BIOCHEMISTRY: AMINO ACID METABOLISM

Lecture 1

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References

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3. Jeremy M Berg, John L Tymoczko, and Lubert Stryer (2002). Biochemistry 6th Edition, New York: W H Freeman
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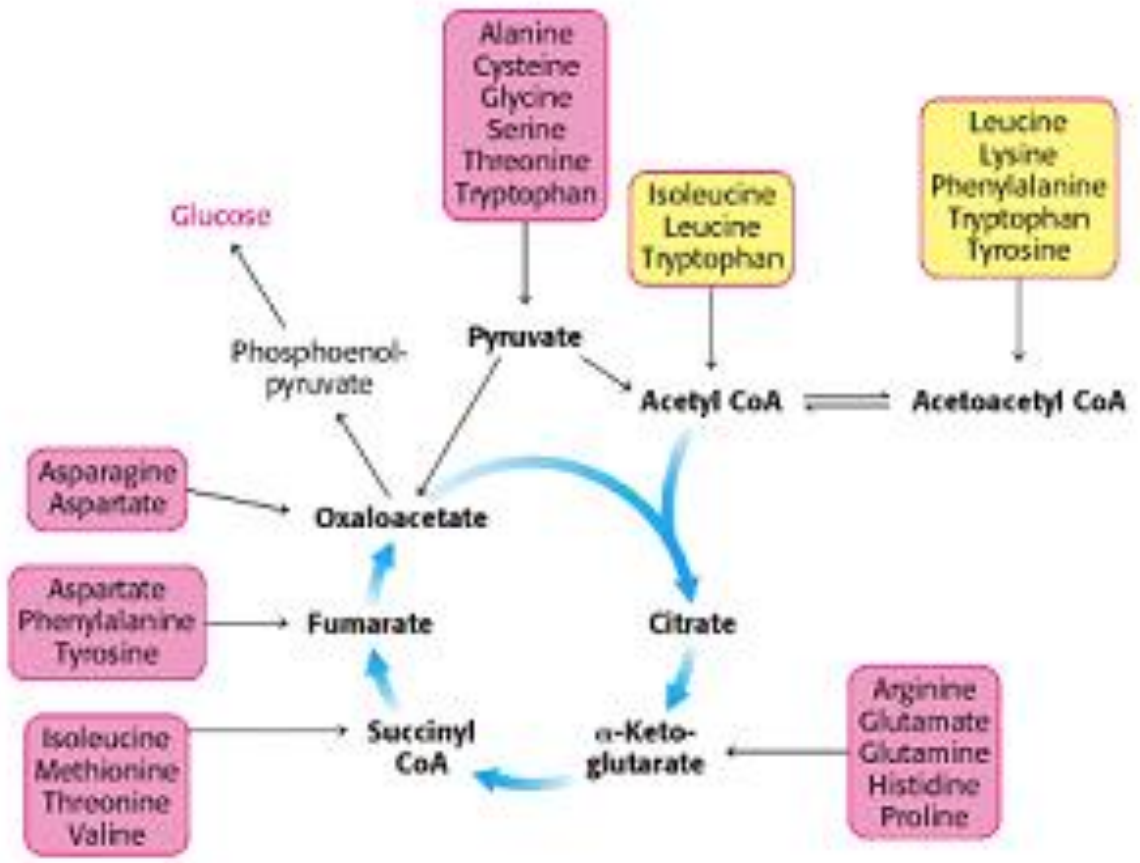
Amino acid degradation

- Amino acids released from protein digestion and not required as building blocks are degraded.
- Amino group is removed and α-ketoacids that result from this oxidative deamination of amino acids are metabolized so that carbon skeletons can be used in synthesis of glucose or as TCA cycle intermediates.
- Amino groups are converted to a less toxic form that is excreted. This is achieved through Urea cycle.

Fate of amino acid carbon skeletons

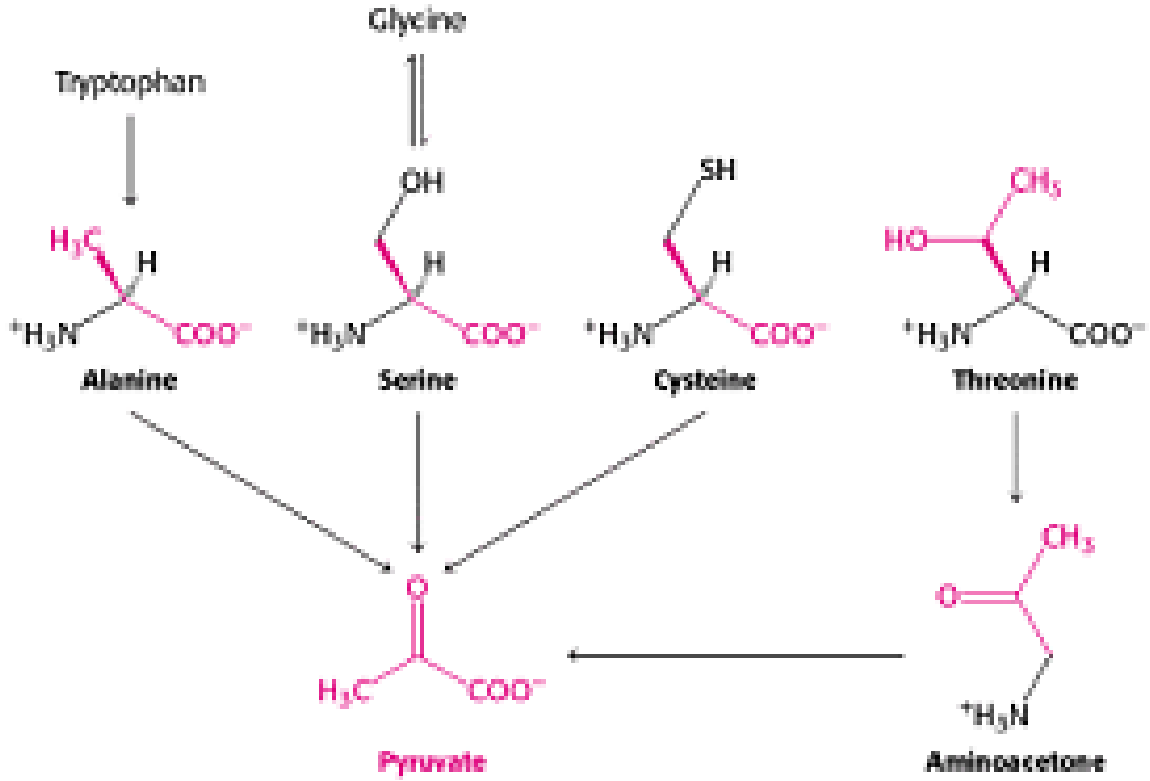


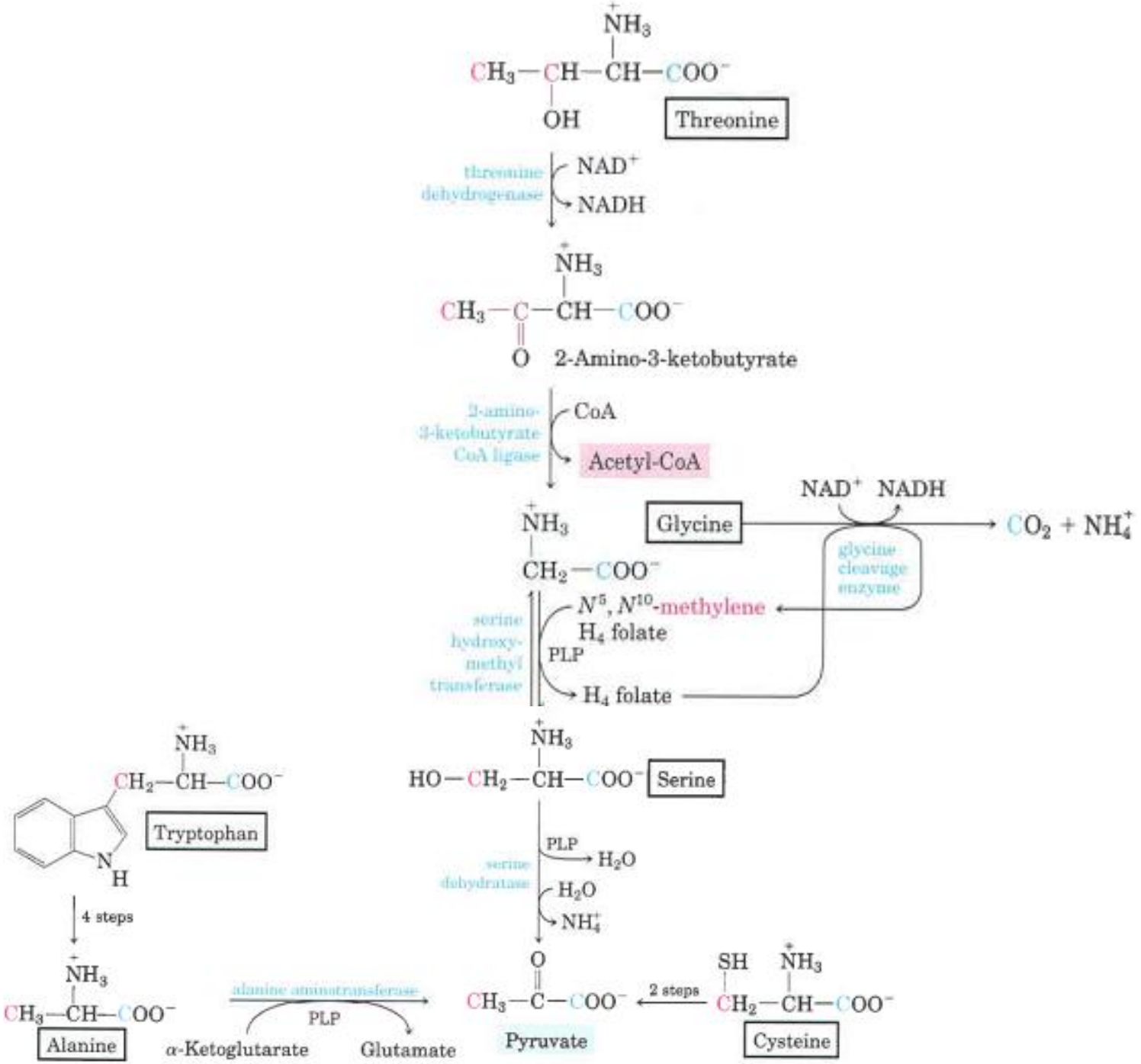
Glucogenic amino acids are shaded purple, and ketogenic amino acids are shaded yellow. Some amino acids are both glucogenic and ketogenic.

Ketogenic and Glucogenic amino acids

- Amino acids that are degraded to acetyl-CoA and/or acetoacetyl-CoA can yield ketone bodies in the liver hence they are called ketogenic amino acids.
- Amino acids that are degraded to pyruvate, α-ketoglutarate, succinyl-CoA, fumarate and/or oxaloacetate can be converted to glucose hence they are referred to as glucogenic amino acids.
- Some amino acids are both ketogenic and glucogenic. These are: Phenylalanine, tyrosine, tryptophan, threonine and isoleucine.

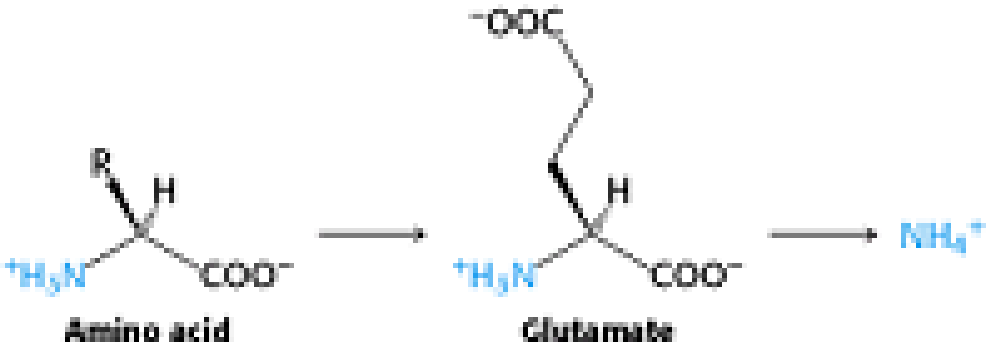
Degradative pathways leading to pyruvate




Threonine
threonine dehydrogenase
NAD+
NADH
2-Amino-3-ketobutyrate
2-amino-3-ketobutyrate CoA ligase
CoA
Acetyl-CoA
Glycine
NAD+ NADH
CO2 + NH4+
glycine cleavage enzyme
N5, N10-methylene H4 folate
serine hydroxymethyl transferase
PLP
H4 folate
Serine
PLP
H2O
serine dehydratase
H2O
NH4+
Tryptophan
4 steps
Alanine
alanine aminotransferase
PLP
α-Ketoglutarate
Glutamate
Pyruvate
2 steps
Cysteine

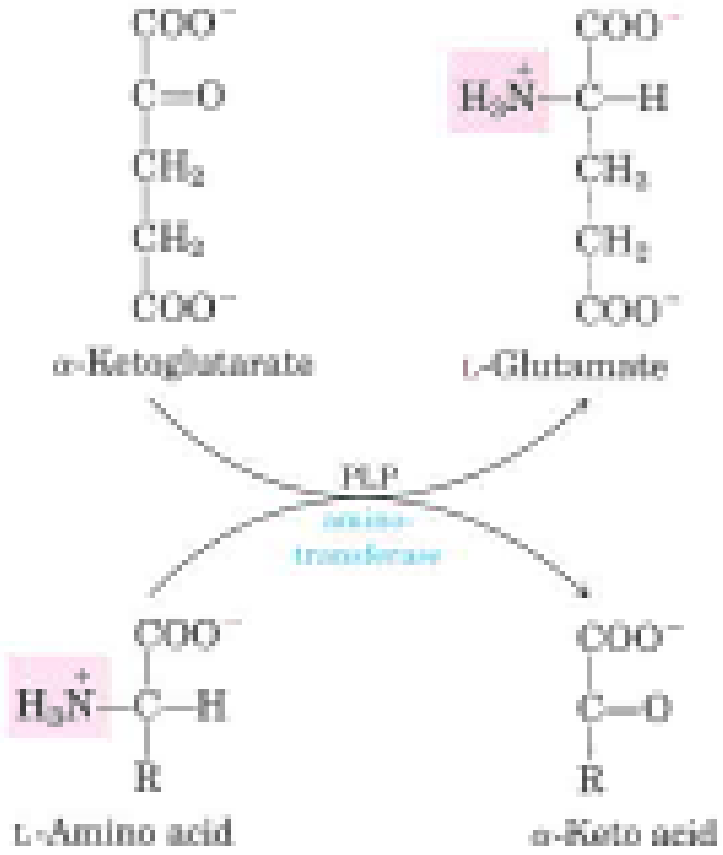
Transamination and oxidative deamination

- The α-amino group of many amino acids is transferred to α-ketoglutarate to form glutamate, which is oxidatively deaminated to yield ammonium ion (NH_4^+).



- Aminotransferases (transaminases) catalyze the transfer of an α -amino group from an α-amino acid to an α-ketoacid. α -amino groups from a variety of amino acids are transferred to α-ketoglutarate for conversion into NH_4^+

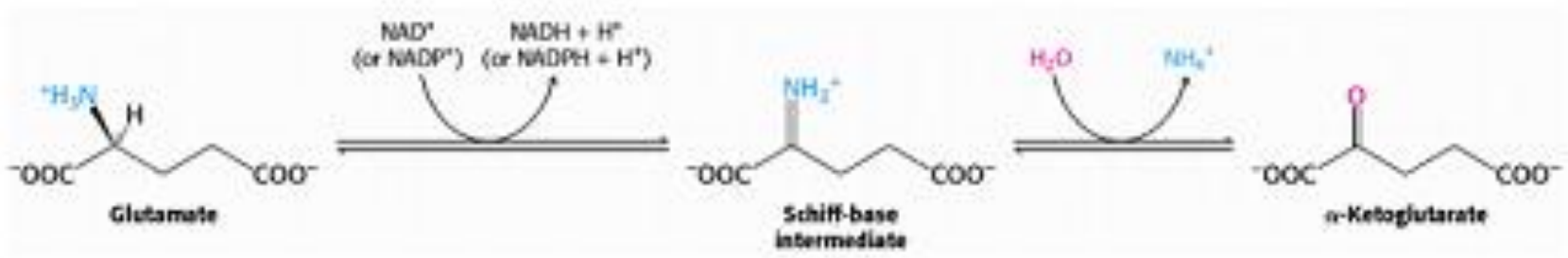

Aminotransferase


α-Ketoglutarate
L-Glutamate
PLP
L-Amino acid
α-Keto acid

- Aspartate aminotransferase (transaminase), one of the most important of these enzymes, catalyzes the transfer of the amino group of aspartate to α-ketoglutarate.

- Alanine aminotransferase catalyzes the transfer of the amino group of alanine to α-ketoglutarate.

- The nitrogen atom that is transferred to α-ketoglutarate in the transamination reaction is converted into free ammonium ion by oxidative deamination.
- This reaction is catalyzed by glutamate dehydrogenase.

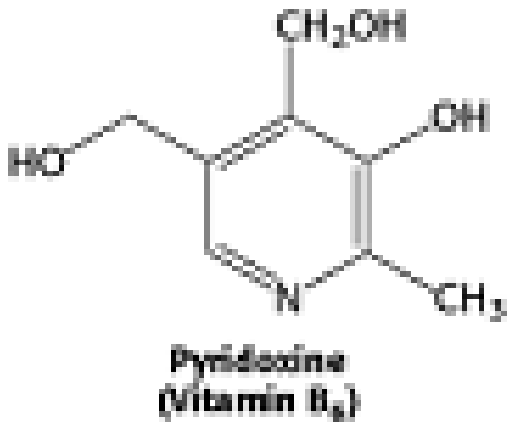


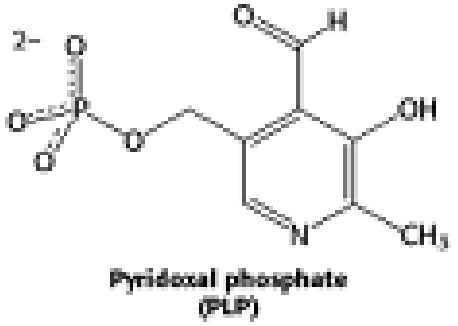
Aminotransferases in assays for tissue damage

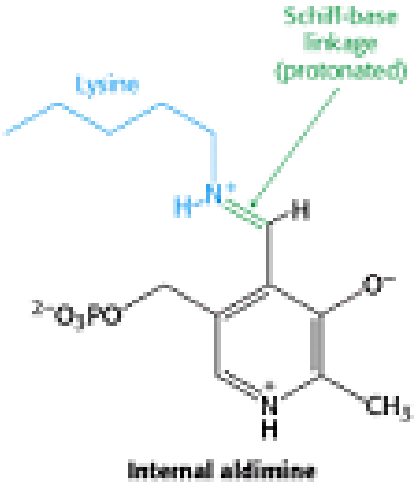
- Analyses of aminotransferases in blood serum give valuable diagnostic information for some disease conditions
- Alanine aminotransferase (ALT; also called glutamate-pyruvate transaminase, GPT) and aspartate aminotransferase (AST; also called glutamate-oxaloacetate transaminase, GOT) are important in the diagnosis of heart and liver damage caused by heart attack, drug toxicity, or infection.
- After a heart attack, a variety of enzymes, including these aminotransferases, leak from injured heart cells into the bloodstream
- Measurements of the blood serum concentrations of the two aminotransferases can provide information about the severity of the damage.

Role of Vitamin B_6 in Transamination

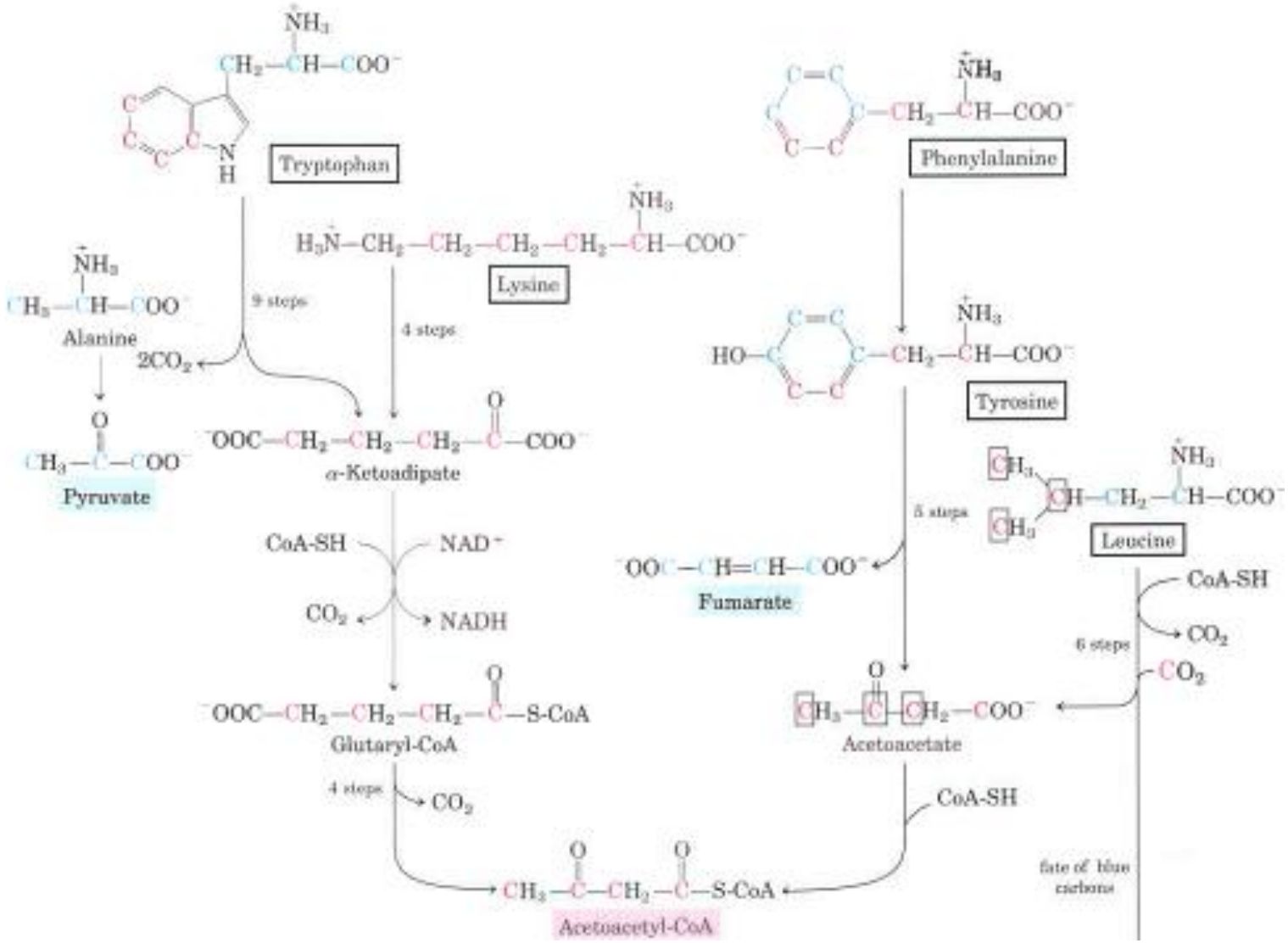
- All aminotransferases contain the prosthetic group pyridoxal phosphate (PLP), which is derived from pyridoxine (vitamin B6).
- The most important functional group on PLP is aldehyde
- This group allows PLP to form covalent Schiff-base intermediates with amino acid substrates

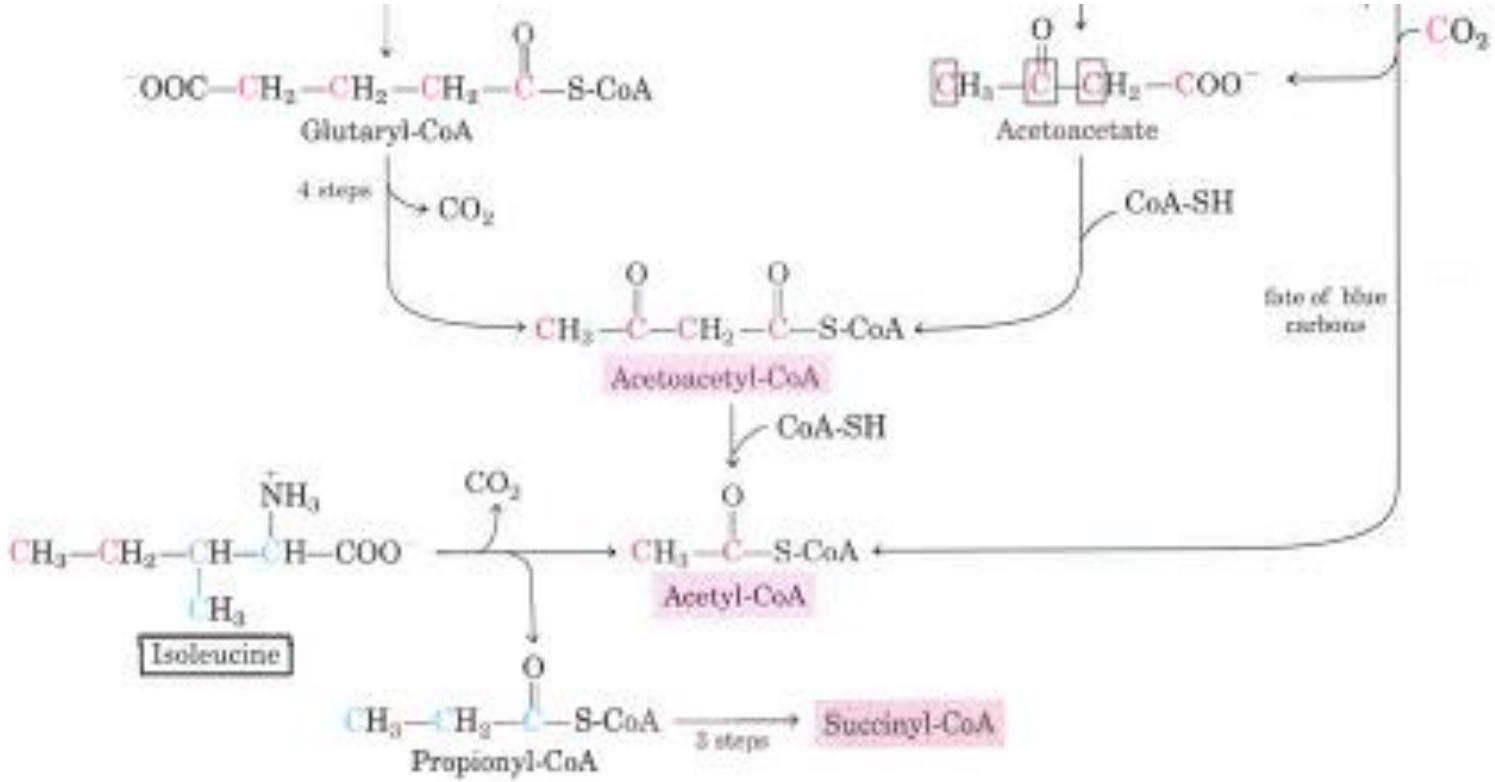




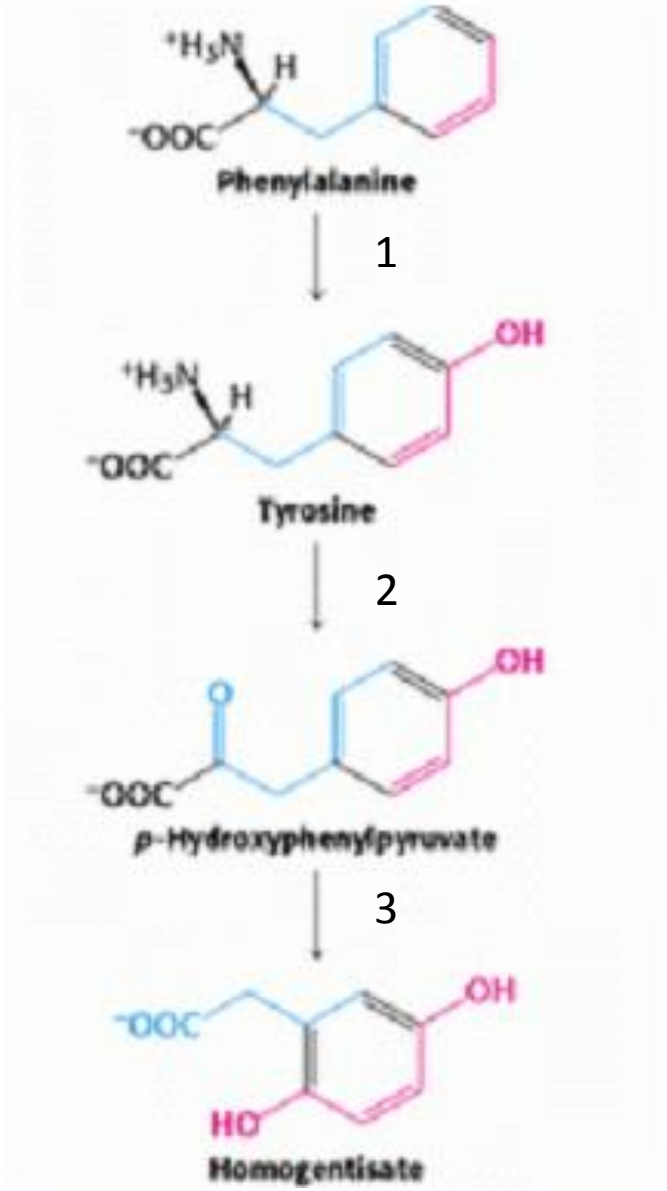


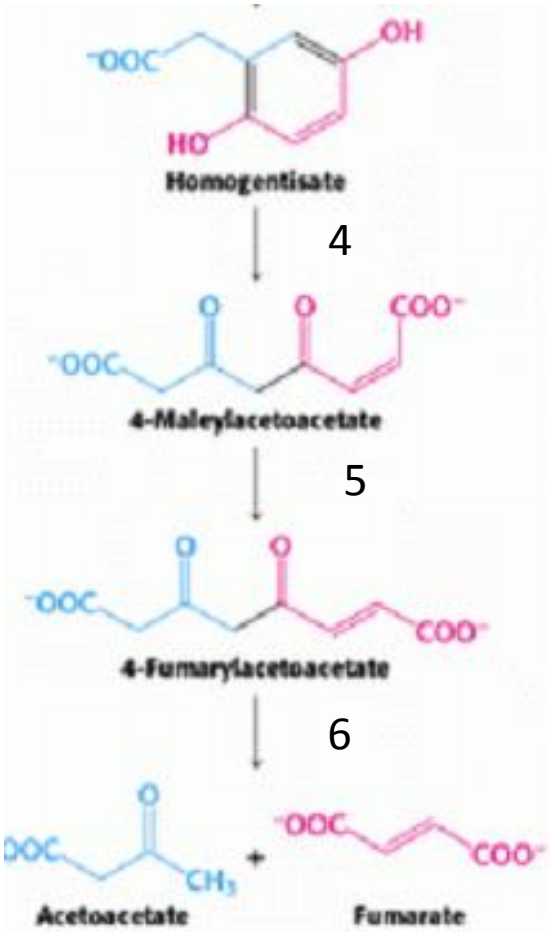
Degradative pathway leading to Acetyl CoA




Glutaryl-CoA
4 steps
CO_2
Acetoacetate
CO_2
CoA-SH
Acetoacetyl-CoA
fate of blue carbons
CoA-SH
CO_2
Acetyl-CoA
Isoleucine
Propionyl-CoA
3 steps
Succinyl-CoA

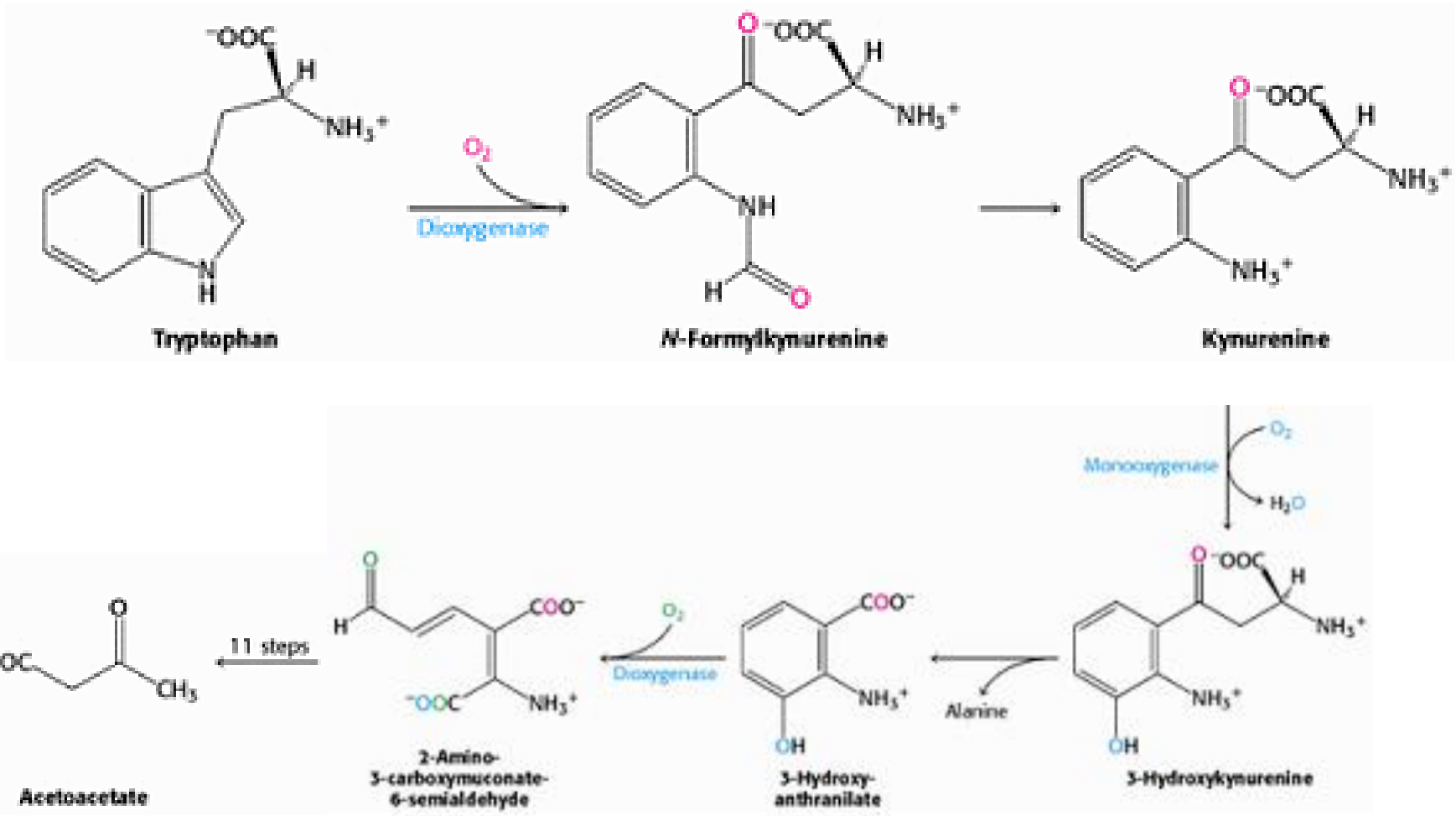
Catabolism of phenylalanine and Tyrosine





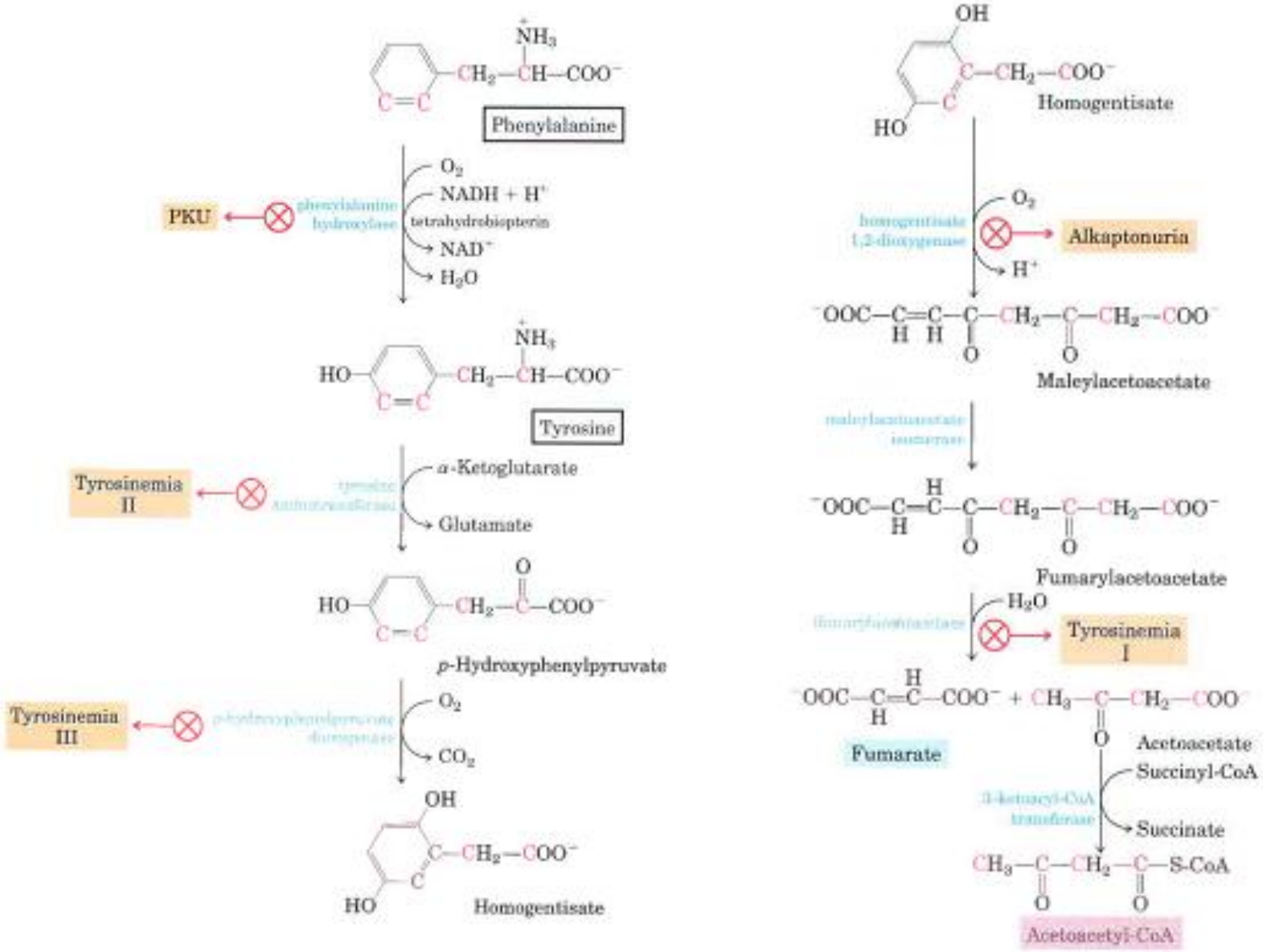
1=Phenylalanine hydroxylase reaction
2=Tyrosine amino-transferase
3=p-hydroxyphenyl pyruvate hydroxylase
4= homogentisate Oxidase
5=Maleylacetoacetate Isomerase
6=Fumarylacetoacetase (fumarylacetoacetate Hydrolase)

Catabolic pathway of Tryptophan



- Oxygenases are required for the degradation of aromatic amino acids
- Molecular oxygen is used to break aromatic ring.

Inborn errors of amino acid metabolism



Phenylketonuria

- Phenylketonuria (PKU) is the most common disease caused by a deficiency of an enzyme of amino acid metabolism
- PKU is an autosomal recessive deficiency of phenylalanine hyd roxylase.
- Over 170 mutations in the gene have been reported
- The name comes from the excretion of phenylpyruvic acid, a phenylketone, in the urine.
- Phenyllactate is also excreted as well as phenylacetate, which gives the urine a ''mousey'' odor.

Symptoms

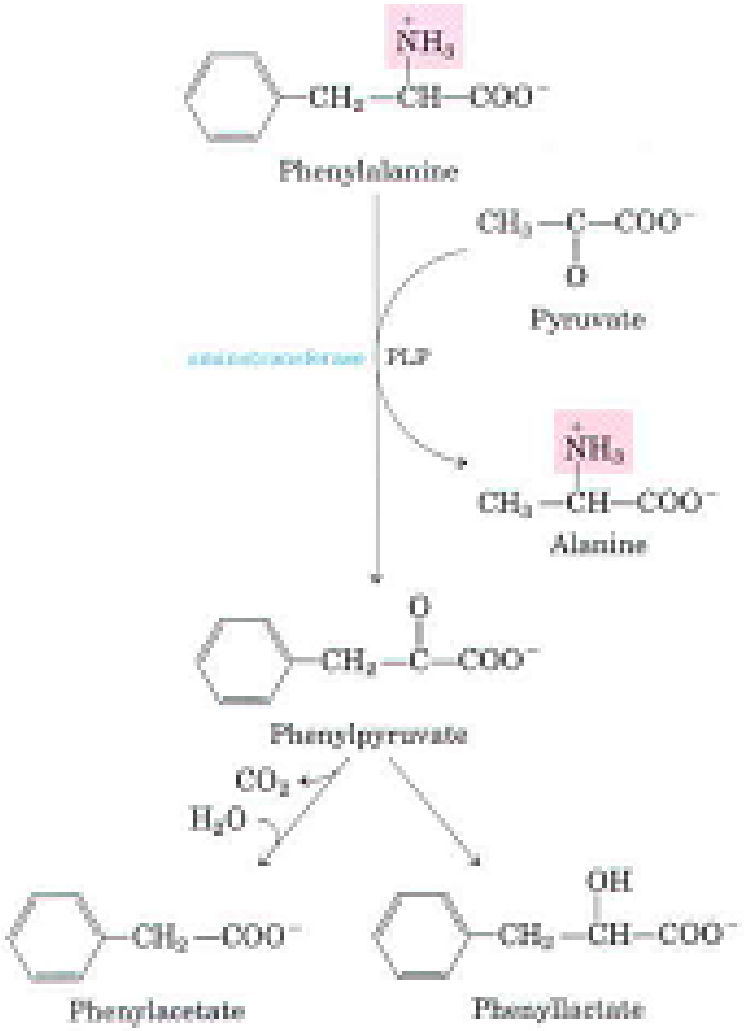
- mental retardation, neurological disorders and very low IQ.
- Light color of skin and eyes, due to under pigmentation because of tyrosine deficiency

- High levels of phenylalanine. However, high levels of phenylalanine can be due to defective synthesis or reduction of biopterin

Prevention/Treatment

- The symptoms of mental retardation associated with this dise ase can be prevented by a phenylalanine-free diet
- Diet including tyrosine and biopterin

Alternative pathway for catabolism of phenylalanine in phenylketonuria



Disorders of Tyrosine metabolism

Tyrosinemias

Deficiency of tyrosine aminotransferase leads to accumulation and excretion of tyrosine and metabolites

Type I (hepatorenal) tyrosinemia

- Is caused by deficiency of fumarylacetoacetate hydrolase.
- It involves Liver failure, renal tubular dysfunction and polyneuropathy.
- Accumulation of fumarylacetoacetate and maleylacetate both of which are alkylating agents can lead to DNA alkylation and tumorigenesis.

Type II (oculocutaneous) tyrosinemia

- Is caused by deficiency of tyrosine aminotransferase
- Results in eye and skin lesions and mental retardation.

Albinism

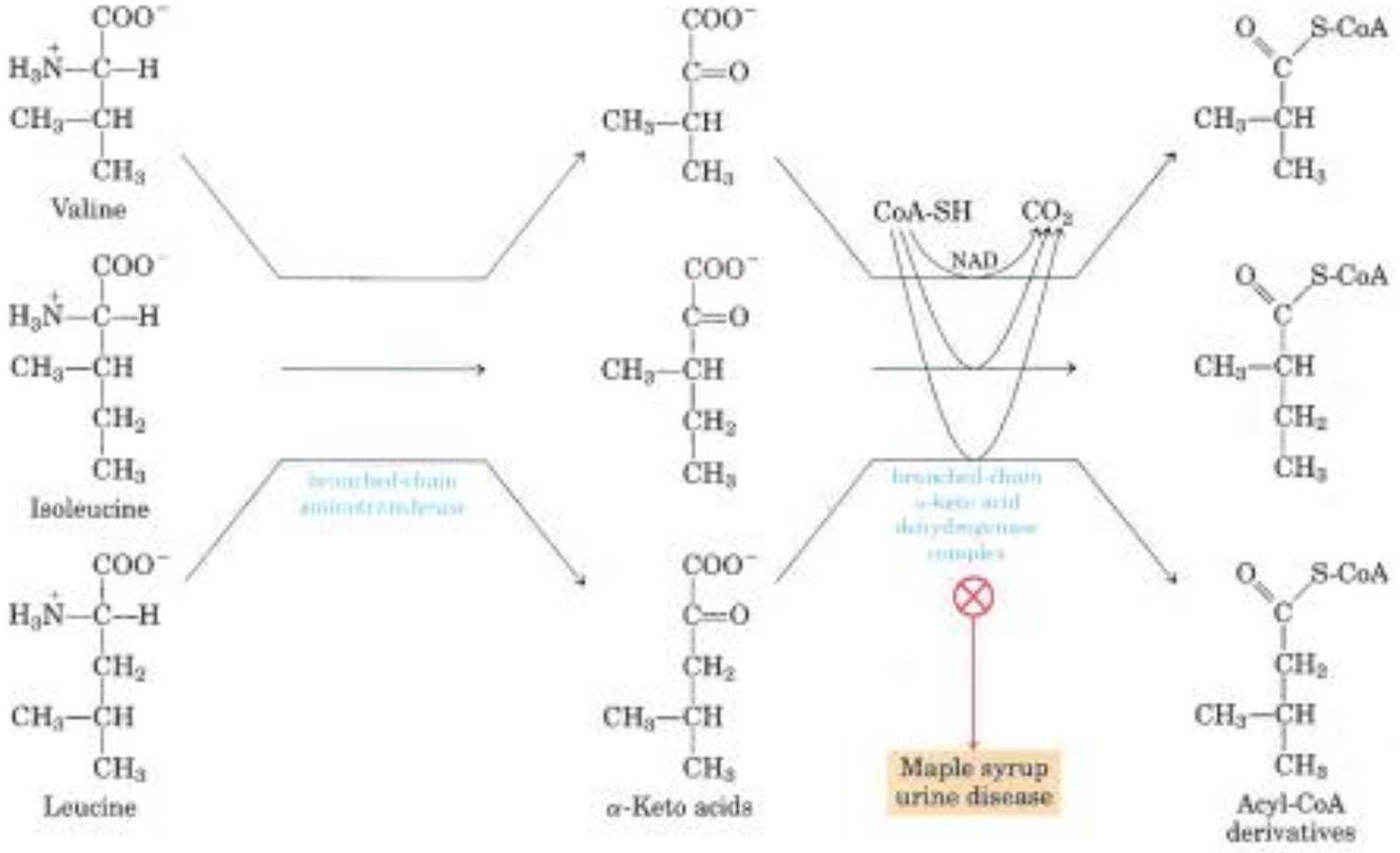
- This results from the lack of enzyme tyrosinase
- Conversion of tyrosine to melanin requires tyrosinase
- This condition is characterized by lack of pigment in skin and hair
- Skin and hair colour are controlled by an unknown number of genetic loci in humans and exist in infinite variation.
- Lack of pigment in the skin makes albinos sensitive to sunlight increasing carcinoma of the skin in addition to burns. Lack of pigment in the eyes may contribute to photophobia.

Alkaptonuria

- This is due to lack of the enzyme homogentisate oxidase
- Individuals deficient in this enzyme excrete almost all ingested tyrosine as colourless homogentisic acid in their urine.
- Homogentisic acid auto-oxidizes to the corresponding quinone which polymerizes to form an intensely dark colour.

Catabolism of branched chain amino acids

- Branched chain amino acids are: Leucine, isoleucine and valine
- They are not degraded in the liver instead they are oxidized in the muscle, adipose, kidney and brain tissue.
- These extrahepatic tissues contain branched-chain aminotransferase that is not present in the liver.
- Branched-chain aminotransferase converts all the three branched-chain amino acids to corresponding α-keto acids.
- The branched-chain α-keto acid dehydrogenase complex then catalyzes oxidative decarboxylation of all 3 α-keto acids in each case releasing the carboxyl group as CO_2 and producing the acyl-CoA derivatives.

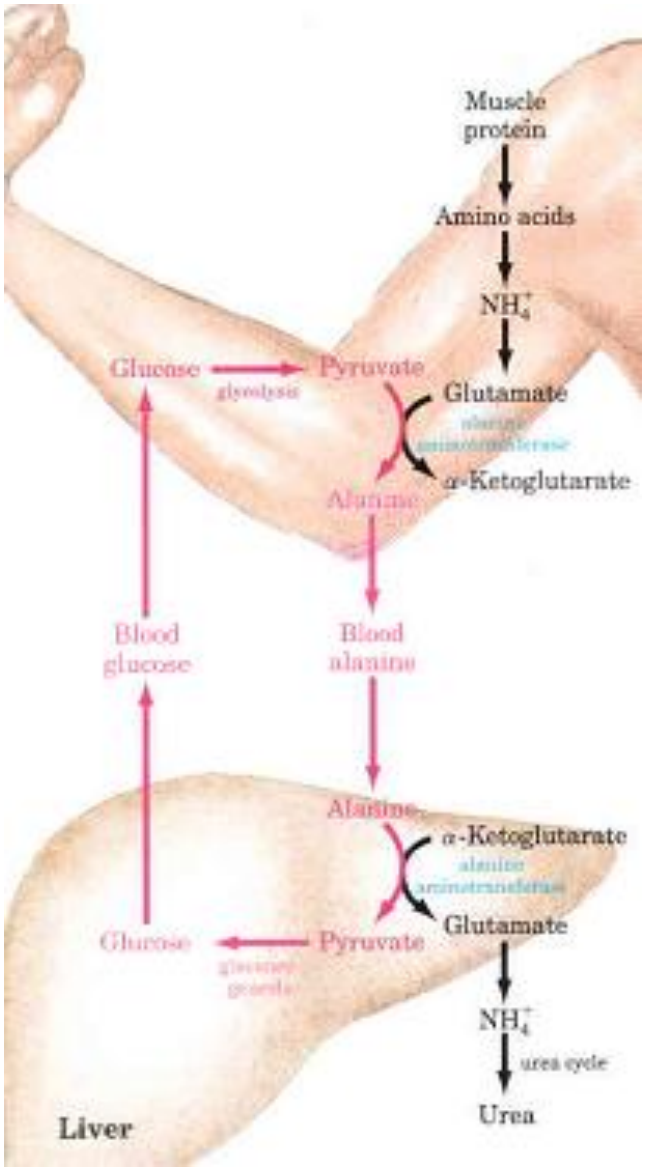


Maple syrup urine disease is a rare genetic disease that results from a defective branched-chain α-keto acid dehydrogenase. The α-keto acids and precursor amino acids accumulate in blood and are excreted in urine.

Disease is characterized by abnormal development of the brain, mental retardation and death in early infancy.

Treatment- control of diet to limit intake of branched chain amino acids

Transport and excretion of ammonium ions
Glucose-alanine cycle

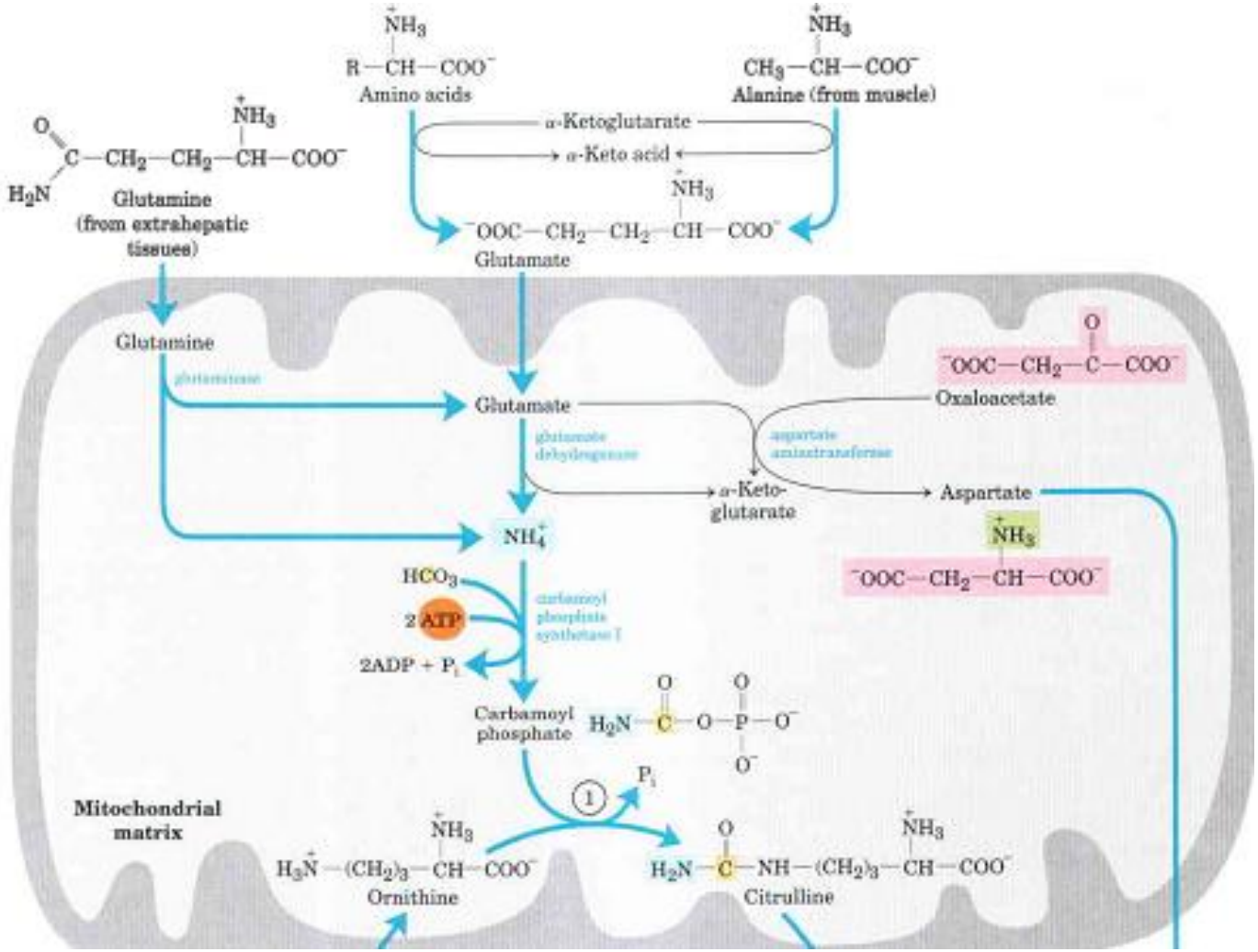


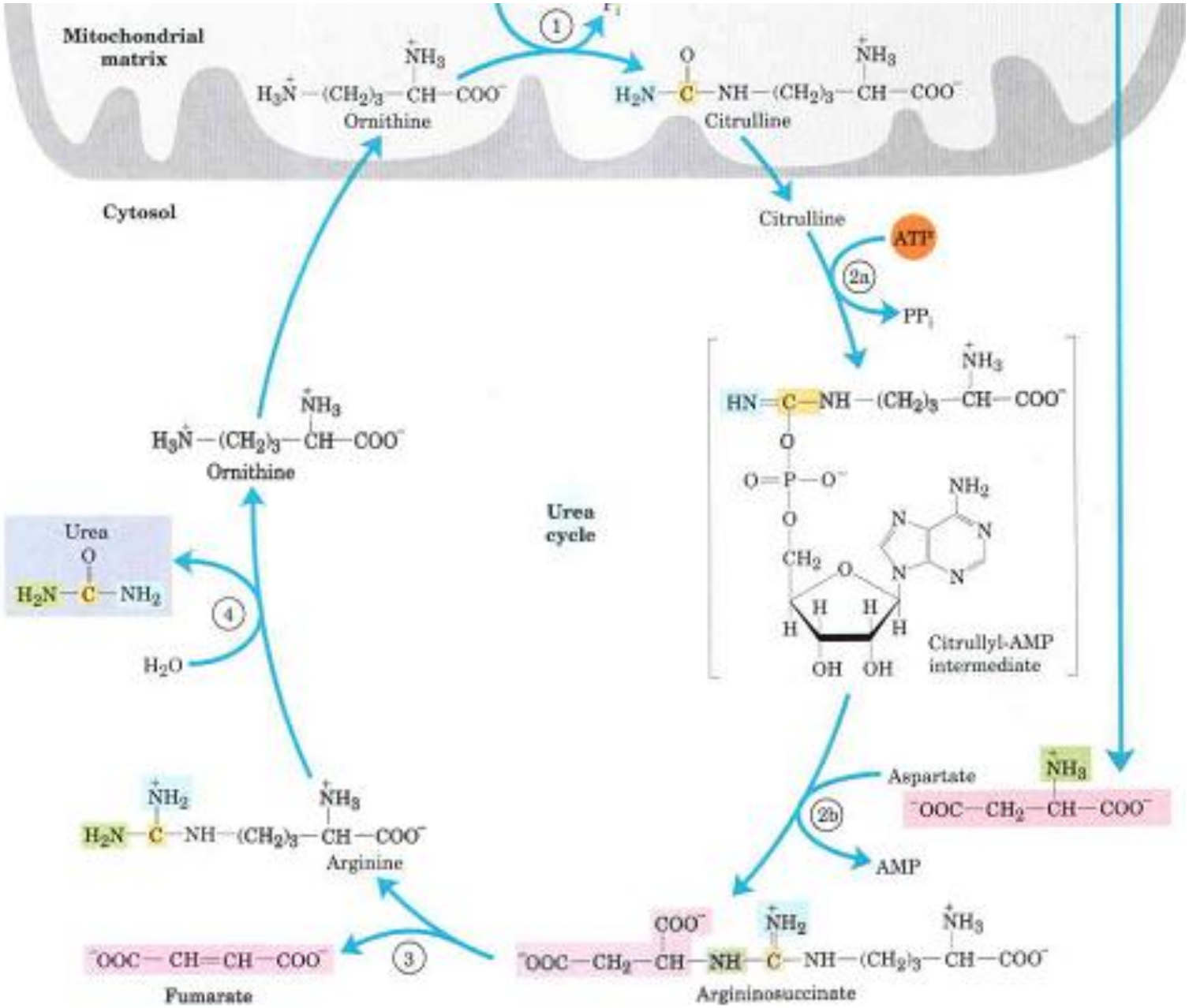
Alanine plays a special role in transporting amino groups to the liver in a nontoxic form, via a pathway called the glucose-alanine cycle

Alanine serves as a carrier of ammonia and of the carbon skeleton of pyruvate from skeletal muscle to liver.

The ammonia is excreted and the pyruvate is used to produce glucose, which is returned to the muscle

Urea cycle


Amino acids
Alanine (from muscle)
α-Ketoglutarate
α-Keto acid
Glutamine
(from extrahepatic tissues)
Glutamate
Glutamine
glutaminase
Glutamate
Oxaloacetate
glutamate dehydrogenase
aspartate aminotransferase
α-Keto-glutarate
Aspartate
NH4+
HCO3−
2 ATP
carbamoyl phosphate synthetase I
2ADP + Pi
Carbamoyl phosphate
Mitochondrial matrix
Pi
Ornithine
Citrulline


Mitochondrial matrix
Ornithine
Citrulline
Cytosol
Citrulline
ATP
2a
PPi
Urea cycle
Citrullyl-AMP intermediate
Ornithine
Urea
4
H2O
Aspartate
2b
AMP
Arginine
Fumarate
3
Argininosuccinate