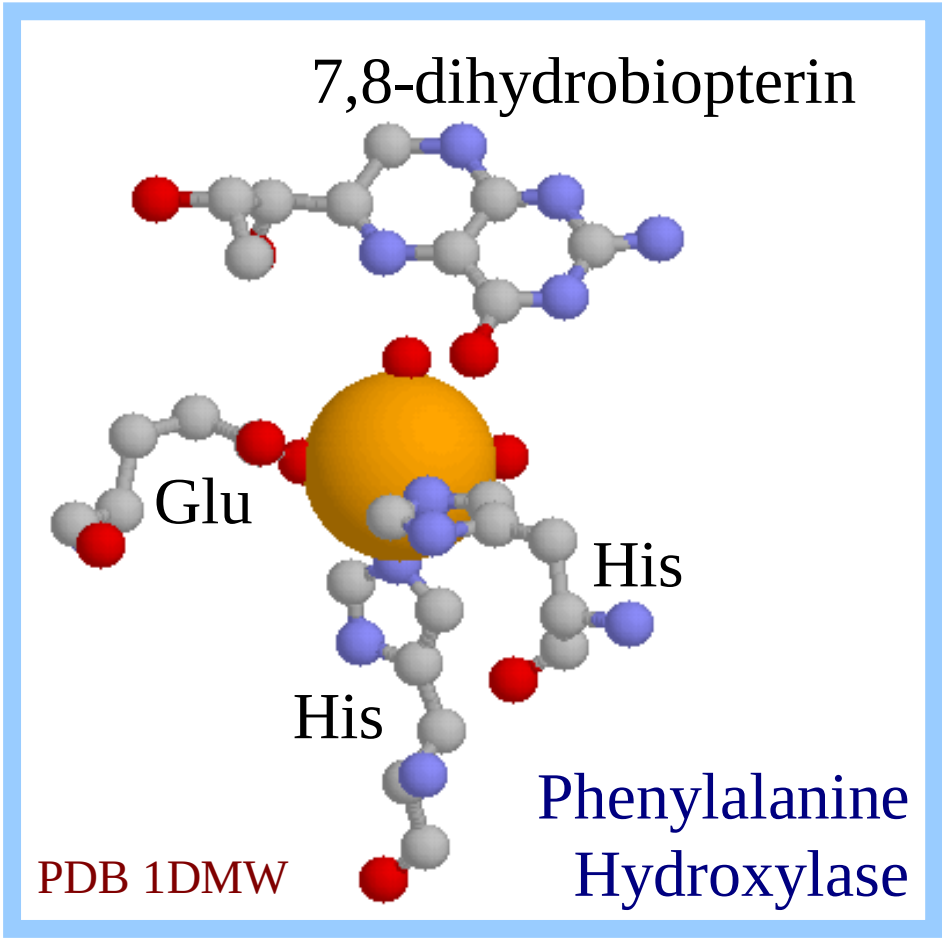


Overall the reaction is considered a **mixed function oxidation**, because one O atom of O_2 is reduced to water while the other is incorporated into the amino acid product.

Phenylalanine Hydroxylase includes a non-heme **iron** atom at its active site.

X-ray crystallography has shown the following are **ligands** to the iron atom:

His N, Glu O & water O. (Fe shown in spacefill & ligands in ball & stick).

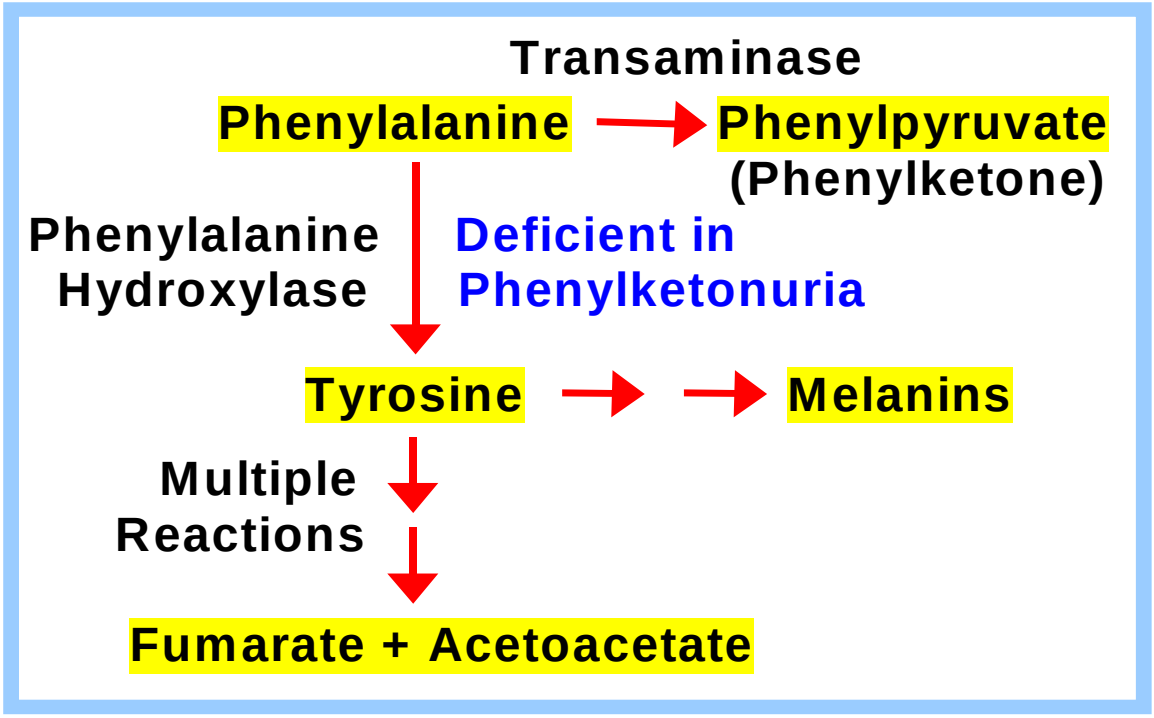


O_2, tetrahydrobiopterin, and the iron atom in the ferrous (Fe^{++}) oxidation state participate in the hydroxylation.

O_2 is thought to react initially with the tetrahydrobiopterin to form a peroxy intermediate.

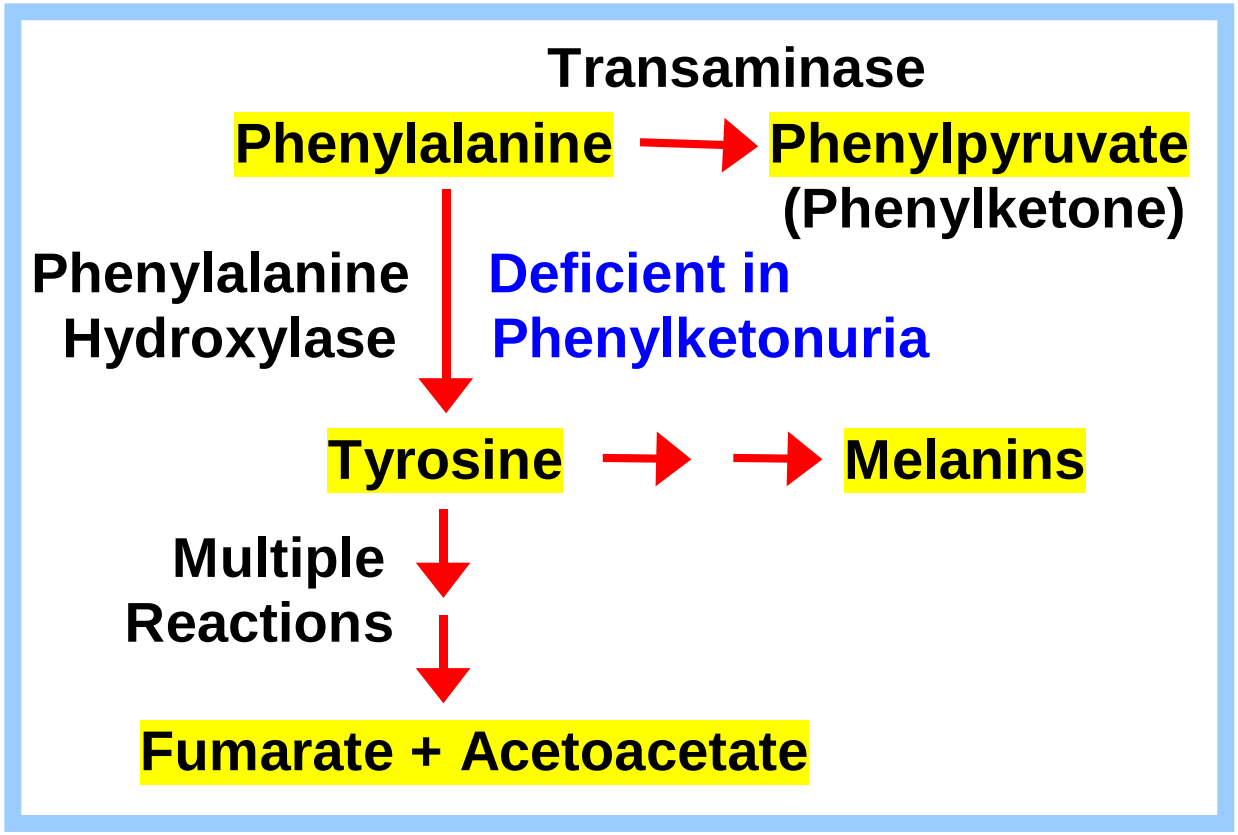
•Genetic deficiency of Phenylalanine Hydroxylase leads to the disease **phenylketonuria**.

•Phenylalanine & phenylpyruvate (the product of phenylalanine deamination via transaminase) accumulate in blood & urine.



•Mental retardation results unless treatment begins immediately after birth. **Treatment** consists of **limiting phenylalanine intake** to levels barely adequate to support growth.

•**Tyrosine**, an essential nutrient for individuals with phenylketonuria, must be supplied in the diet.

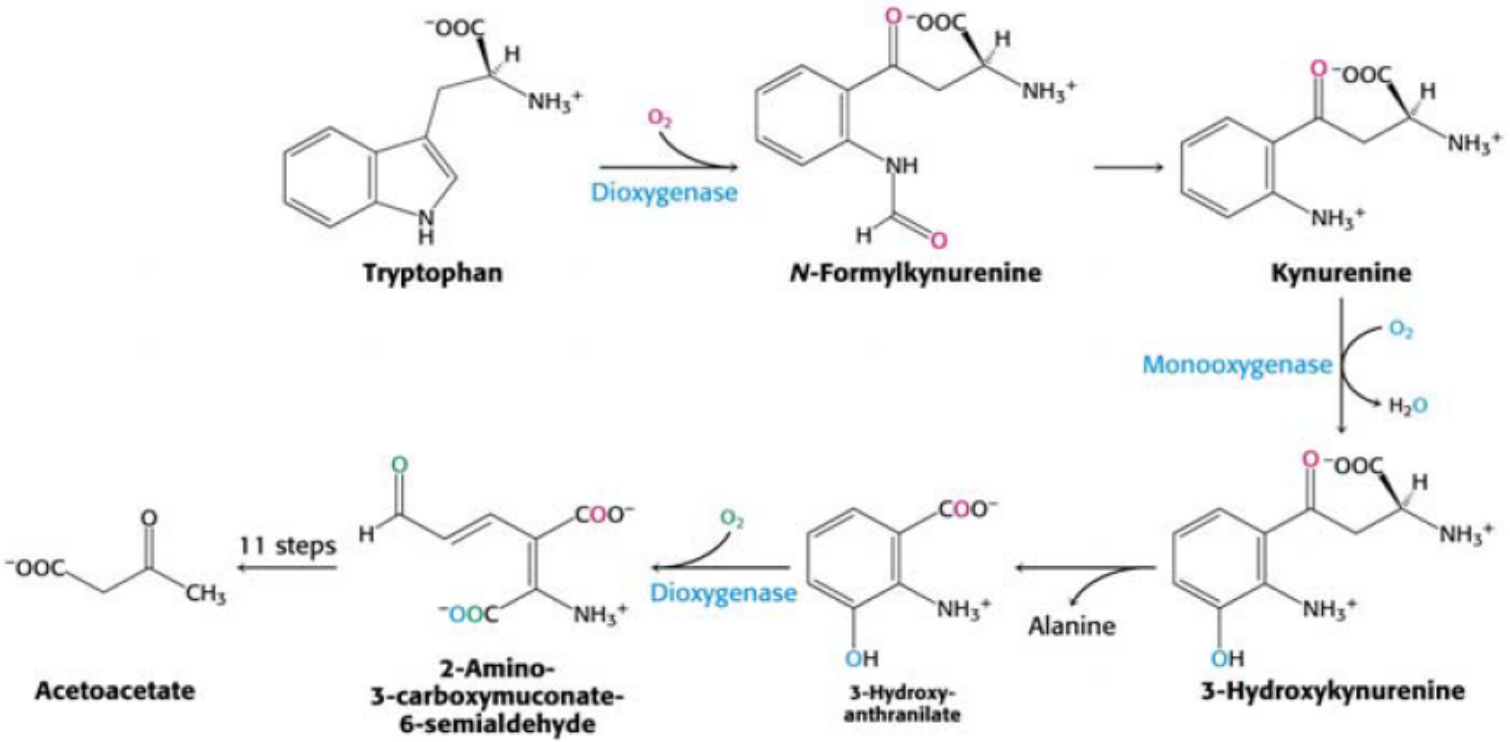


Tyrosine is a precursor for synthesis of melanins and of epinephrine and norepinephrine.

High [phenylalanine] inhibits Tyrosine Hydroxylase, on the pathway for synthesis of the pigment **melanin** from tyrosine. Individuals with phenylketonuria have light skin & hair color.

Tryptophan metabolism forms acetoacetate

Tryptophan catabolism is shown below:



Like phenylalanine catabolism, dioxygenases are required to catabolize the aromatic rings.

Catabolic pathways of Sulfur containing Amino Acids

1) Methionine

2) Cysteine

1) Methionine enter metabolism as succinyl CoA

•Converted into S-adenosylmethionine (SAM), (a major universal methyl donor in one-carbon metabolism)
•It is also a source of homocysteine---a metabolite associated with artherosclerotic vascular disease

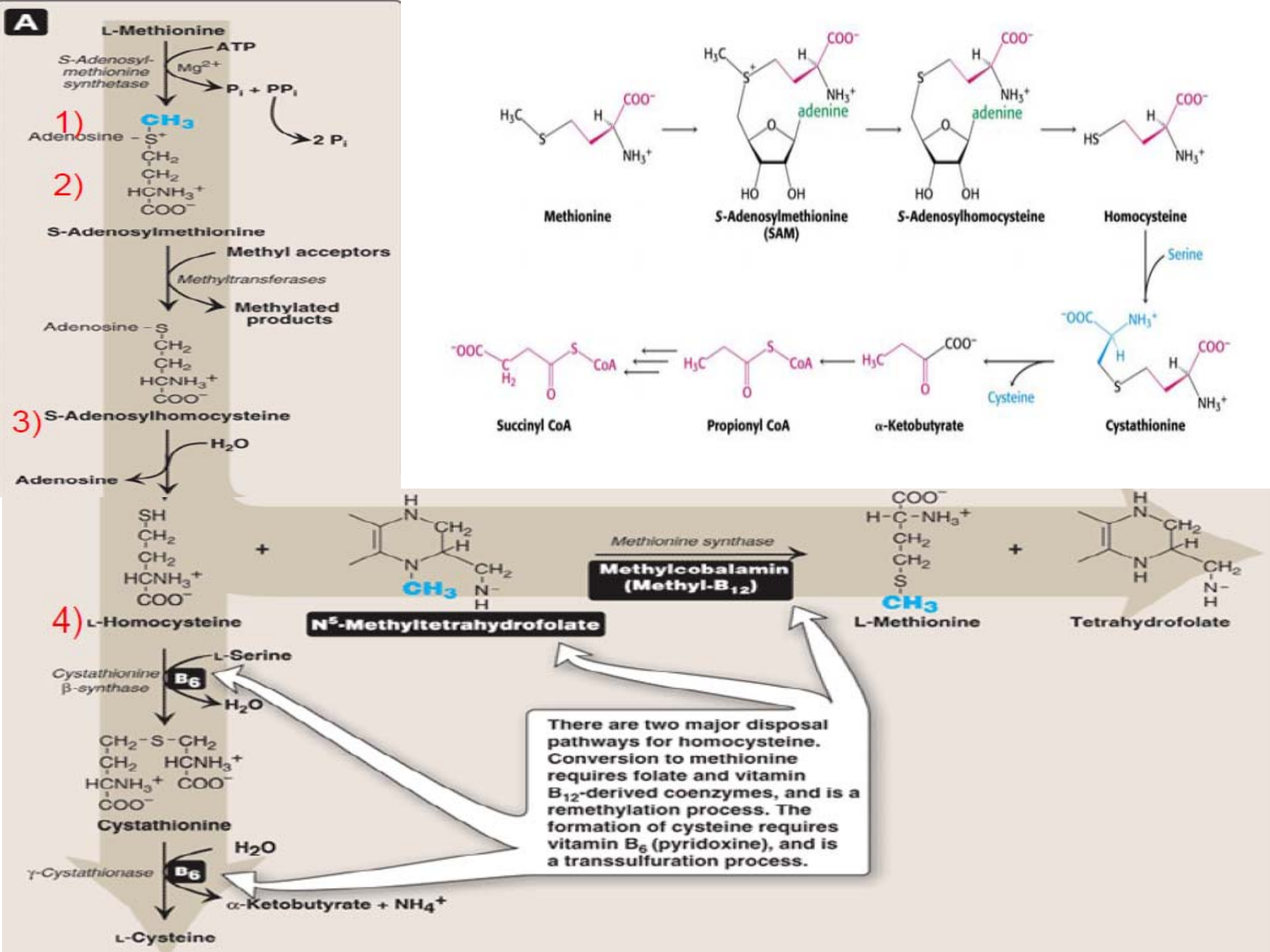
1) Methionine condenses with ATP to form S-adenosylmethionine

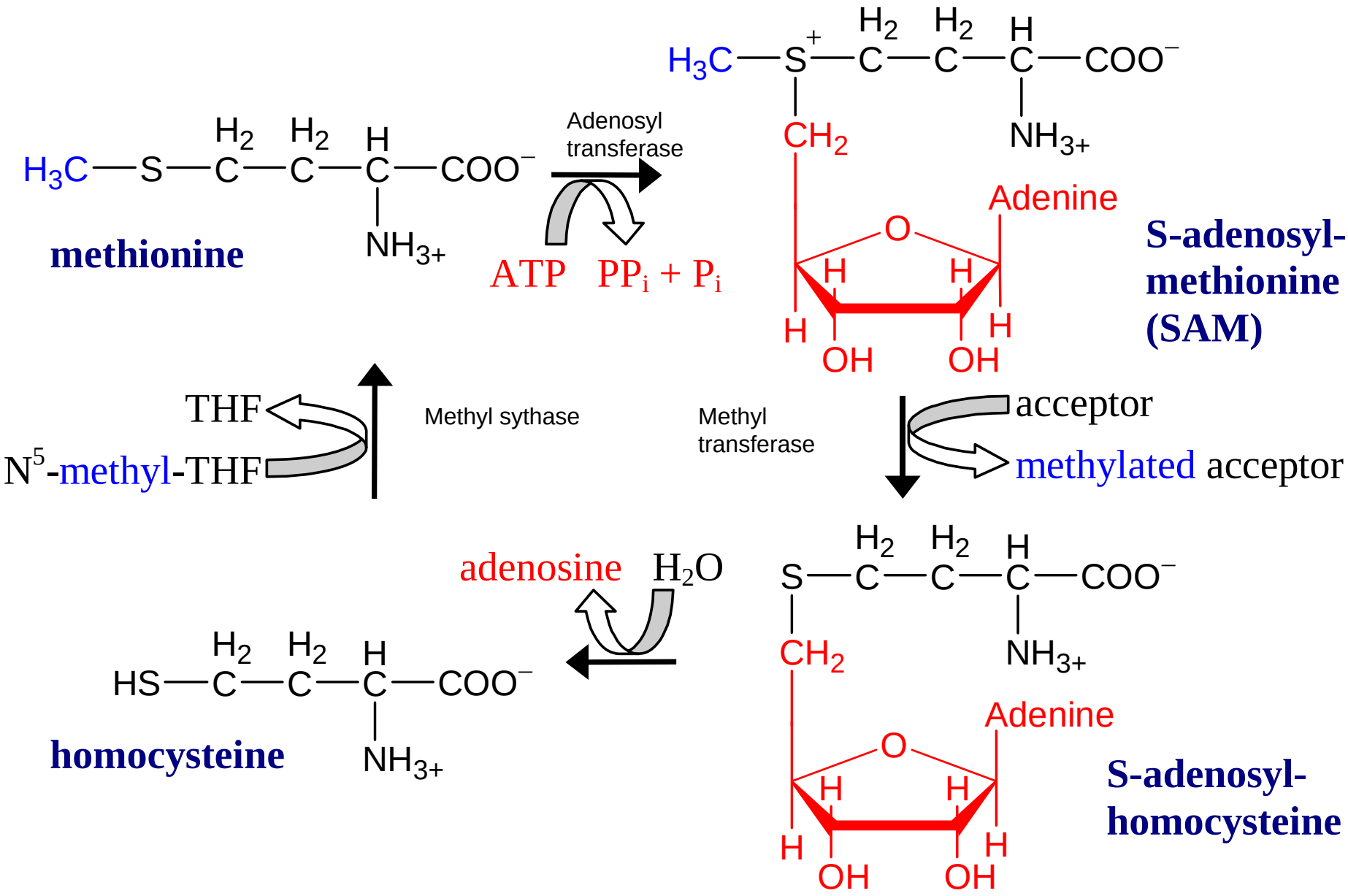
2) Methyl group is activated and transferred to oxygen, nitrogen or carbon atoms.

3) The reaction product is S-adenosylhomocysteine

4) S-adenosylhomocysteine is hydrolyzed to homocysteine.

Homocysteine has two fates:
a) In case of methionine deficiency it is remethylated to methionine
b) If methionine stores are adequate, it enters transulferation pathway to form cysteine and α-ketobutyrate, which is oxidatively decarboxylated to form propionyl CoA which is then converted to Succinyl CoA.


A
L-Methionine
ATP
S-Adenosyl-methionine synthetase
Mg2+
Pi + PPi
2 Pi
1)
Adenosine
2)
S-Adenosylmethionine
Methyl acceptors
Methyltransferases
Methylated products
Adenosine
3)
S-Adenosylhomocysteine
H2O
Adenosine
4)
L-Homocysteine
N5-Methyltetrahydrofolate
Methionine synthase
Methylcobalamin (Methyl-B12)
L-Methionine
Tetrahydrofolate
L-Serine
Cystathionine β-synthase
B6
H2O
Cystathionine
γ-Cystathionase
B6
H2O
α-Ketobutyrate + NH4+
L-Cysteine
There are two major disposal pathways for homocysteine. Conversion to methionine requires folate and vitamin B12-derived coenzymes, and is a remethylation process. The formation of cysteine requires vitamin B6 (pyridoxine), and is a transsulfuration process.
Methionine
S-Adenosylmethionine (SAM)
S-Adenosylhomocysteine
Homocysteine
Serine
Cystathionine
Cysteine
α-Ketobutyrate
Propionyl CoA
Succinyl CoA



Methionine Cycle: Methionine → *S*-Adenosylmethionine by ATP-dependent reaction.

Significance of Methionine cycle

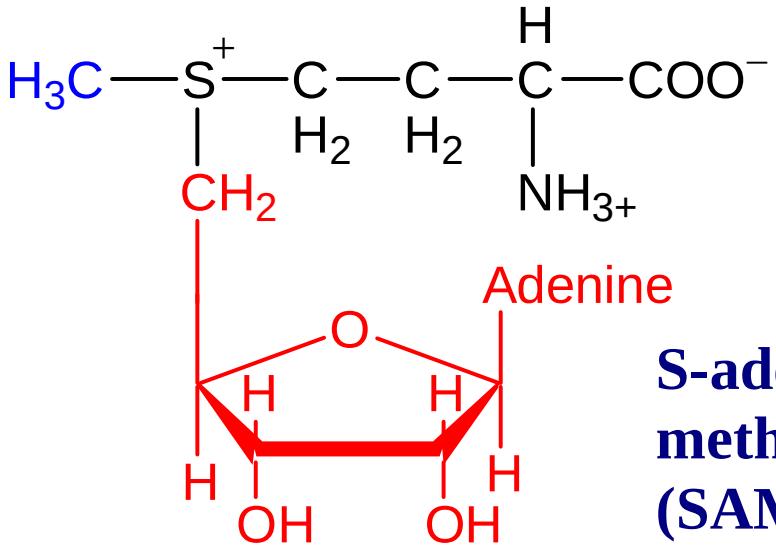
(1) SAM is the direct donor of methyl in body. Methylation can synthesize many important materials such as: choline, creatine, etc.

(2) N^5-CH_3FH_4 is the indirect donor of methyl in the body.

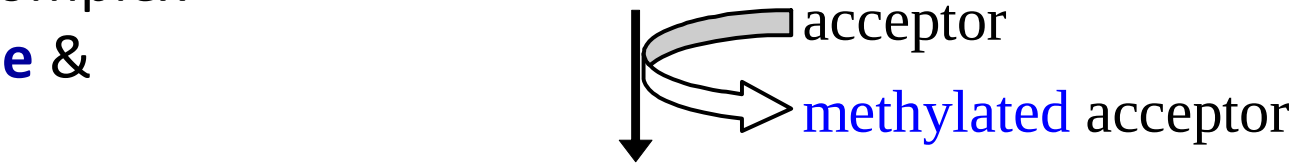
SAM is a **methyl group donor** in synthetic reactions.

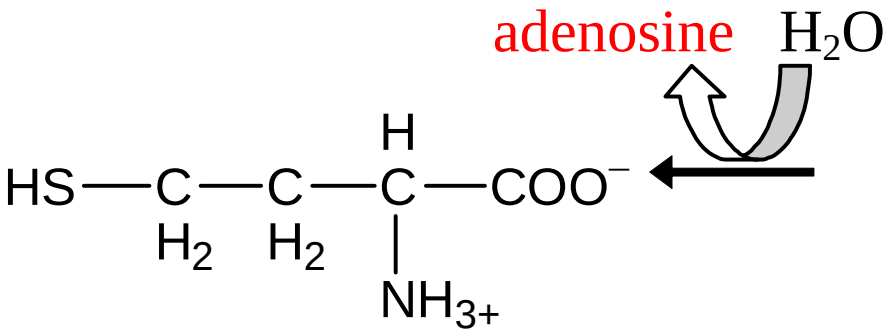
The resulting ***S*-adenosylhomocysteine** is hydrolyzed to **homocysteine**.

Homocysteine may be catabolized via a complex pathway to **cysteine** & **succinyl-CoA**.

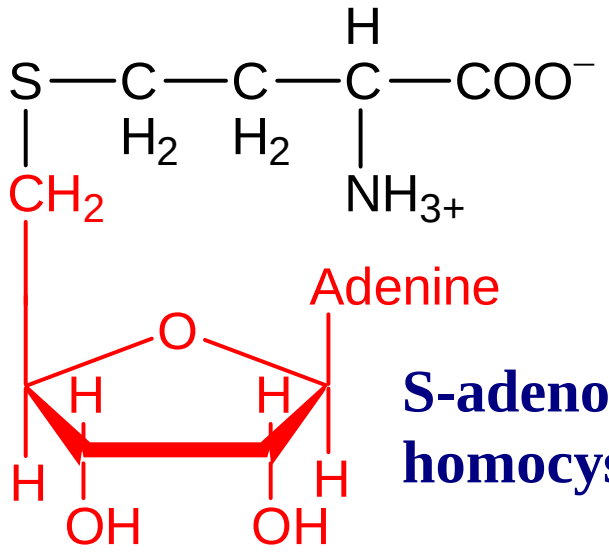


S-adenosyl-methionine (SAM)





homocysteine

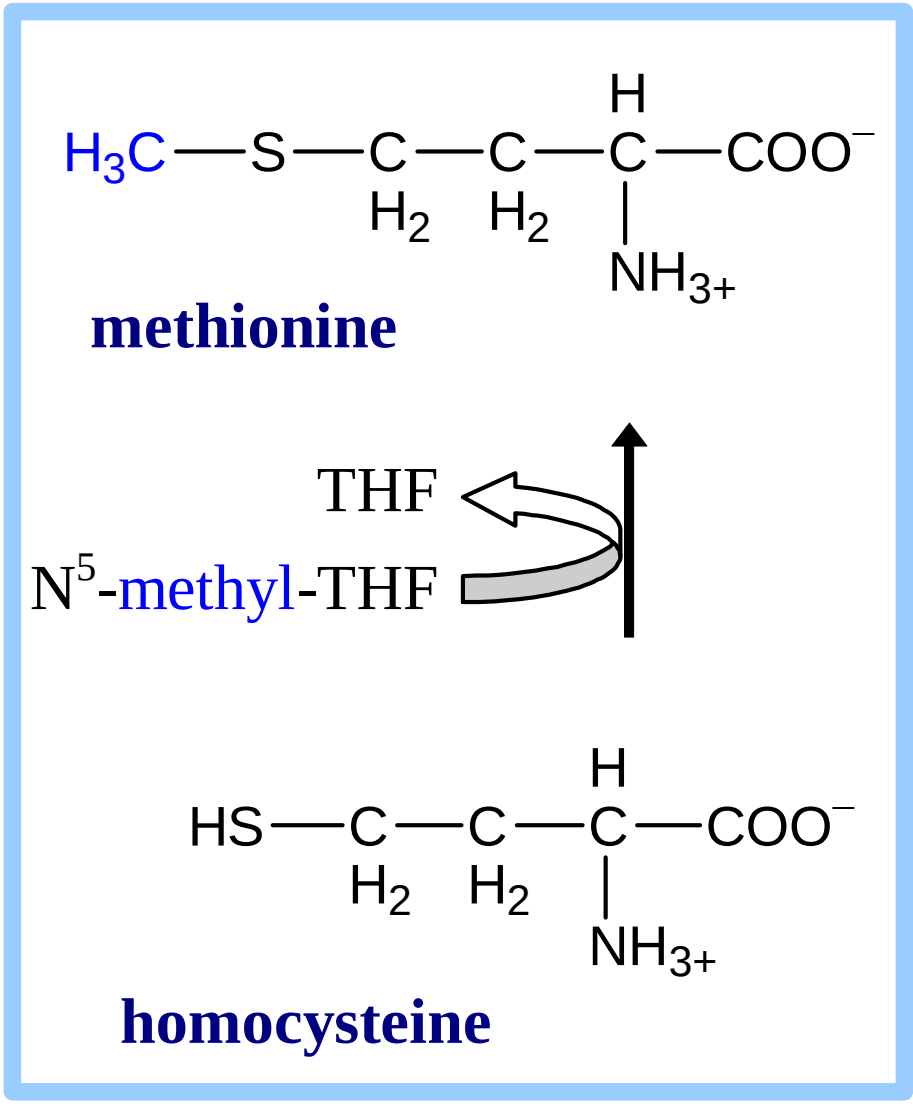


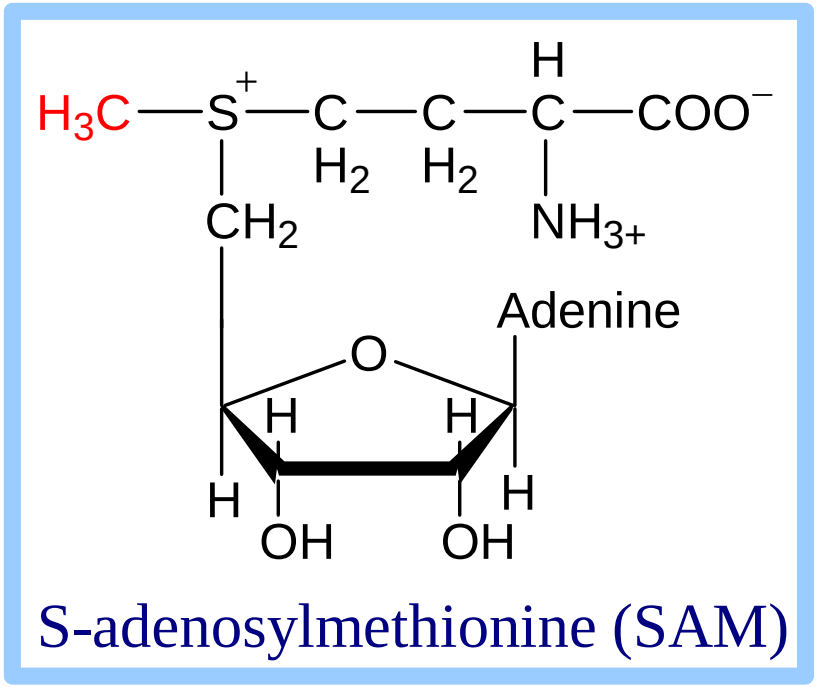
S-adenosyl-homocysteine

Or **methionine** may be regenerated from homocysteine by methyl transfer from ***N*^{5}-methyl-tetrahydrofolate**, via a methyltransferase enzyme that uses **B_{12}** as prosthetic group.

The methyl group is transferred from THF to B_{12} to homocysteine.

Another pathway converts **homocysteine** to **glutathione**.

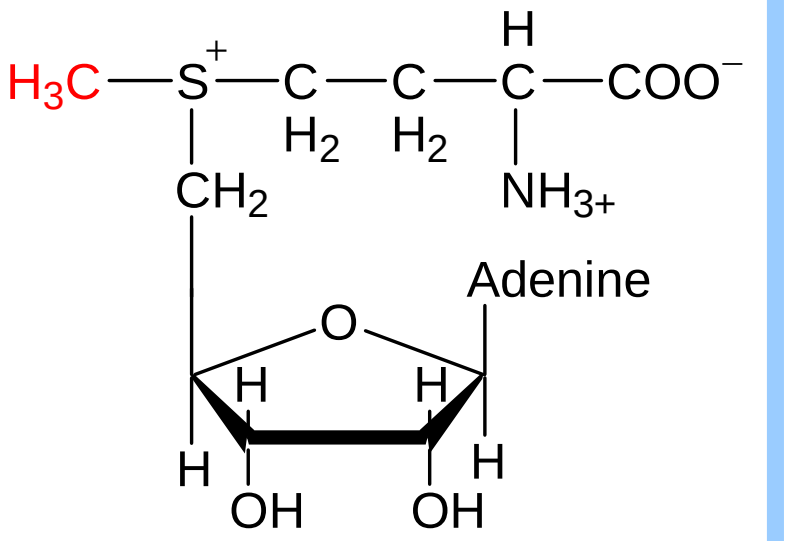




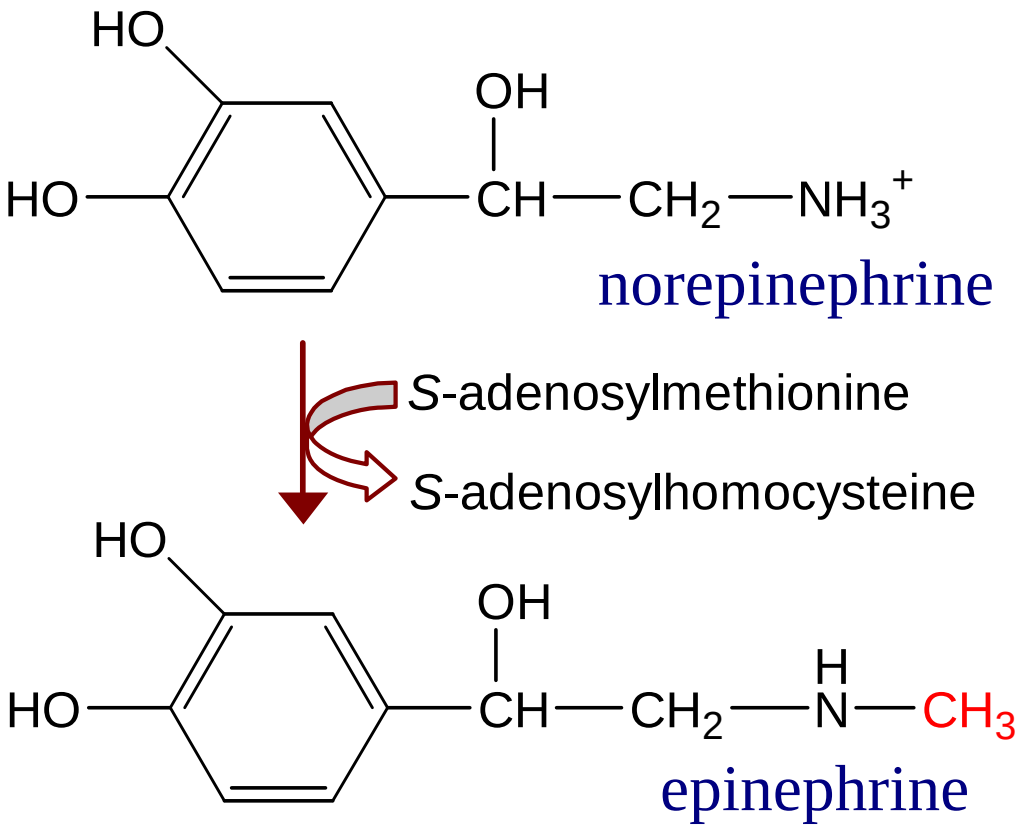
S-adenosylmethionine (SAM)

In various reactions, **S-adenosylmethionine (SAM)** is a donor of diverse chemical groups including methylene, amino, ribosyl and aminoalkyl groups, and a source of 5'-deoxyadenosyl radicals.

But SAM is best known as a **methyl group donor**.



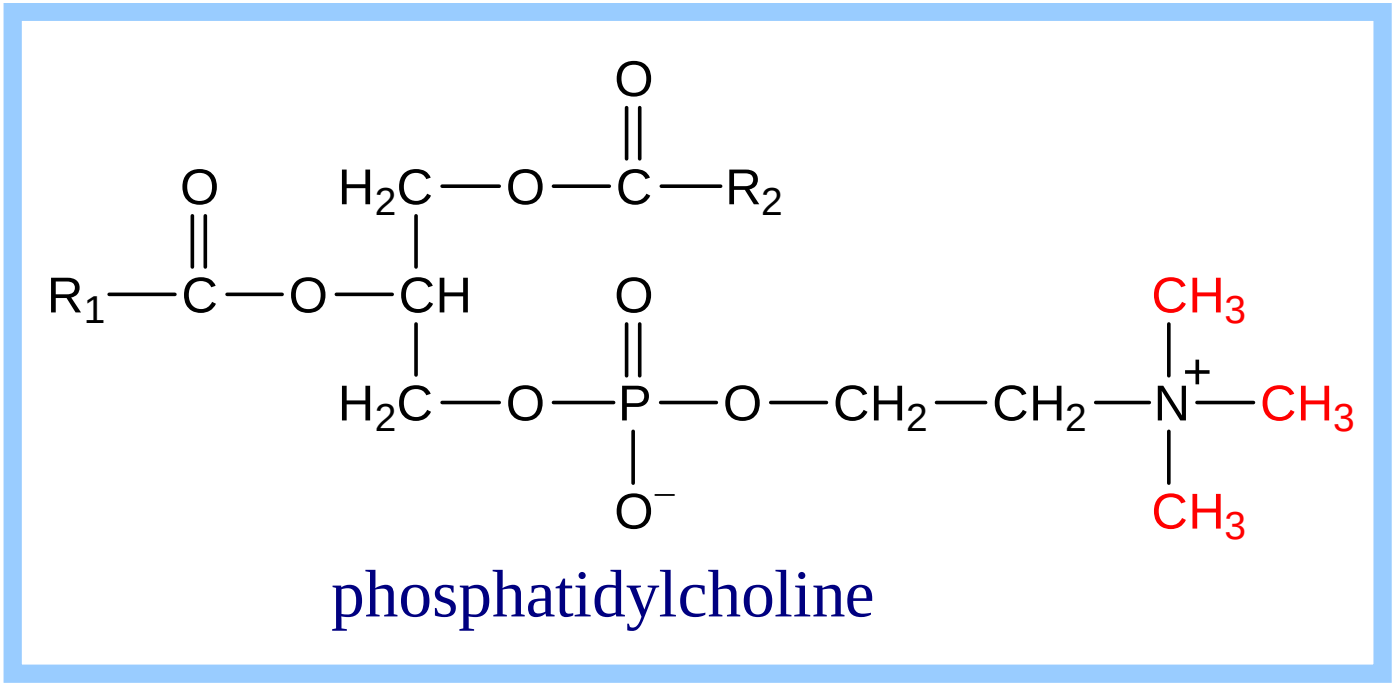
S-adenosylmethionine (SAM)



Examples:

***S*-adenosylmethionine** as **methyl group donor**

- methylation of bases in **tRNA**
- methylation of **cytosine** residues in **DNA**
- methylation of **norepinephrine** → **epinephrine**



- conversion of the glycerophospholipid **phosphatidyl ethanolamine → phosphatidylcholine** via methyl transfer from SAM.

Enzymes involved in formation and utilization of *S*-adenosylmethionine are particularly active in **liver**.

Liver has important roles in synthetic pathways involving methylation reactions, & in regulation of blood methionine.

Methyl Group Donors

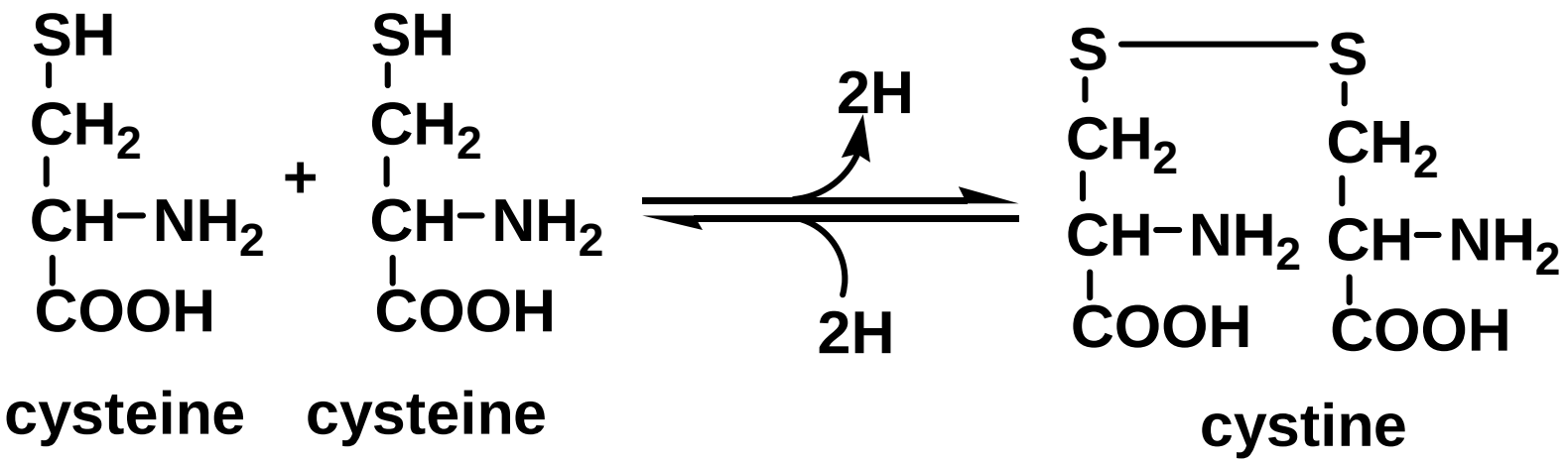
Methyl group donors in synthetic reactions include:

- **methyl-B_{12}**
- ***S*-adenosylmethionine (SAM)**
- ***N^5*-methyl-tetrahydrofolate (*N^5*-methyl-THF)**

2) Cystine/Cysteine enter metabolism as pyruvate

Cystine

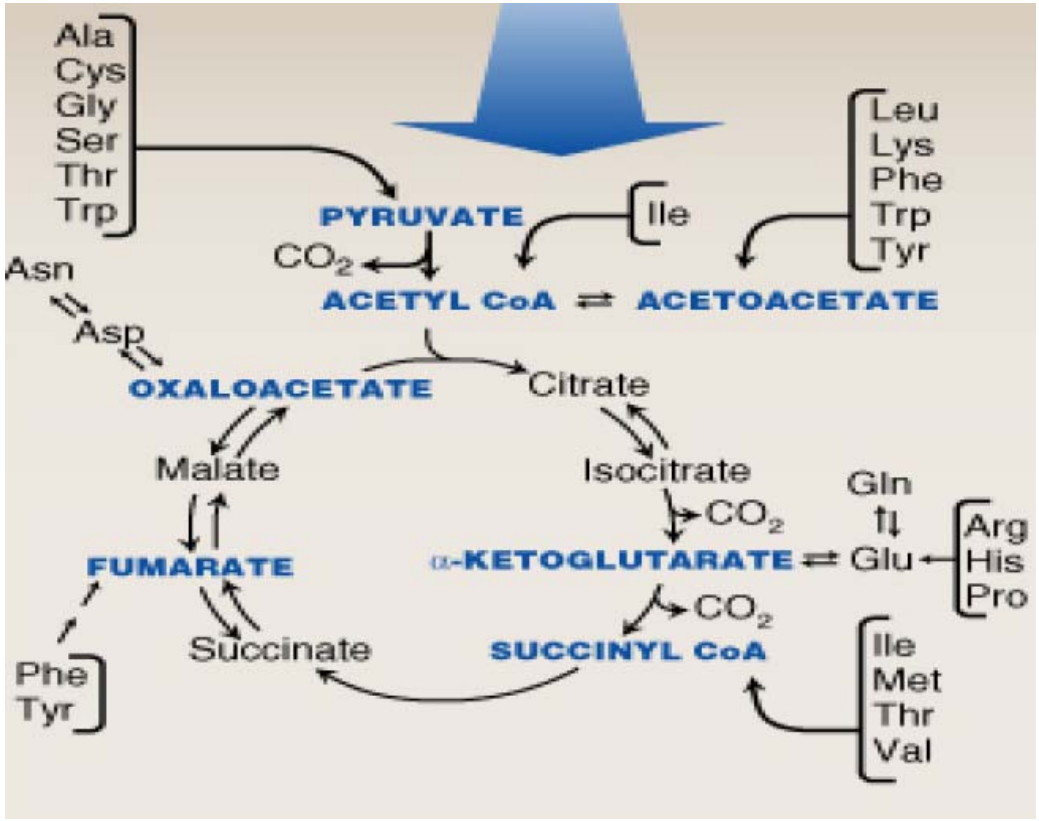
Cystine —(reduced by NADH + H+)→ Cysteine —(desulfuration)→ pyruvate



cysteine cysteine cystine

Overview of Amino Acid Catabolism

	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine* Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Histidine* Proline Serine	Tyrosine	
Essential	Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine



Enter as acetoacetate intermediates

Enter as both TCA cycle and acetyl derived intermediates

Enter as TCA cycle intermediates