BIOCHEMISTRY

Amino acid metabolism

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Chapter Description

- Overview

  This chapter is related to amino acid catabolism and anabolism. Some fundamental understanding on transamination, removal of amino group, oxidative deamination, urea cycle, terms of glucogenic and ketogenic types of amino acids and various other topics presented.

- Expected Outcomes

  You should be able to understand metabolism of amino acid in general. The relevance of removal of the nitrogen from the amino acid prior to utilizing the carbon skeleton for energy needs. The management of the toxicity exerted by the ammonia ion by urea cycle.

- Other related Information

  Some relevant questions been provided for improving your understanding of the topic. You are expected to search for external sources for information to adequately answer the questions. All pictures and figures within this chapter categorized as creative commons for the purpose of education only.

Catabolism of Amino Acids

Proteins Are Degraded to Amino Acids

- **Dietary protein** is digested in the intestine, **producing amino acids** that are transported throughout the body.
- Cellular proteins are degraded at widely variable rates, ranging from **minutes to the life** of the organism.
- This protein turnover is **tightly regulated**

The Initial Step in Amino Acid Degradation Is the Elimination of Nitrogen

- Surplus amino acids are used as metabolic fuel. The first step in their degradation is the **removal of their α-amino groups** by **transamination** to an α-keto acid.
- Pyridoxal phosphate (**PLP**) is the coenzyme in all aminotransferases and in many other enzymes catalyzing amino acid transformations.
- The α-amino group funnels into α-ketoglutarate to form glutamate, which is **then oxidatively deaminated** by glutamate dehydrogenase to give NH_4^+ and α-ketoglutarate.
- NAD^+ or $NADP^+$ is the electron acceptor in this reaction.

The Initial Step in Amino Acid Degradation Is the Elimination of Nitrogen

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

- ***Aminotransferases*** *catalyzes the transfer of an α-amino group from an* ***α-amino acid*** *to an* ***α-keto acid****. These enzymes,* also called *transaminases, generally funnel α-amino groups from a variety of amino acids to α-keto-glutarate for* conversion into NH_4^+.

- These transamination reactions are reversible and can thus be used to synthesize amino acids from α-ketoacids.

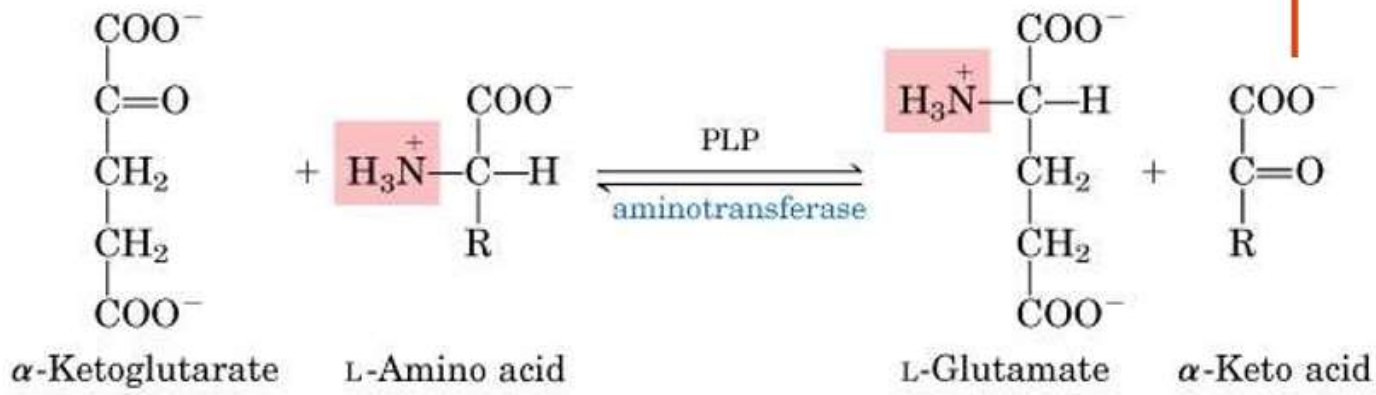
Transamination:

Transfer of amino group to a-ketoglutarate. There are several aminotransferases specific to different amino acids. In this step amino group from all the amino acids are transferred to a-ketoglutarate and they exist as glutamate.

Transaminases or aminotransferases require pyridoxal-5'-phophate, PLP (vitamine B6 derivative)

PLP is very important cofactor for many enzymatic reactions.

Metabolism of carbon skeleton



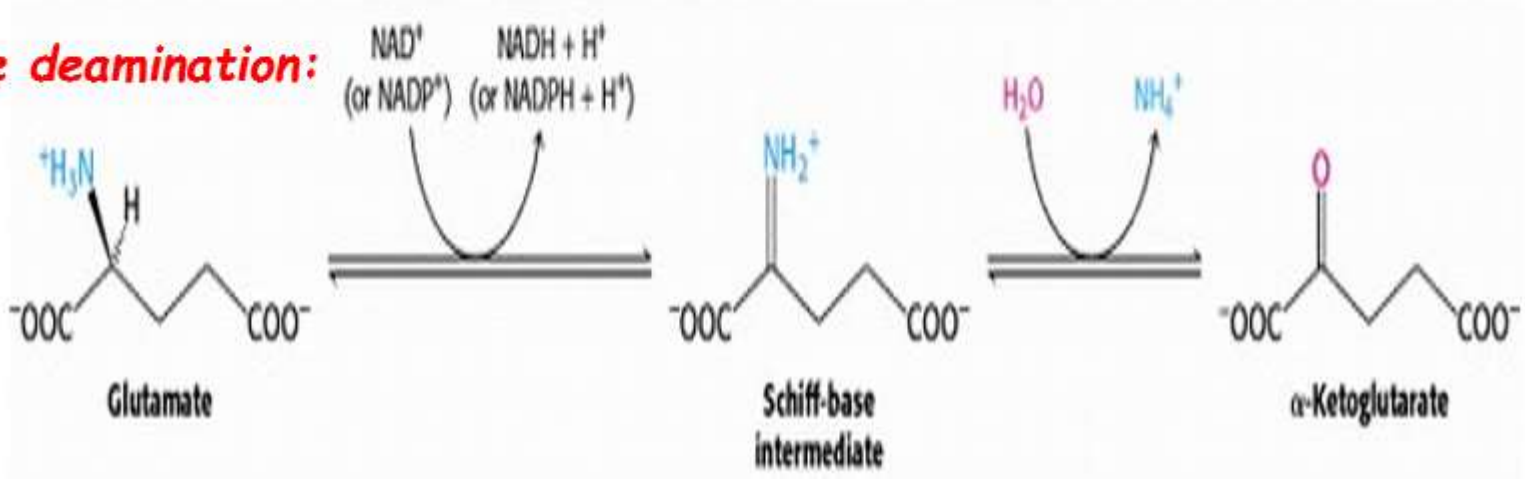
α-Ketoglutarate L-Amino acid L-Glutamate α-Keto acid

- The **nitrogen atom that is transferred** to glutamate in the transamination reaction is converted **into free ammonium ion** by **oxidative deamination**.

- This reaction is catalyzed by ***glutamate dehydrogenase***. *This enzyme is unusual in being* able to utilize either NAD+ or NADP+, at least in some species.

- The reaction proceeds by dehydrogenation of the C-N bond, followed by hydrolysis of the resulting Schiff base.

Oxidative deamination:



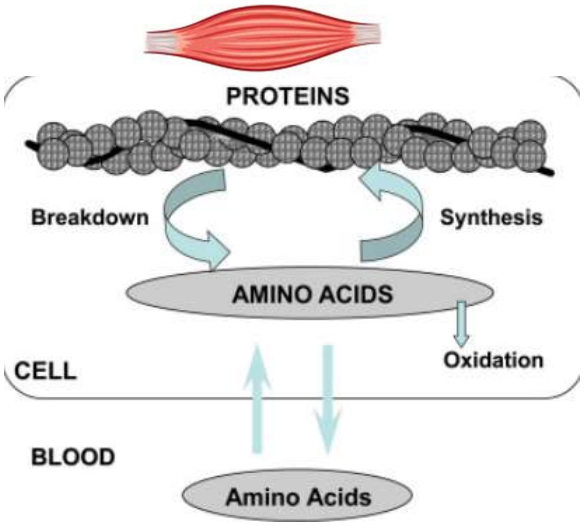
- The equilibrium for this reaction favors glutamate; the reaction is **driven by the consumption of ammonia**.

- Glutamate dehydrogenase is **located in mitochondria**, as are some of the other enzymes required for the production of urea.

- This compartmentalization sequesters **free ammonia**, which is **toxic**.

- In most terrestrial vertebrates, NH_4^+ **is converted into urea**, which is excreted.

Summary



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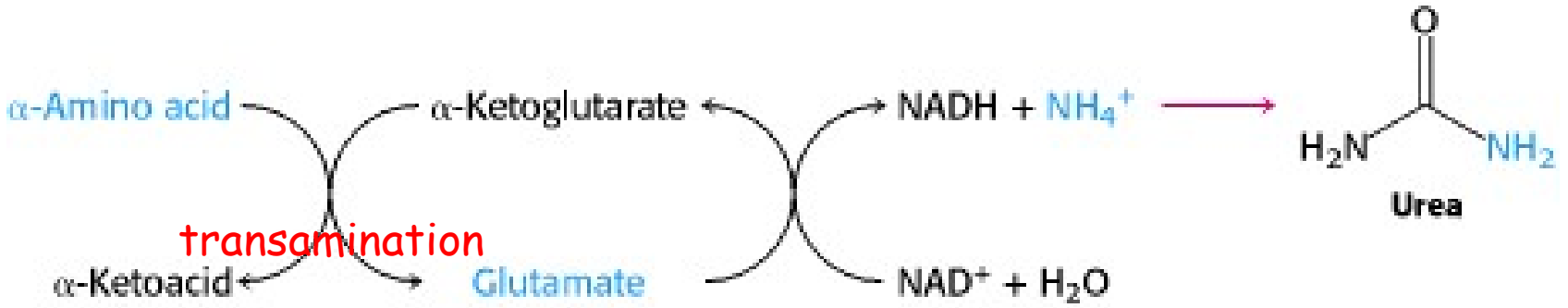


(e.g pyruvate)

How is the nitrogen processed in tissues other than liver?

- Most amino acid degradation takes place in tissues other than the liver. For instance, muscle uses amino acids as a source of fuel during prolonged exercise and fasting.
- As in the liver, the first step is the removal of the nitrogen from the amino acid. However, muscle lacks the enzymes of the urea cycle, so the nitrogen must be released in a form that can be absorbed by the liver and converted into urea.
- Nitrogen is transported from muscle to the liver in two principal transport forms.
- Glutamate is formed by transamination reactions, but the nitrogen is then

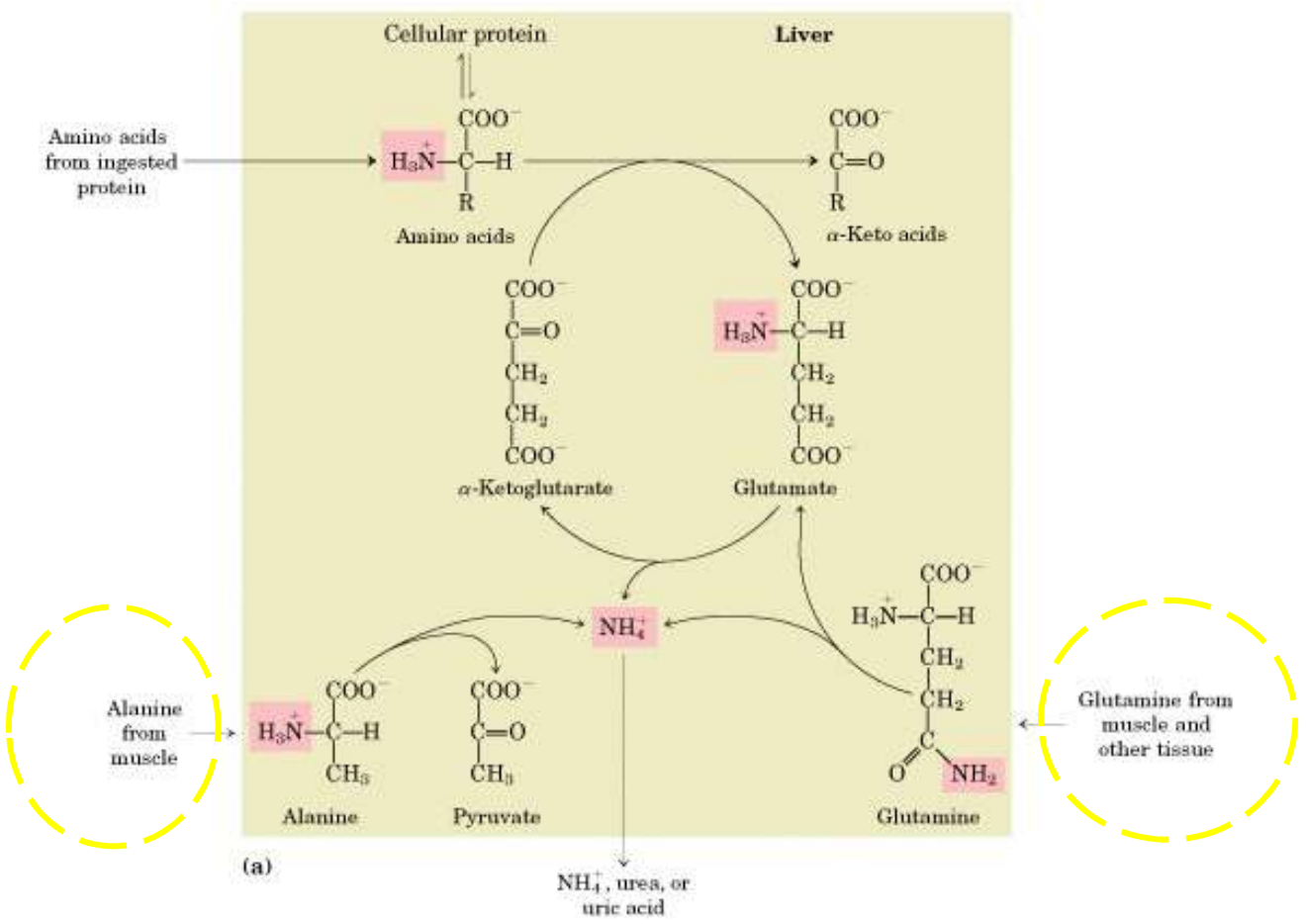
- The liver takes up the alanine and converts it back into pyruvate.

- The pyruvate can be used for **gluconeogenesis** and the amino group eventually appears as urea. This transport is referred to as the ***alanine cycle***.

- Nitrogen can also be transported as **glutamine**. Glutamine synthetase catalyzes the synthesis of glutamine from glutamate and NH_4^+ in an ATP-dependent reaction.

- The nitrogen of glutamine and alanine can be converted into urea in the liver.

Overall:


Cellular protein
Liver
Amino acids from ingested protein
Amino acids
α-Keto acids
α-Ketoglutarate
Glutamate
NH4+
Alanine from muscle
Alanine
Pyruvate
Glutamine
Glutamine from muscle and other tissue
(a)
NH4+, urea, or uric acid

UREA CYCLE

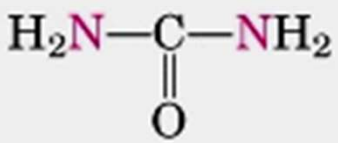
Ammonium Ion Is Converted Into Urea in Most Terrestrial Vertebrates

- Some of the NH_4^+ formed in the breakdown of amino acids is consumed in the biosynthesis of nitrogen compounds.
- In most terrestrial vertebrates, the excess NH4+ is converted into *urea and then excreted. Such organisms are referred to as ureotelic.*
- One of the nitrogen atoms of the urea is transferred from an amino acid, aspartate. The other nitrogen atom is derived directly from free NH4+, and the carbon atom comes from HCO3- (derived by hydration of CO2).

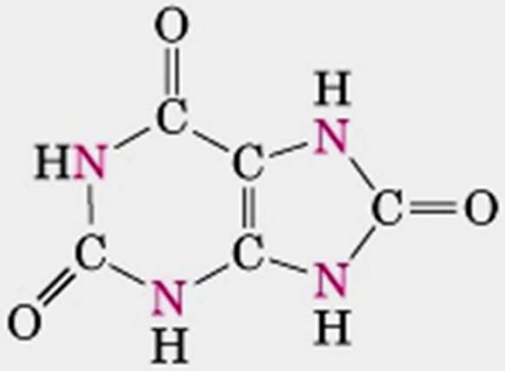
Excretory forms of Nitrogen

NH_4^+

Ammonia (as ammonium ion)



Urea

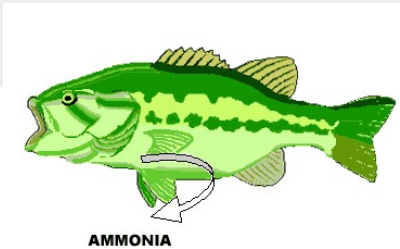


Uric acid

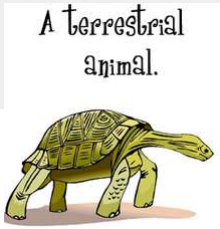
Ammonotelic animals: most aquatic vertebrates, such as bony fishes and the larvae of amphibia

Ureotelic animals: many terrestrial vertebrates; also sharks

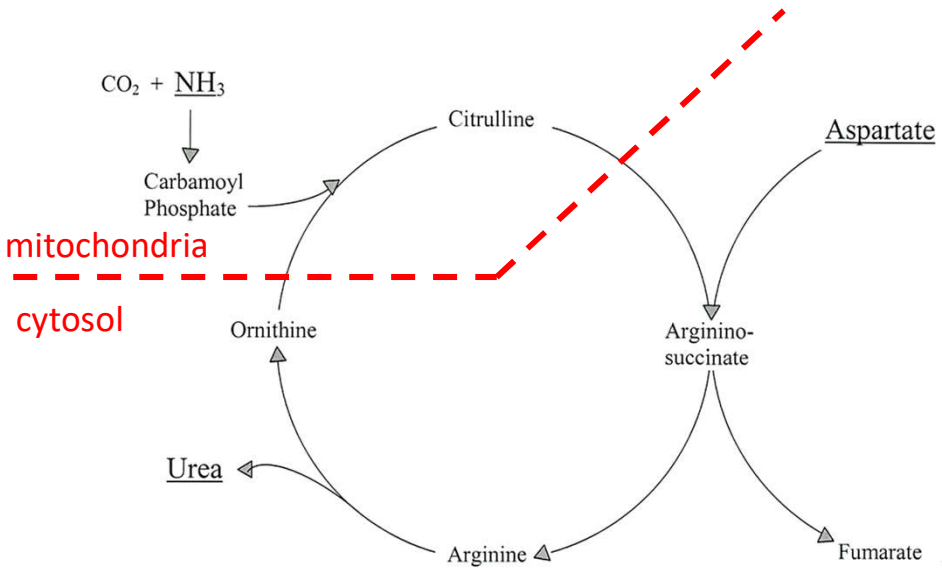
Uricotelic animals: birds, reptiles



AMMONIA

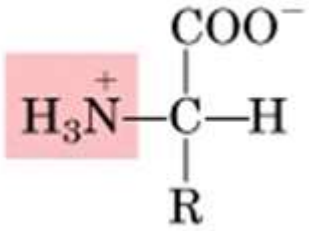


Urea Cycle



Function: detoxification of ammonia
(prevents hyperammonemia)

THE CARBON SKELETON OF AMINO ACIDS



Carbon Atoms of Degraded Amino Acids Emerge as Major Metabolic Intermediates

- The carbon atoms of degraded amino acids are converted into pyruvate, acetyl CoA, acetoacetate, or an intermediate of the citric acid cycle.
- Most amino acids are solely glucogenic, two are solely ketogenic, and a few are both ketogenic and glucogenic.

FATE OF THE CARBON SKELETON

Carbon skeletons are used for energy.

Glucogenic: TCA cycle intermediates or pyruvate (gluconeogensis)

Ketogenic: acetyl CoA, acetoacetyl CoA, or acetoacetate

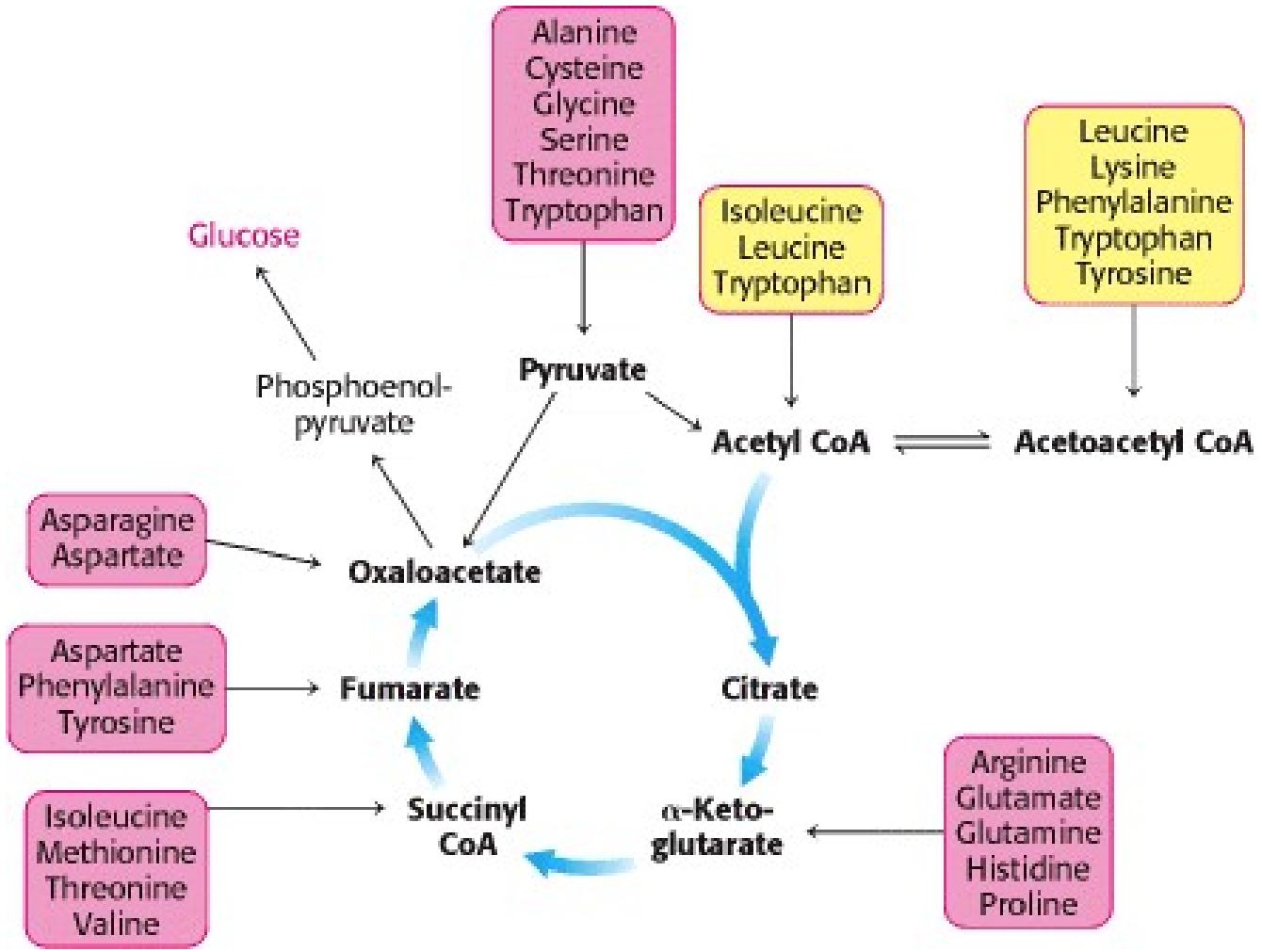
Glucogenic and Ketogenic Amino Acids

Glucogenic	*Glucogenic and Ketogenic*	*Ketogenic*
Alanine	Isoleucine	Leucine
Arginine	Phenylalanine	Lysine
Asparagine	Threonine	
Aspartate	Tryptophan	
Cysteine	Tyrosine	
Glutamine		
Glutamate		
Glycine		
Histidine		
Hydroxyproline		
Methionine		
Proline		
Serine		
Valine		

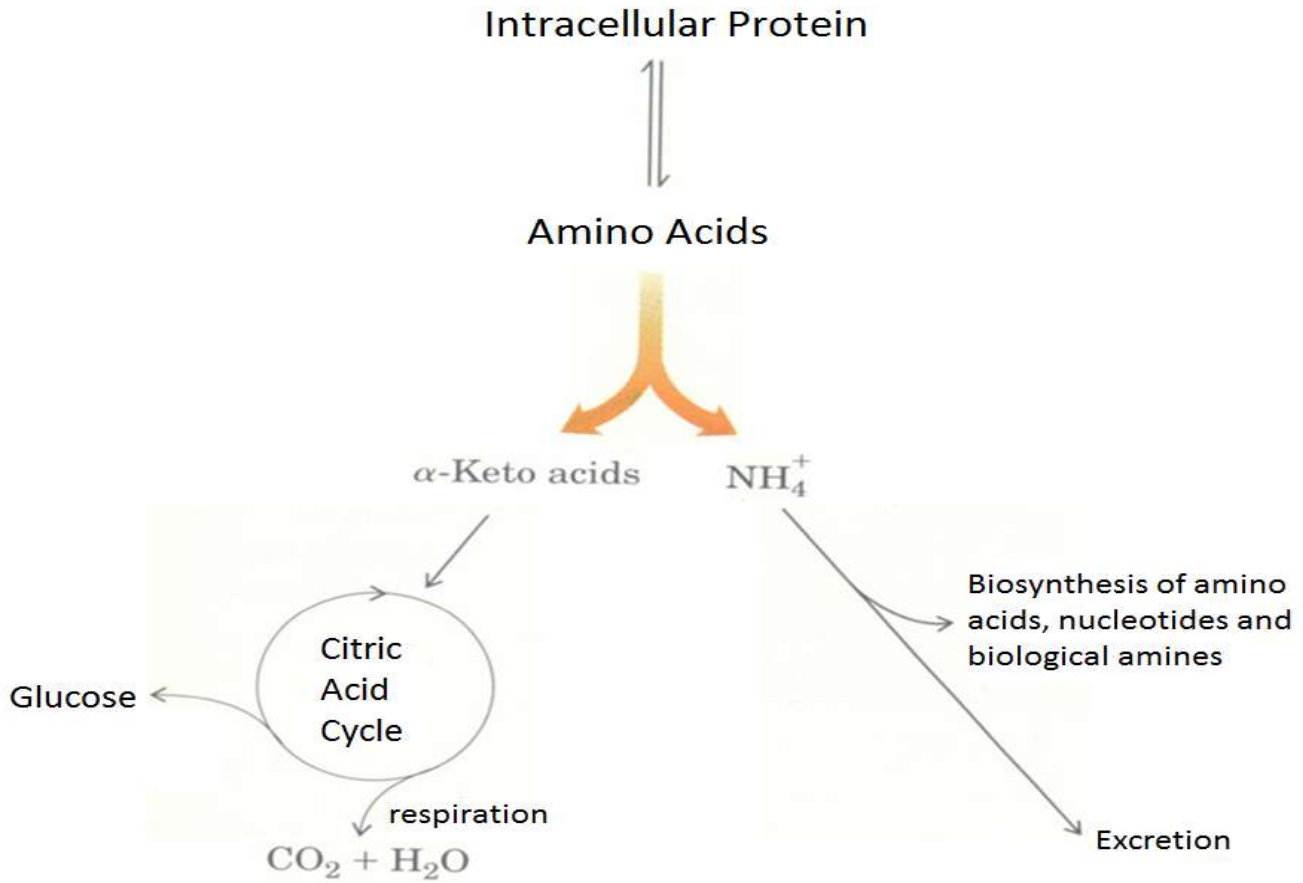
- Alanine, serine, cysteine, glycine, threonine, and tryptophan are degraded to pyruvate.
- Asparagine and aspartate are converted into oxaloacetate.
- a-Ketoglutarate is the point of entry for glutamate and four amino acids (glutamine, histidine, proline, and arginine) that can be converted into glutamate.
- Succinyl CoA is the point of entry for some of the carbon atoms of three amino acids (methionine, isoleucine, and valine).
- Leucine is degraded to acetoacetyl CoA and acetyl CoA.
- The breakdown of valine and isoleucine is like that of leucine.

Fates of the Carbon Skeletons of Amino Acids.

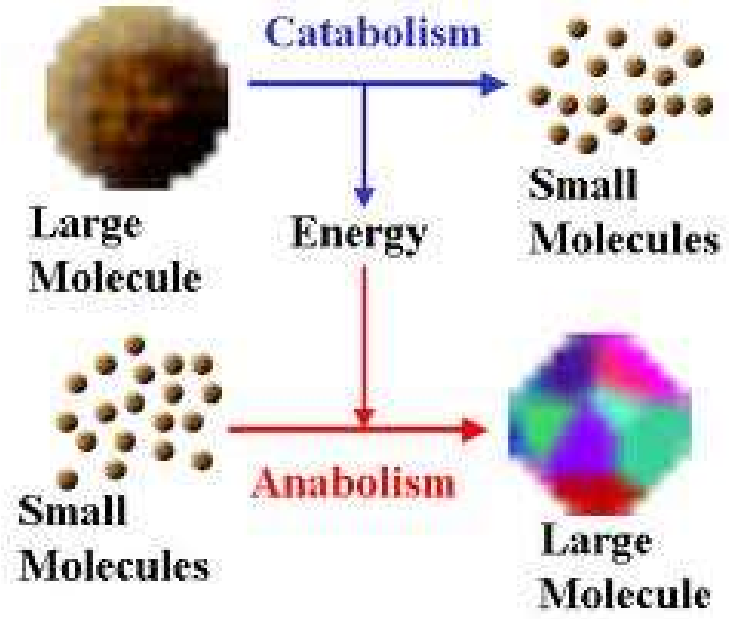
(Glucogenic amino acids are shaded red, and ketogenic amino acids are shaded yellow. Most amino acids are both glucogenic and ketogenic.)



OVERVIEW


Intracellular Protein
Amino Acids
α-Keto acids
NH_4^+
Citric Acid Cycle
Glucose
respiration
$CO_2 + H_2O$
Biosynthesis of amino acids, nucleotides and biological amines
Excretion

Amino acid metabolism- anabolism



Ammonium Ion Is Assimilated into an Amino Acid Through Glutamate and Glutamine

- The next step in the assimilation of nitrogen into biomolecules is the entry of NH_4^+ into amino acids. Glutamate and glutamine play pivotal roles in this regard. The α-amino group of most amino acids comes from the α-amino group of glutamate by transamination .

- Glutamine, the other major nitrogen donor, contributes its side-chain nitrogen atom in the biosynthesis of a wide range of important compounds, including the amino acids tryptophan and histidine.

- Glutamate is synthesized from NH_4^+ and α-ketoglutarate, a citric acid cycle intermediate, by the action of *glutamate dehydrogenase*. We have already encountered this enzyme in the degradation of amino acids. Recall that NAD^+ is the oxidant in catabolism, whereas NADPH is the reductant in biosyntheses.

Human Beings Can Synthesize Some Amino Acids but Must Obtain Others from the Diet

- Most microorganisms such as *E. coli can synthesize the entire basic set of 20 amino acids, whereas human beings cannot* make 9 of them.

- The amino acids that must be supplied in the diet are called essential amino acids, whereas the others are termed nonessential amino acids. These designations refer to the needs of an organism under a particular set of conditions. For example, enough arginine is synthesized by the urea cycle to meet the needs of an adult but perhaps not those of a growing child.

- *A deficiency of even one amino acid results in a negative nitrogen balance. In* this state, more protein is degraded than is synthesized, and so more nitrogen is excreted than is ingested.

Ability to synthesize amino acids

Microorganisms and plants: Able to synthesize all amino acids.

Animals: Unable to synthesize certain amino acids (essential amino acids). The essential amino acids must be obtained from the diet.

Non-essential	Essential	Conditionally essential
Alanine	Histidine	Arginine
Asparagine	Isoleucine	
Aspartate	Leucine	
Cysteine	Lysine	
Glutamate	Methionine	
Glycine	Phenylalanine	
Proline	Threonine	
Serine	Tryptophan	
Tyrosine*	Valine	

*formed from Phenylalanine, which is essential

- The α-ketoacids, α-ketoglutarate, oxaloacetate, and pyruvate can be converted into amino acids in one step through the addition of an amino group.

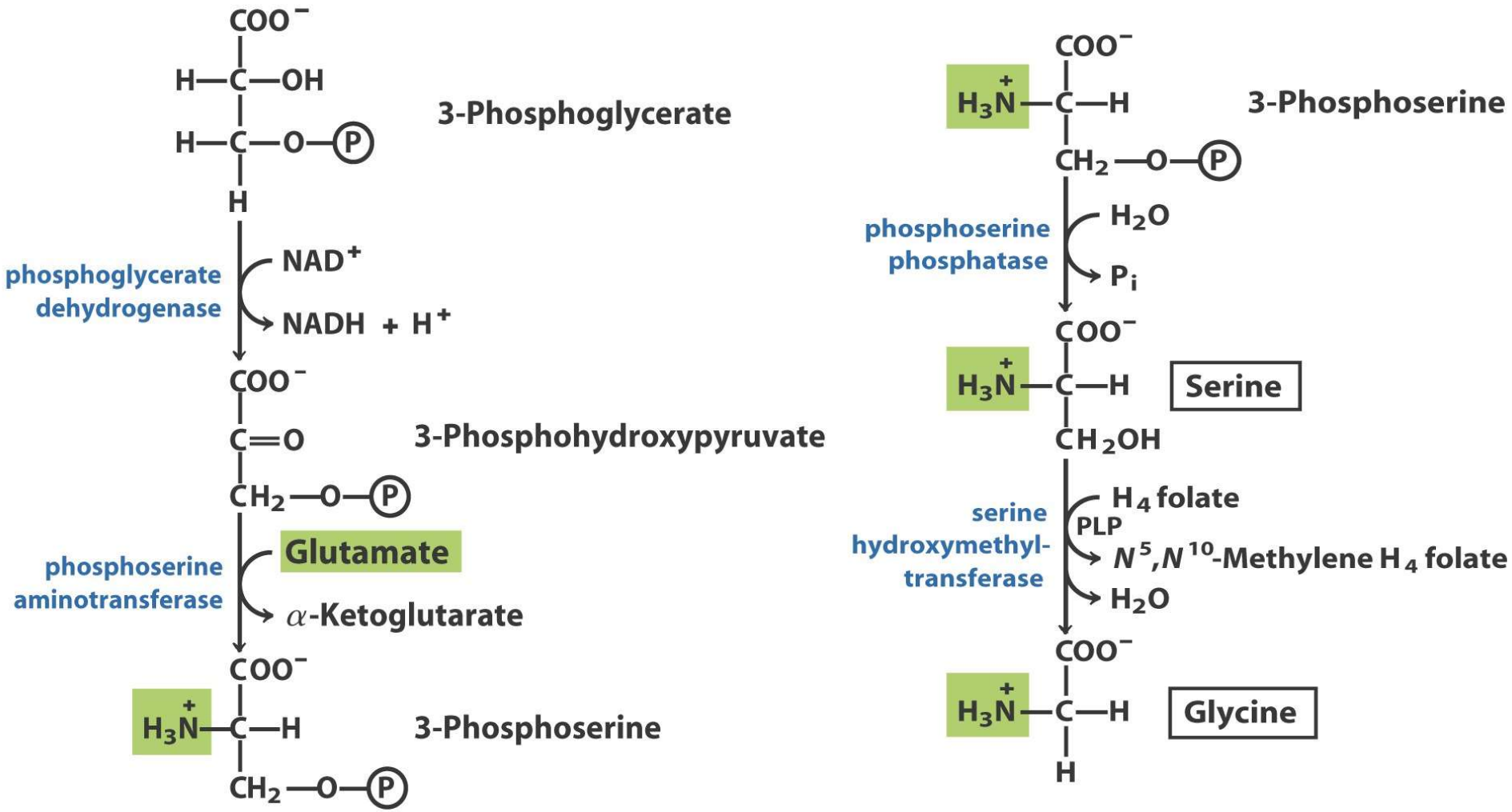
- We have seen that α-ketoglutarate can be converted into glutamate by reductive amination. The amino group from glutamate can be transferred to other α-ketoacids by transamination reactions.

- Thus, aspartate and alanine can be made from the addition of an amino group to oxaloacetate and pyruvate, respectively.

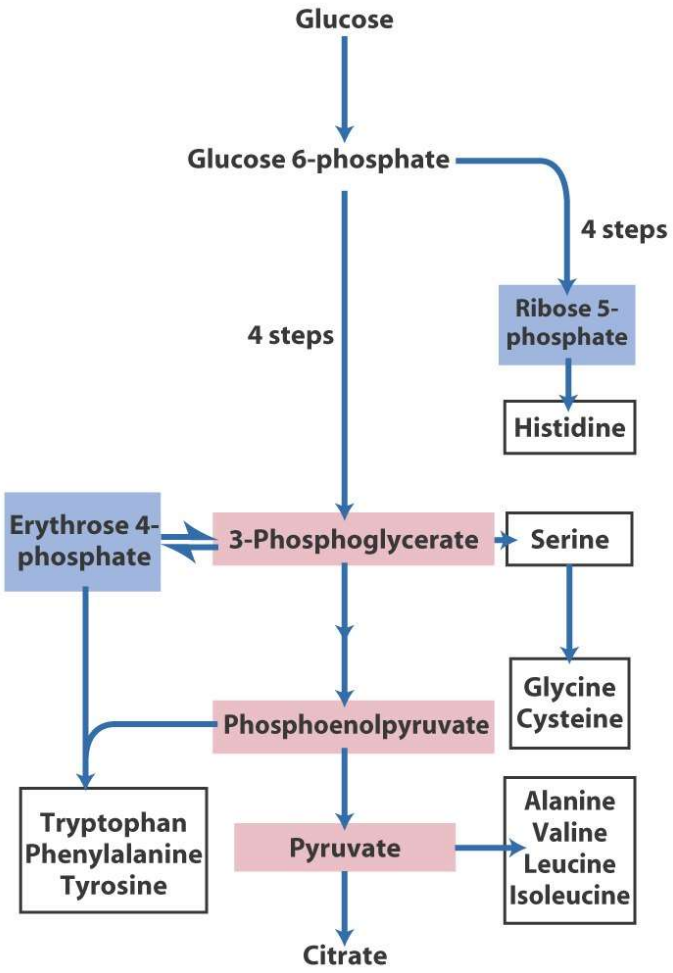
- These reactions are carried out by *pyridoxal phosphate-dependent transaminases.*

- *Transamination reactions* participate in the synthesis of most amino acids.

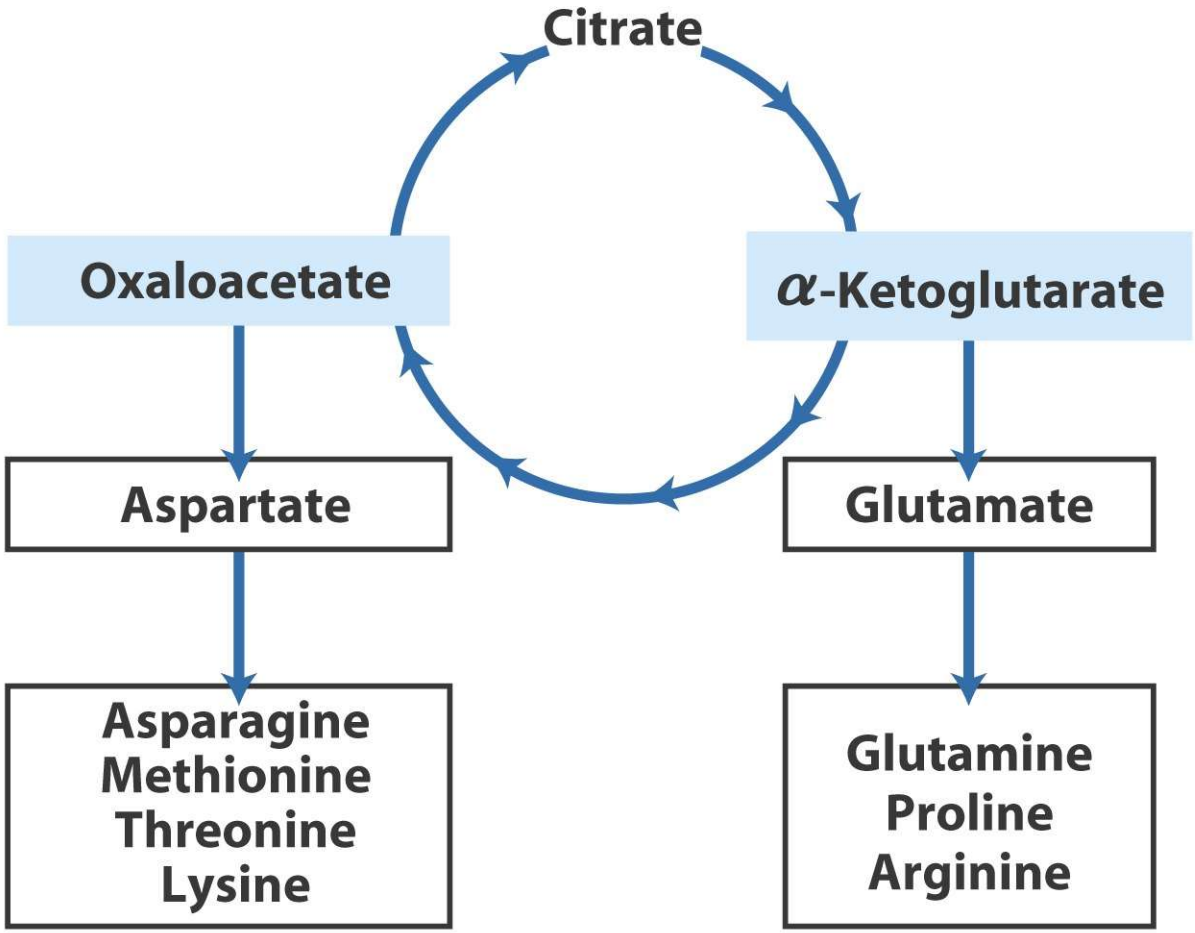
Synthesis of Serine and Glycine as e.g.



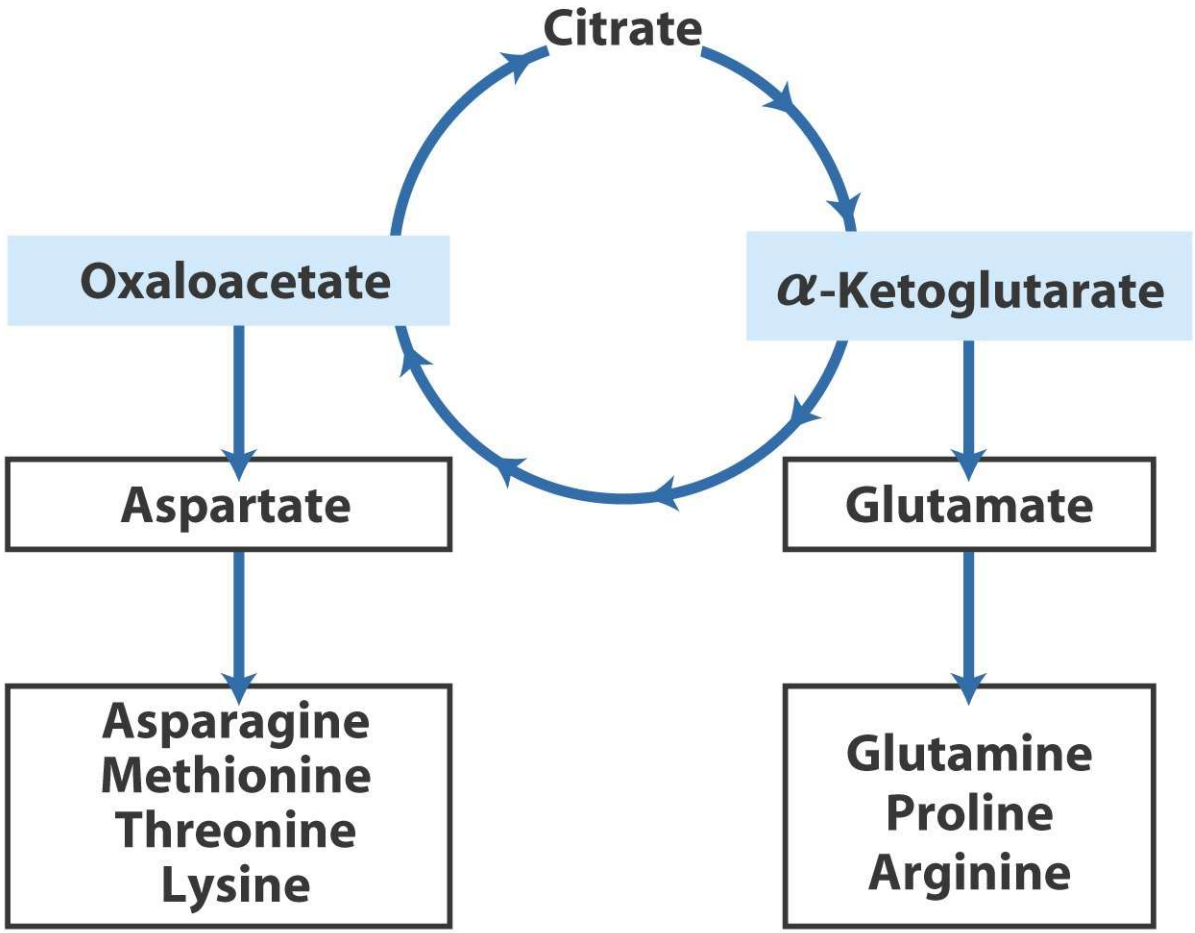
Sources of carbon skeletons needed for amino acid synthesis



Sources of carbon skeletons needed for amino acid synthesis (cont.)



Sources of carbon skeletons needed for amino acid synthesis (cont.)



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Google with keyword of biochemistr	Various Online Biochemi	various	
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