Amino Acids Metabolism

Transamination reactions

Transamination involves the transfer of an amino group from one amino acid (which is converted to its corresponding α-ketoacid) to an α-ketoacid (which is converted to its corresponding α-amino acid). Thus, the nitrogen from one amino acid appears in another amino acid.

The enzymes that catalyze transamination reactions are known as transaminases or aminotransferases.

Glutamate and α -ketoglutarate are often involved in transamination reactions, serving as one of the amino acid/ α -ketoacid pairs.

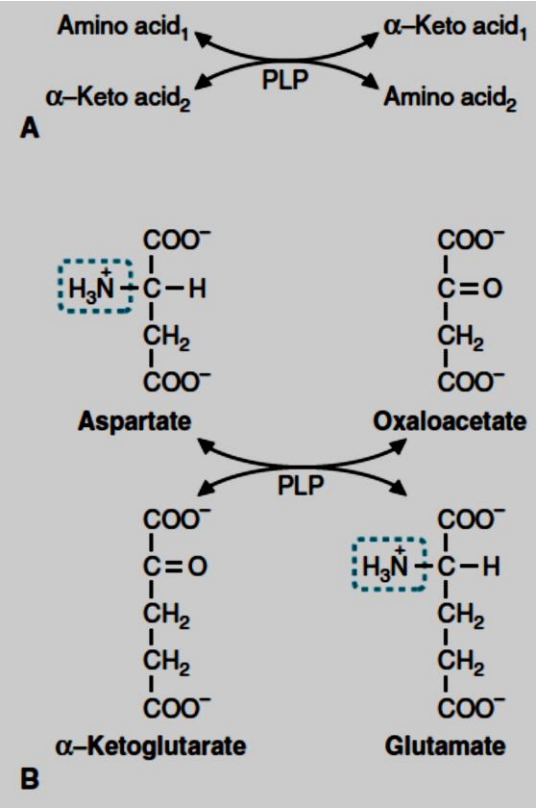
Transamination reactions are readily reversible and can be used in the synthesis or the degradation of amino acids.

Most amino acids participate in transamination reactions. Lysine is an exception; it is not transaminated.

Pyridoxal phosphate (PLP) serves as the cofactor for transamination reactions. PLP is derived from vitamin B6.

Removal of amino acid nitrogen as ammonia

A number of amino acids undergo reactions in which their nitrogen is released as ammonia (NH_3) or ammonium ion (NH_4^+).



Glutamate dehydrogenase catalyzes the oxidative deamination of glutamate. Ammonium ion is released, and α -ketoglutarate is formed. The glutamate dehydrogenase reaction, which is readily reversible, requires NAD or NADP.

Histidine is deaminated by histidase to form NH_4^+ and urocanate.

Serine and threonine are deaminated by serine dehydratase, which requires PLP. Serine is converted to pyruvate, and threonine is converted to α - ketobutyrate; NH_4^+ is released.

The amide groups of glutamine and asparagine are released as ammonium ions by hydrolysis.

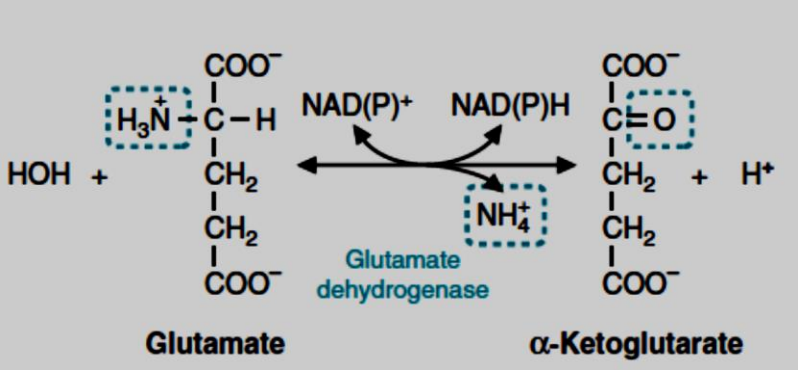
Glutaminase converts glutamine to glutamate and NH_4^+. Asparaginase converts asparagine to aspartate and NH_4^+.

The purine nucleotide cycle serves to release NH_4^+ from amino acids, particularly in muscle.

a. Glutamate collects nitrogen from other amino acids and transfers it to aspartate by a transamination reaction.

b. Aspartate reacts with inosine monophosphate (IMP) to form adenosine monophosphate (AMP) and generate fumarate.

c. NH_4^+ is released from AMP, and IMP is re-formed.

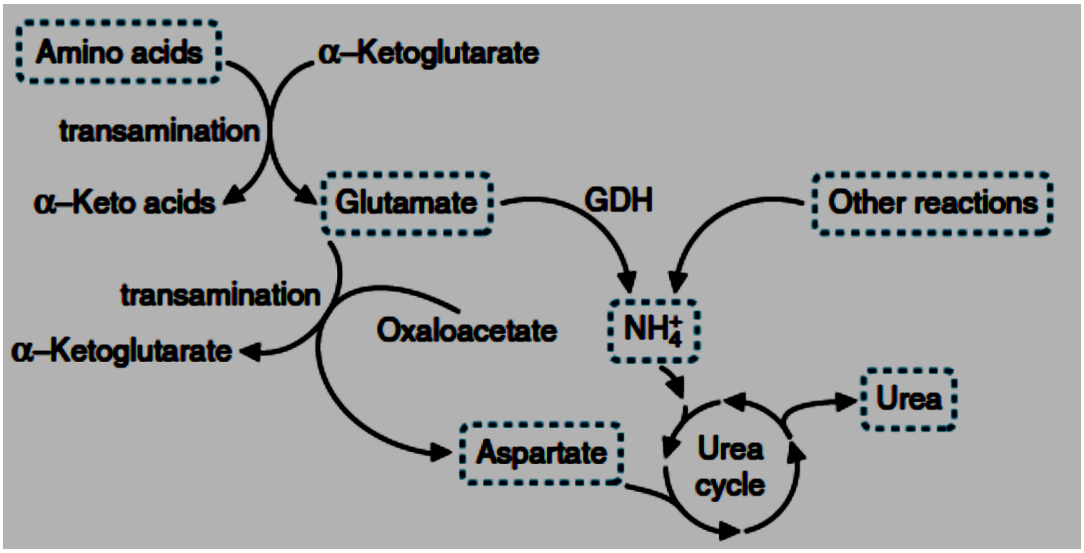


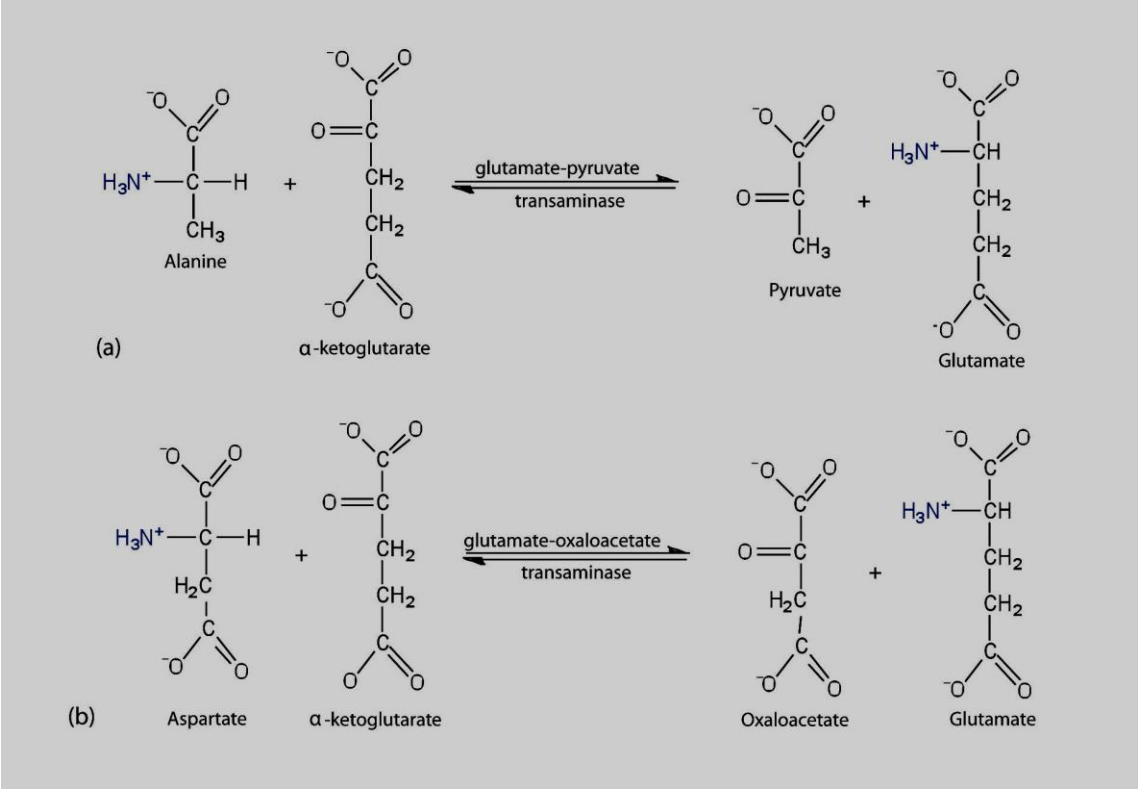
The role of glutamate

1. Glutamate provides nitrogen for synthesis of many amino acids.

a. NH_4^+ provides the nitrogen for amino acid synthesis by reacting with α – ketoglutarate to form glutamate in the glutamate dehydrogenase reaction.

b. Glutamate transfers nitrogen by transamination reactions to α –ketoa cids to form their corresponding α -amino acids.


Amino acids
α–Ketoglutarate
transamination
α–Keto acids
Glutamate
GDH
Other reactions
transamination
α–Ketoglutarate
Oxaloacetate
NH_4^+
Urea
Aspartate
Urea cycle


Alanine
α-ketoglutarate
glutamate-pyruvate
transaminase
Pyruvate
Glutamate
(a)
Aspartate
α-ketoglutarate
glutamate-oxaloacetate
transaminase
Oxaloacetate
Glutamate
(b)

2. Glutamate plays a key role in removing nitrogen from amino acids.

a. α -Ketoglutarate collects nitrogen from other amino acids by means of transamination reactions, forming glutamate.

b. The nitrogen of glutamate is released as NH_4^+ via the glutamate dehydrogenase reaction.

c. NH_4^+ and aspartate provide nitrogen for urea synthesis via the urea cycle. Aspartate obtains its nitrogen from glutamate by transamination of oxaloacetate.

Urea Cycle

Introduction:

As we discussed under **amino acids metabolism section,** ammonia produced is toxic to the body. Hence, if it is not reused to synthesize new amino acids or other nitrogen containing compounds, it is excreted out of the body as urea. This process of formation of urea occurs via the urea cycle for most animals, also known as ureotelic species. There are exceptions to this, like aquatic species which excrete ammonia directly into the surroundings, abd ammonia then is diluted with water and these species are called ammonotelic species. Also, certain species like birds and reptiles excrete ammonia as uric acid and hence are known as uricotelic species. The urea once produced, is excreted out by the kidneys in the urine. Urea is also called carbamide and when dissolved in water has a neutral pH.

Urea cycle

Ammonia is converted to urea in the hepatocytes of the liver in five steps via urea cycle- in the mitochondria (first 2 steps) and cytosol (last 3 steps). The urea then travels through the blood stream to the kidney and is excreted in the urine. The urea cycle was discovered by Hans Krebs (who also discovered Citric acid or Krebs cycle.

Steps of Urea Cycle

Urea cycle is a series of five reactions catalyzed by several key enzymes. The first two steps in the cycle take place in the mitochondrial matrix and the rest of the steps take place in the cytosol. Thus, urea cycle is carried out two cellular compartments of the liver cell.

- In the first step, ammonia produced in the mitochondria is converted to carbamoyl phosphate by an enzyme called carbamoyl phosphate synthetase I. The reaction can be given as follows:

$$NH_3 + CO_2 + 2ATP \rightarrow \text{carbamoyl phosphate} + 2ADP + Pi$$

- The second step involves the transfer of the carbamoyl group from carbamoyl phosphate to ornithine to form citrulline. This step is catalyzed by the enzyme ornithine transcarbamoylase (OTC) . The reaction is given as follows:

$$\text{Carbamoyl phosphate} + \text{ornithine} \rightarrow \text{citrulline} + Pi$$

Citrulline thus formed is released into the cytosol for usage in the rest of the steps of the cycle.

- The third step is catalyzed by an enzyme called argininosuccinate synthetase, which uses citrulline and ATP to form a citrullyl-AMP intermediate, which

reacts with an amino group from aspartate to produce argininosuccinate. This reaction can be given as follows:

Citrulline + ATP + aspartate → argininosuccinate + AMP + PPi

- The fourth step involves the cleavage of argininosuccinate to form fumarate and arginine. Argininosuccinate lyase is the enzyme catalyzing this reaction, which can be represented as follows:

Argininosuccinate → arginine + fumarate

- In the fifth and last step of the urea cycle, arginine is hydrolyzed to form urea and ornithine. This is catalyzed by arginase and can be given as follows:

Arginine → urea + ornithine

The overall reaction can be given as follows:

$2NH_3 + CO_2 + 3ATP = urea + 2ADP + AMP + PPi + 2Pi$

Energetics of Urea Cycle

On considering only, the urea cycle, and not considering the other biopathways linked, to produce one urea molecule, 4 ATP molecules are used up as shown below:

NH_4^+ ions to carbamoyl phosphate- utilization of 2ATP. Citrulline to arginosuccintae- breakdown of 1 ATP to AMP + PPi which is equivalent to 2 Pi

Therefore, the entire energetic reaction can be summarised as follows:

$2NH_4^+ + HCO_3^- + H_2O + 3ATP + Aspartate \rightarrow Urea + 2ADP + 4Pi + AMP + 2H^+ +$ Fumarate

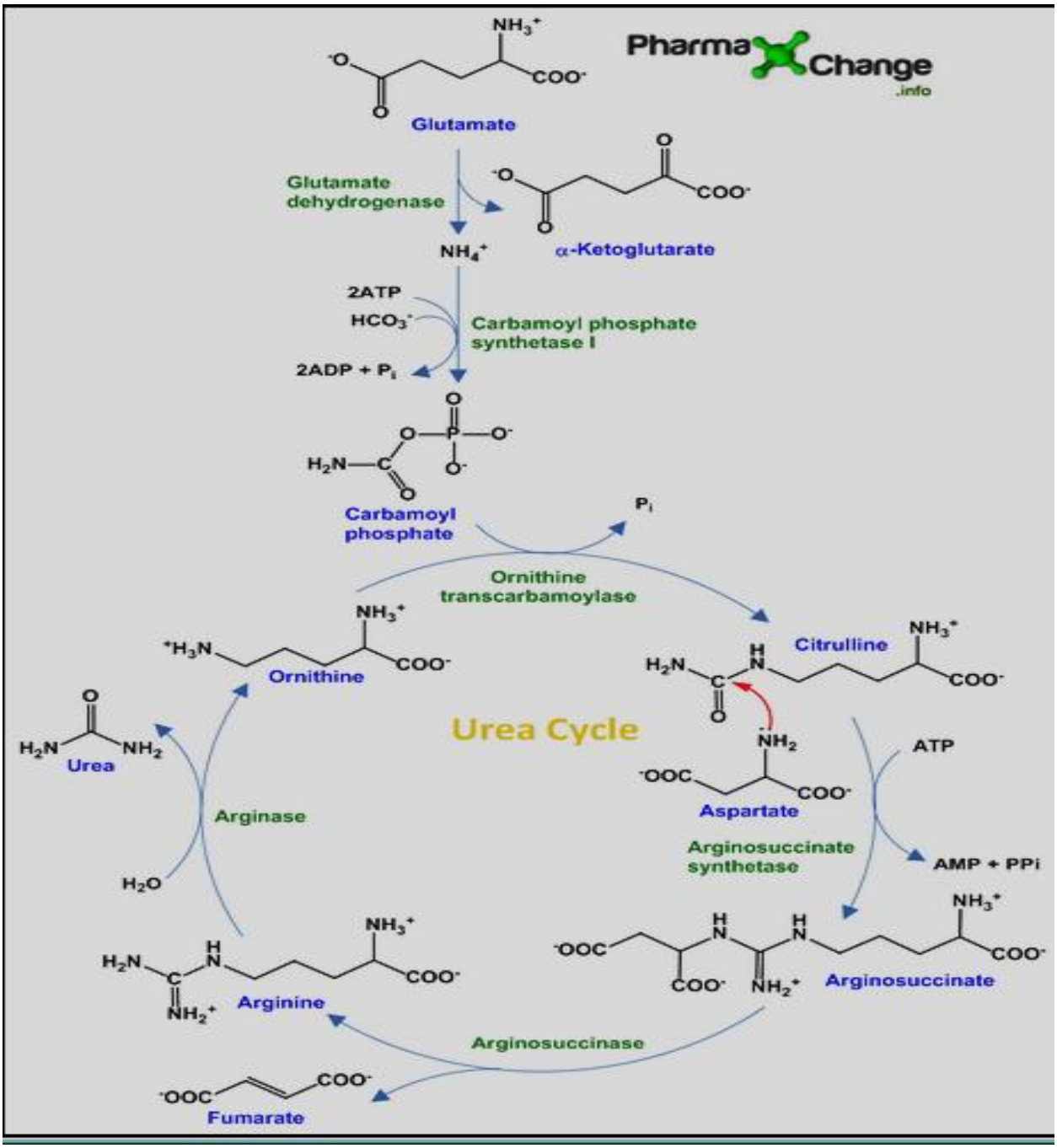
Rate limiting steps of urea cycle

The conversion of ammonium ions to carbamoyl phosphate catalyzed by carbamoyl synthetase I is a rate limiting step. This enzyme (carbamoyl synthetase I) is activated by N-acetylglutamate (NAG) which is formed by a reaction between acetyl CoA and glutamate catalyzed by the enzyme N-acetylglutamate synthase (activated by arginine). Thus, concentrations of glutamate and acetyl CoA as well as levels of arginine determine the steady state levels of N-acetylglutamate (NAG) which in turn regulates the concentration of urea. When a high protein diet is consumed, levels of NAG increases and in turn urea levels increase. Also during starvation, when muscle proteins start breaking down to source out energy, urea levels increase in response. The rest of all enzymes participating in the urea cycle are mostly regulated by the concentrations of their respective substrates.

Diagnosis of urea cycle defects

A blood aminogram is routinely used in the diagnosis of urea cycle disorders. The concentration of the nitrogen-carrying amino acids, glutamine and asparagine, in plasma is elevated in cases of ornithine transcarbamykase deficiency (OTC). In babies, elevated levels of orotic acid in the urine may be an indicator of OTC deficiency. Increased levels of blood citrulline and argininosuccinate are also seen in cases of citrullinemia.

In older children, these disorders may present in the form of growth failure, psychomotor retardation and behavioral abnormalities. Hence, blood ammonia and urinary orotic acid monitoring and quantitation are crucial in patients with unexplained neurological symptoms.


PharmaXChange .info
Glutamate
Glutamate dehydrogenase
α-Ketoglutarate
2ATP
HCO3-
Carbamoyl phosphate synthetase I
2ADP + Pi
Carbamoyl phosphate
Pi
Ornithine transcarbamoylase
Citrulline
Ornithine
Urea Cycle
Urea
Arginase
H2O
ATP
Aspartate
Arginosuccinate synthetase
AMP + PPi
Arginosuccinate
Arginine
Arginosuccinase
Fumarate

Amino Acids Biosynthesis

All amino acids are derived from intermediates in glycolysis, the citric acid cycle, or the pentose phosphate pathway. Nitrogen enters these pathways by way of glutamate and glutamine. Ten of the amino acids are only one or a few enzymatic steps removed from their precursors. The pathways for others, such as the aromatic amino acids, are more complicated.

Different organisms vary greatly in their ability to synthesize the 20 amino acids. Whereas most bacteria and plants can synthesize all 20, mammals can synthesize only about half of them.

Those that are synthesized in mammals are generally those with simple pathways. These are called the nonessential amino acids to denote the fact that they are not needed in the diet. The remaining, the essential amino acids, must be obtained from the diet.

Essential amino acids (EAA)	EAA (%)
Arginine	1.2
Histidine	1.08
Isoleucine	12.3
Leucine	5.63
Lysine	13.42
Methionine	13.06
Phenylalanine	1.27
Tryptophan	1.3
Valine	23.72
Total	72.98

Non essential amino acids (NEAA)	NEAA (%)
Alanine	1
Asparagine	0.056
Aspartic acid	1.46
Cystine	5.56
Glutamic acid	2.51
Glycine	9.8
Proline	4.26
Serine	2.66
Tyrosine	2.51
Total	29.816

Intermediates of glycolysis serve as precursors for serine, glycine, cysteine, and alanine.

Serine can be synthesized from the glycolytic intermediate 3-phosphoglycerate, which is oxidized, transaminated by glutamate, and dephosphorylated.

Glycine and cysteine can be derived from serine.

Glycine can be produced from serine by a reaction in which a methylene group is transferred to tetrahydrofolate (FH4).

Cysteine derives its carbon and nitrogen from serine. The essential amino acid methionine supplies the sulfur.

Alanine can be derived by transamination of pyruvate.

Amino acids derived from TCA cycle intermediates

Aspartate can be derived from oxaloacetate by transamination.

Asparagine is produced from aspartate by amidation.

Glutamate is derived from α-ketoglutarate by the addition of NH_4^+ via the glutamate dehydrogenase reaction or by transamination. Glutamine, proline, and arginine can be derived from glutamate.

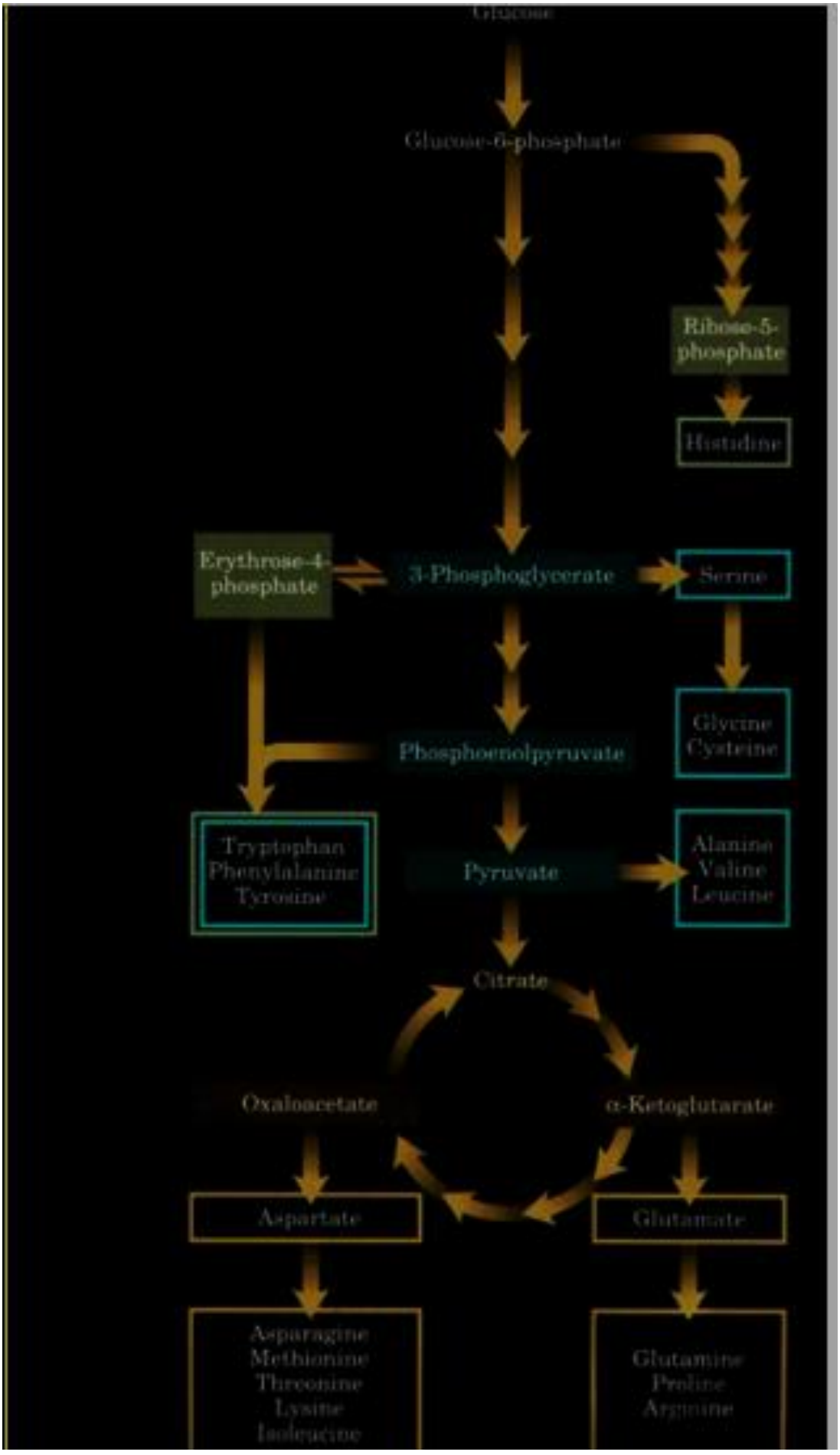
Glutamine is produced by amidation of glutamate.

Proline and arginine can be derived from glutamate semialdehyde, which is formed by reduction of glutamate.

Proline can be produced by cyclization of glutamate semialdehyde.

Arginine, via three reactions of the urea cycle, can be derived from ornithine, which is produced by transamination of glutamate semialdehyde.

Tyrosine, the 11th nonessential amino acid, is synthesized by hydroxylation of the essential amino acid phenylalanine in a reaction that requires tetrahydrobiopterin.


Glucose
Glucose-6-phosphate
Ribose-5-phosphate
Histidine
Erythrose-4-phosphate
3-Phosphoglycerate
Serine
Glycine
Cysteine
Phosphoenolpyruvate
Tryptophan
Phenylalanine
Tyrosine
Pyruvate
Alanine
Valine
Leucine
Citrate
Oxaloacetate
α-Ketoglutarate
Aspartate
Glutamate
Asparagine
Methionine
Threonine
Lysine
Isoleucine
Glutamine
Proline
Arginine

Degradation of amino acids

Occures in the liver. These pathways are mainly glucogenic (or gluconeogenic) which provide carbon for the synthesis of glucose.

Amino acids that form acetyl CoA or acetoacetate are ketogenic; which form ketone bodies.

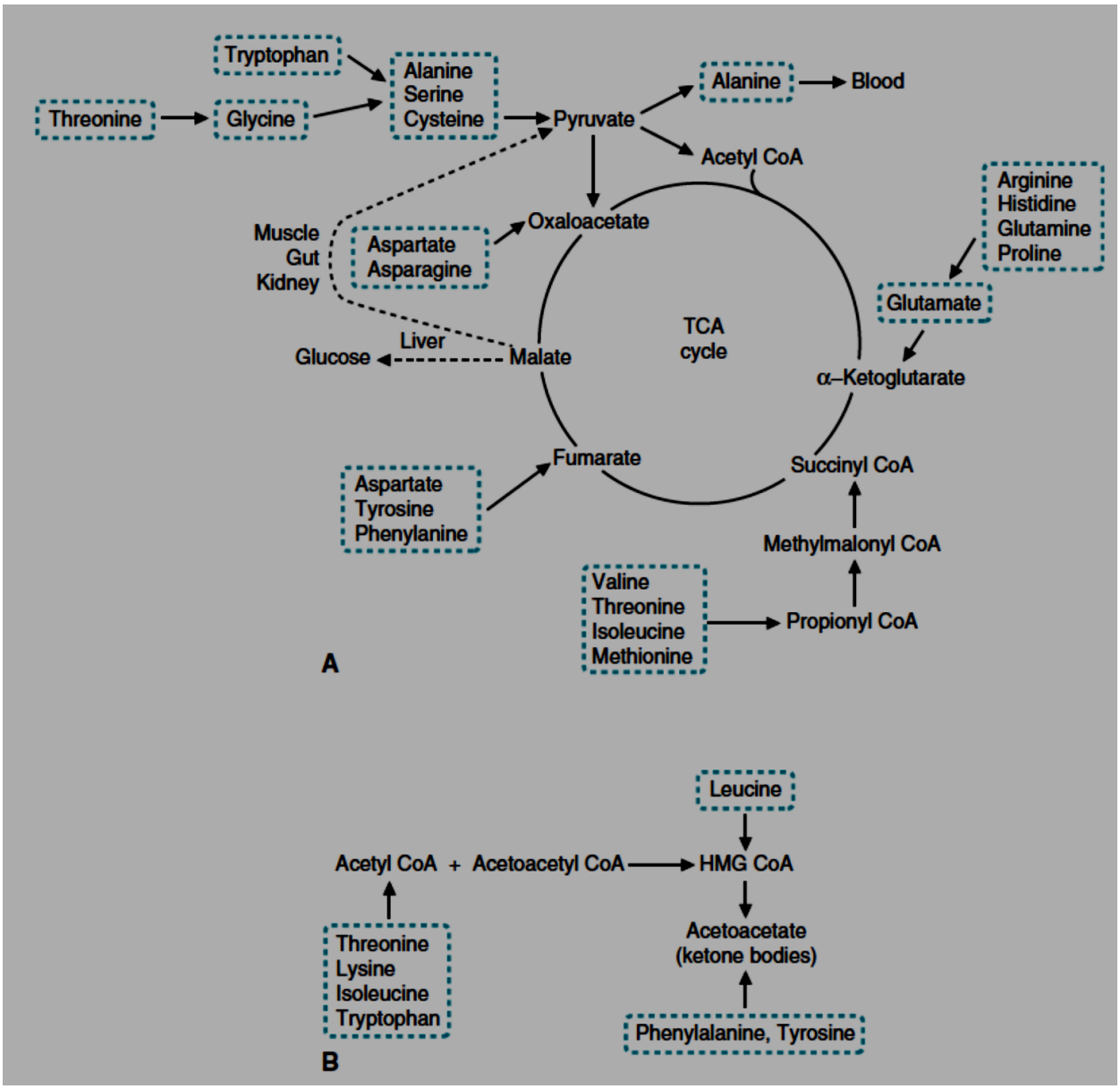
Isoleucine, tryptophan, phenylalanine, and tyrosine are glucogenic and ketogenic in the same time.

Amino acids that are converted to pyruvate

Occures in the liver. These pathways are mainly glucogenic (or gluconeogenic) which provide carbon for the synthesis of glucose. Amino acids that are synthesized from intermediates of glycolysis (serine, glycine, cysteine, and alanine) are degraded to form pyruvate.

Serine is converted to 2-phosphoglycerate, an intermediate of glycolysis, or directly to pyruvate and NH_4^+ by serine dehydratase, which is an enzyme that requires PLP.

Glycine reacts with methylene FH_4 to form serine.



Cysteine forms pyruvate. Its sulfur, which was derived from methionine, is converted to sulfuric acid (H_2SO_4), which is excreted by the kidneys.

Alanine can be transaminated to pyruvate.

Amino acids that are converted to intermediates of the TCA cycle

Carbons from four groups of amino acids form the TCA cycle intermediates α-ketoglutarate, succinyl CoA, fumarate, and oxaloacetate.

Amino acids that form α-ketoglutarate:

(1) Glutamate can be deaminated by glutamate dehydrogenase or transaminated to form α-ketoglutarate.

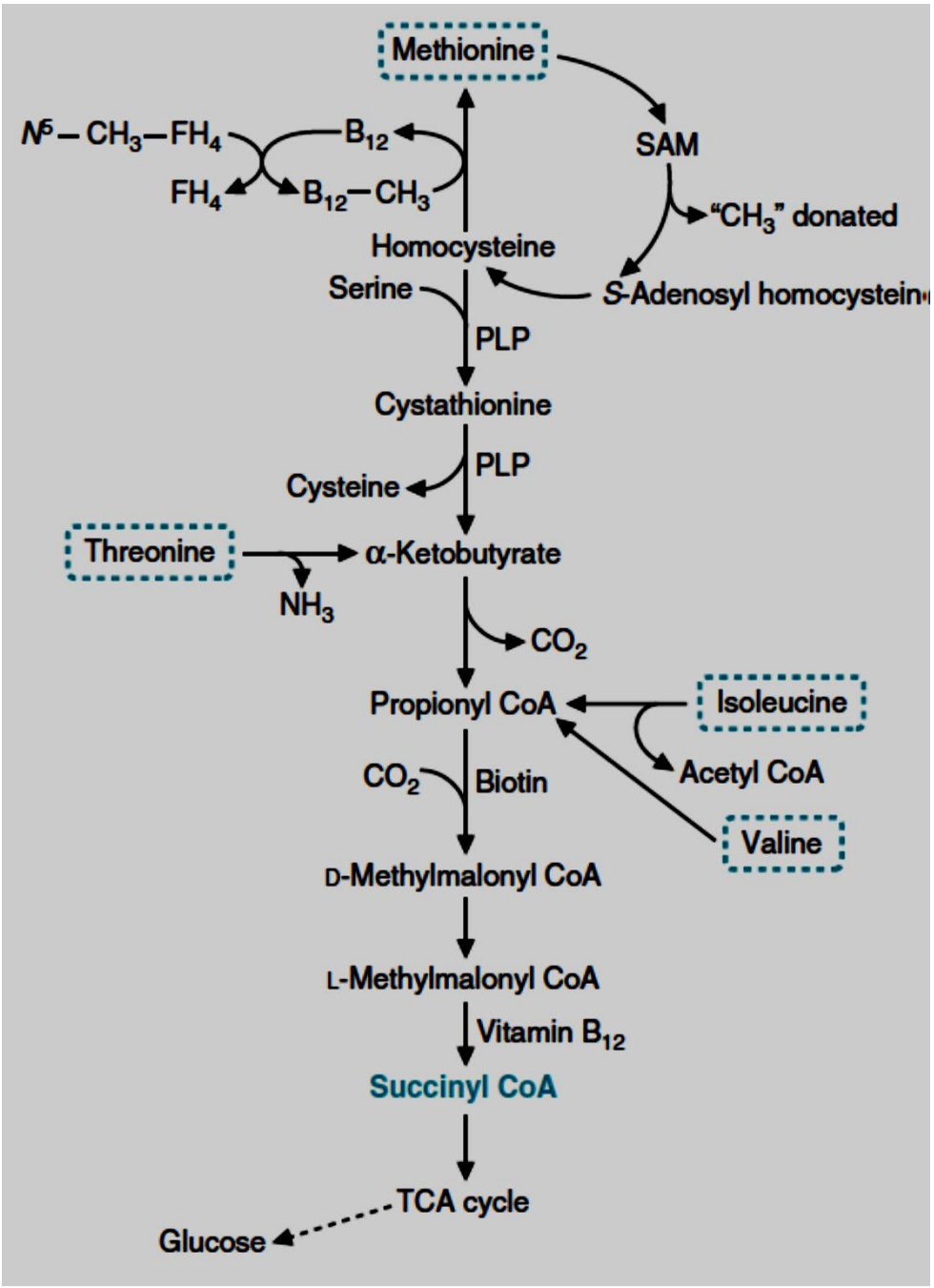
(2) Glutamine is converted by glutaminase to glutamate with the release of its amide nitrogen as NH_4^+.

(3) Proline is oxidized so that its ring opens, forming glutamate semialdehyde, which is reduced to glutamate.

(4) Arginine is cleaved by arginase in the liver to form urea and ornithine. Ornithine is transaminated to glutamate semialdehyde, which is oxidized to glutamate.

(5) Histidine is converted to formiminoglutamate (FIGLU). The formimino group is transferred to FH_4, and the remaining five carbons form glutamate.

Amino acids that form succinyl CoA



Threonine, methionine, valine, and isoleucine are converted to succinyl CoA which utilizes vitamin B12.

In a different set of reactions, threonine is converted to glycine and acetyl CoA. Methionine provides methyl groups for the synthesis of various compounds; its sulfur is incorporated into cysteine; and the remaining carbons form succinyl CoA. Valine and isoleucine, two of the three branched-chain amino acids, form succinyl CoA.

Degradation of all three branched-chain amino acids begins with a transamination, ketoacid dehydrogenase complex. This enzyme, like pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, requires thiamine pyrophosphate, lipoic acid, CoA, flavin adenine dinucleotide (FAD), and NAD^+.

Amino acids that form fumarate

Phenylalanine, tyrosine, and aspartate are converted to fumarate.

(1) Phenylalanine is converted to tyrosine by phenylalanine hydroxylase in a reaction requiring tetrahydrobiopterin and O_2.

(2) Tyrosine, which is obtained from the diet or by hydroxylation of phenylalanine, is converted to homogentisic acid. The aromatic ring is opened and cleaved, forming fumarate and acetoacetate.

(3) Aspartate is converted to fumarate through reactions of the urea cycle and the purine nucleotide cycle. Aspartate reacts with IMP to form AMP and fumarate in the purine nucleotide cycle.

Amino acids that form oxaloacetate

(1) Aspartate is transaminated to form oxaloacetate.

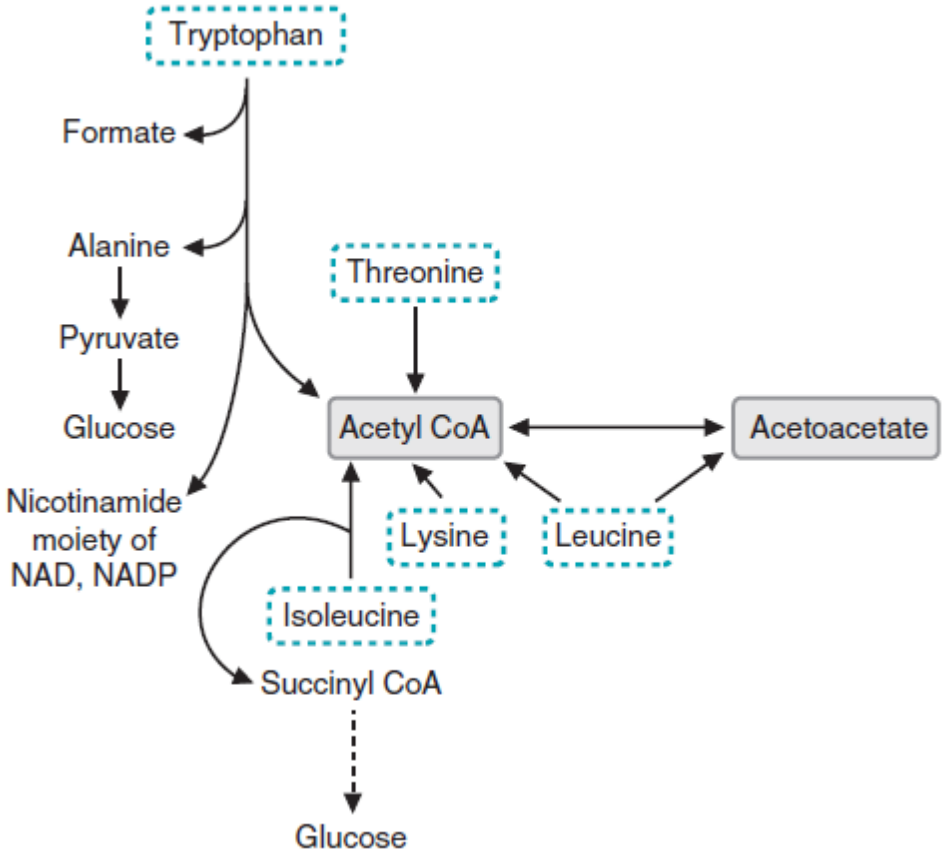
(2) Asparagine loses its amide nitrogen as NH_4^+, forming aspartate in a reaction catalyzed by asparaginase.

Amino acids that are converted to acetyl CoA or acetoacetate

Lysine, threonine, isoleucine, and tryptophan can form acetyl CoA.

Phenylalanine and tyrosine form acetoacetate.

Leucine is degraded to form both acetyl CoA and acetoacetate.


Tryptophan
Formate
Alanine
Pyruvate
Glucose
Nicotinamide moiety of NAD, NADP
Threonine
Acetyl CoA
Acetoacetate
Lysine
Leucine
Isoleucine
Succinyl CoA
Glucose