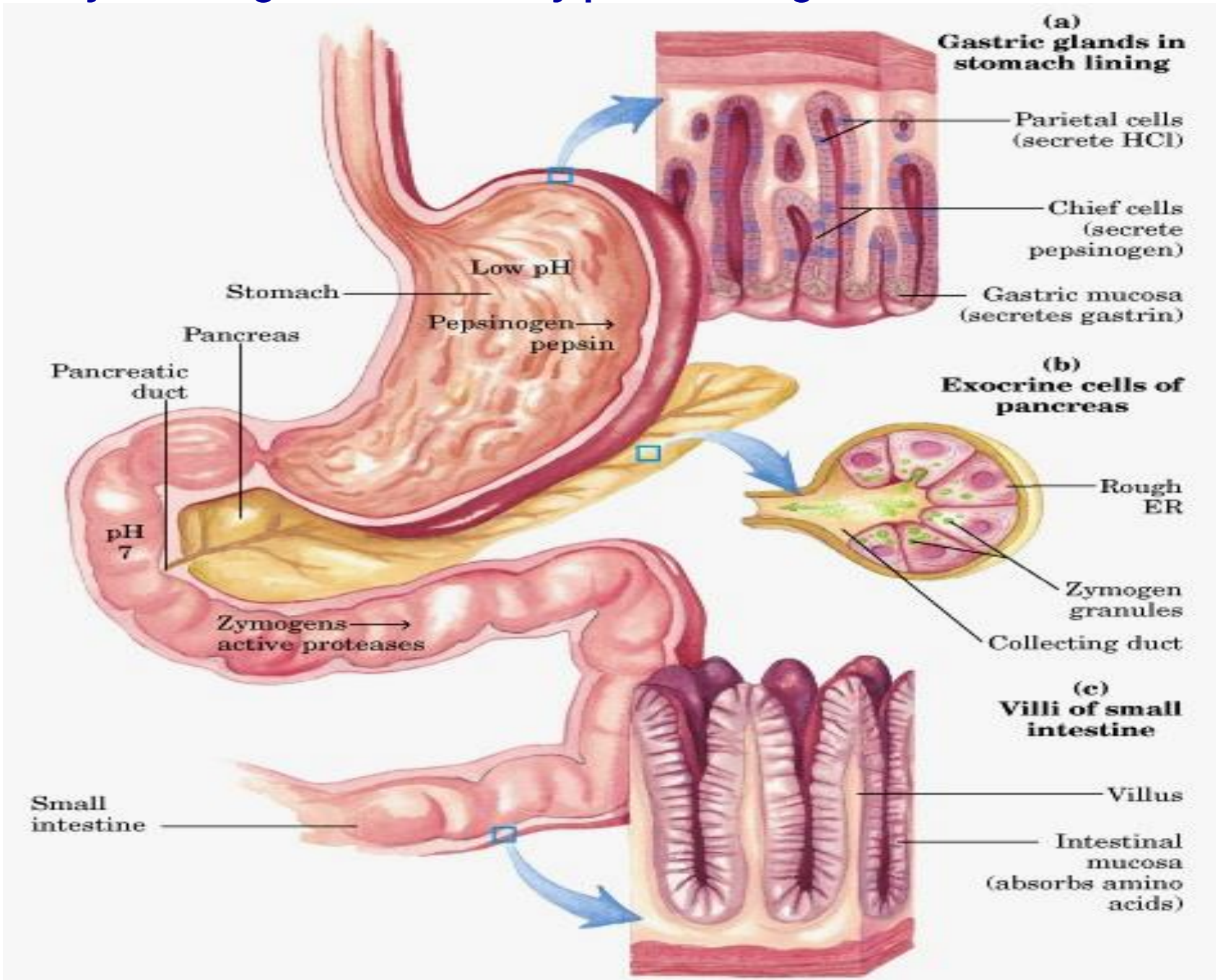
Amino Acids Metabolism

Enzymatic digestion of dietary proteins in gastro-intestinal-tract.



Enzymatic digestion of dietary proteins in gastro-intestinal-tract.

In stomach:

Dietary proteins stimulates gastric mucosa to secrete gastrin Hormone → stimulates HCl & pepsinogen secretion

HCl: denature globular proteins

Pepsinogen: is converted to active pepsin …hydrolyzes long peptide chains into smaller peptides.

In small intestine:

Low pH of stomach triggers secretion of secretin hormone into the blood … stimulates pancreas to secrete bicarbonate into the small intestine to neutralize gastric HCl

Arrival of amino acids causes release of hormone cholecystokinin into blood … stimulates the secretion of pancreatic enzymes: trypsinogen, chymotrypsinogen & procarboxypeptidases …active proteases further hydrolyze peptides into free amino acids … transported into epithelial cells of small intestine … enter blood … travel to liver.

Amino acids

- **There are 20 different amino acid.**
- **They are monomeric constituents of proteins**

➢ **Can be used as energy source.**

➢ **They act as precursors of other nitrogen containing biologically important compounds, like hormones, neurotransmitters,….etc.**

Amino acids undergo oxidative degradation in three different metabolic circumstances

1. During the normal synthesis & degradation of cellular proteins: some amino acids released during protein breakdown undergo oxidative degradation if they are not needed for new protein synthesis.

2. When a diet is rich in protein & ingested amino acids exceed the body's needs for protein synthesis, the surplus is catabolized.

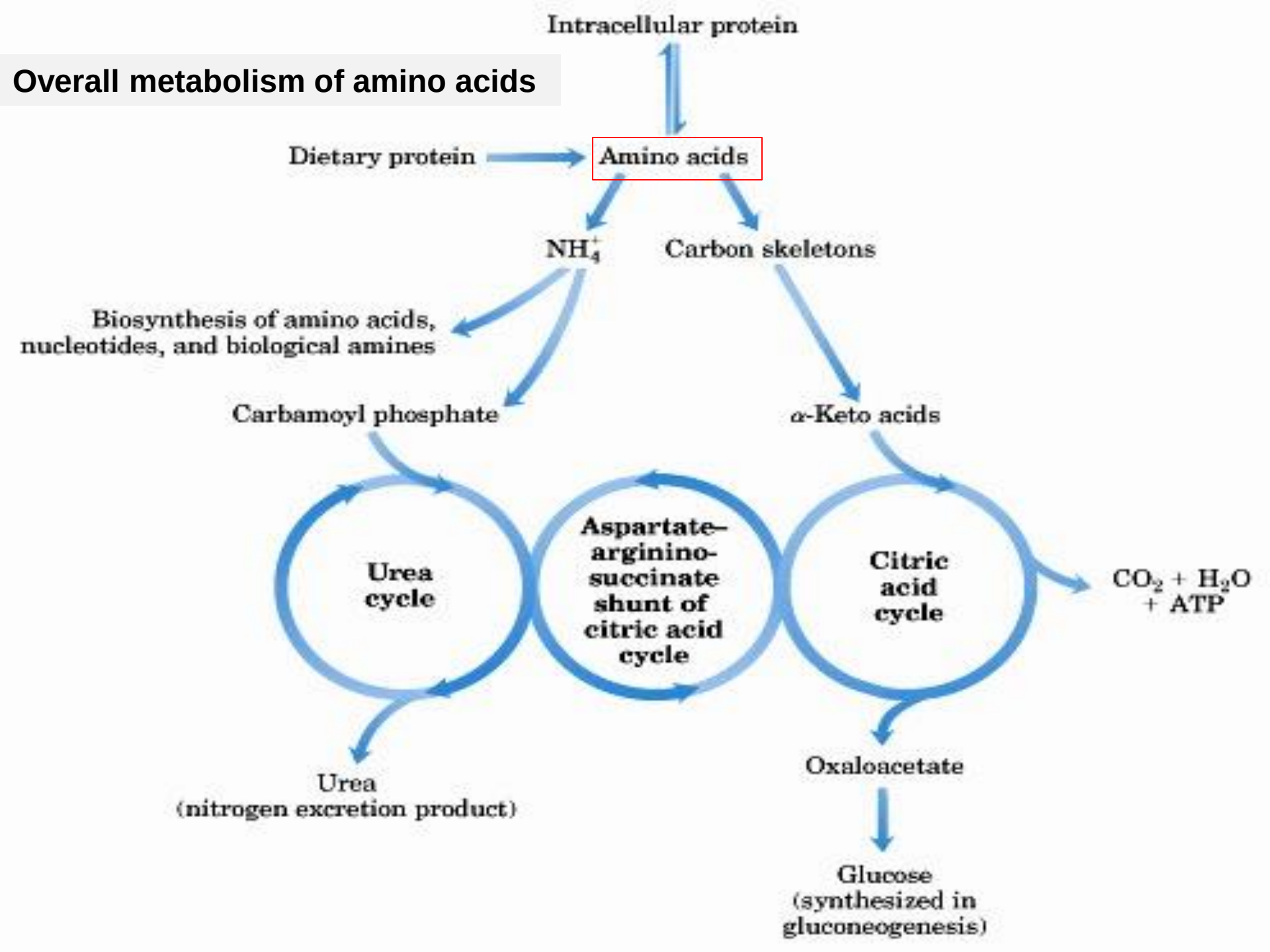
3. During starvation or in diabetes mellitus, when carbohydrates are either unavailable or not properly utilized, cellular proteins are used as fuel.

Amino acids - oxidative degradation

Under the previous conditions:

- **Amino acids lose their amino groups to form α-keto acids (carbon skeletons) that will undergo oxidation to CO_2 & H_2O**
- **OR provide 3 or 4-C units that can be converted by Gluconeogenesis into glucose (the fuel for brain, skeletal muscle, & other tissues).**

Overall metabolism of amino acids



Amino acids - oxidative degradation

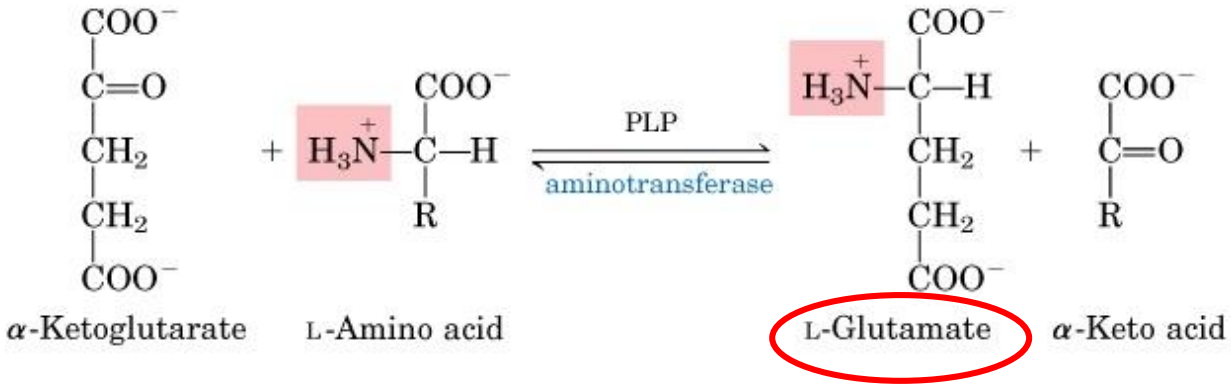
There are three major steps in catabolism of amino acids:

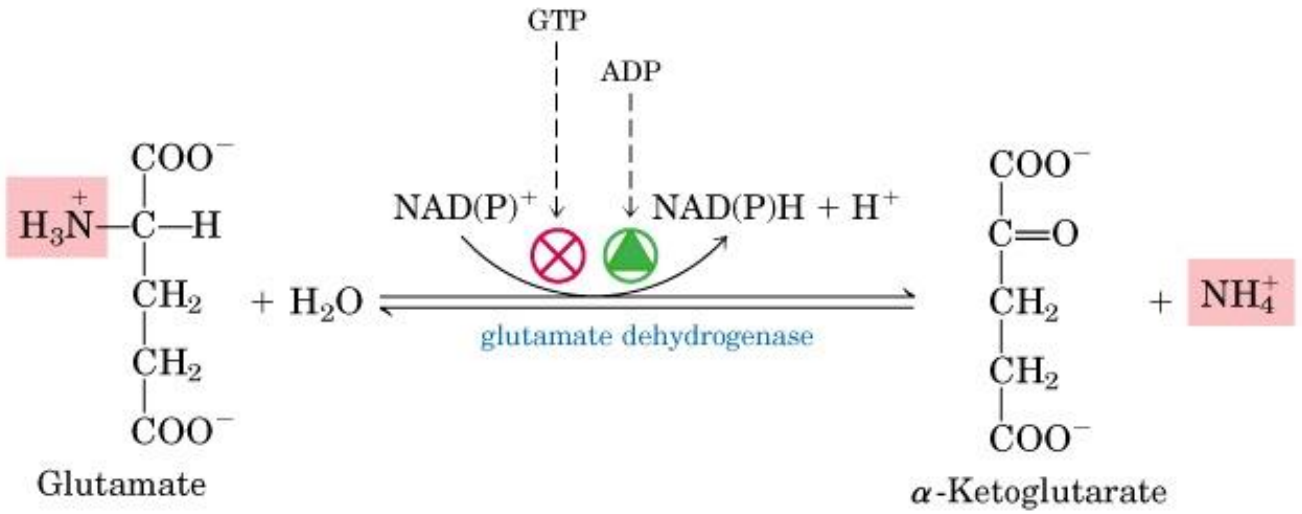
1. **Removal of amino group (deamination)**
   - I. **Transamination : Transfer of amino group to α-ketoglutarate yielding glutamate**
   - II. **Oxidative deamination: removal of amino group from glutamate to release ammonia**

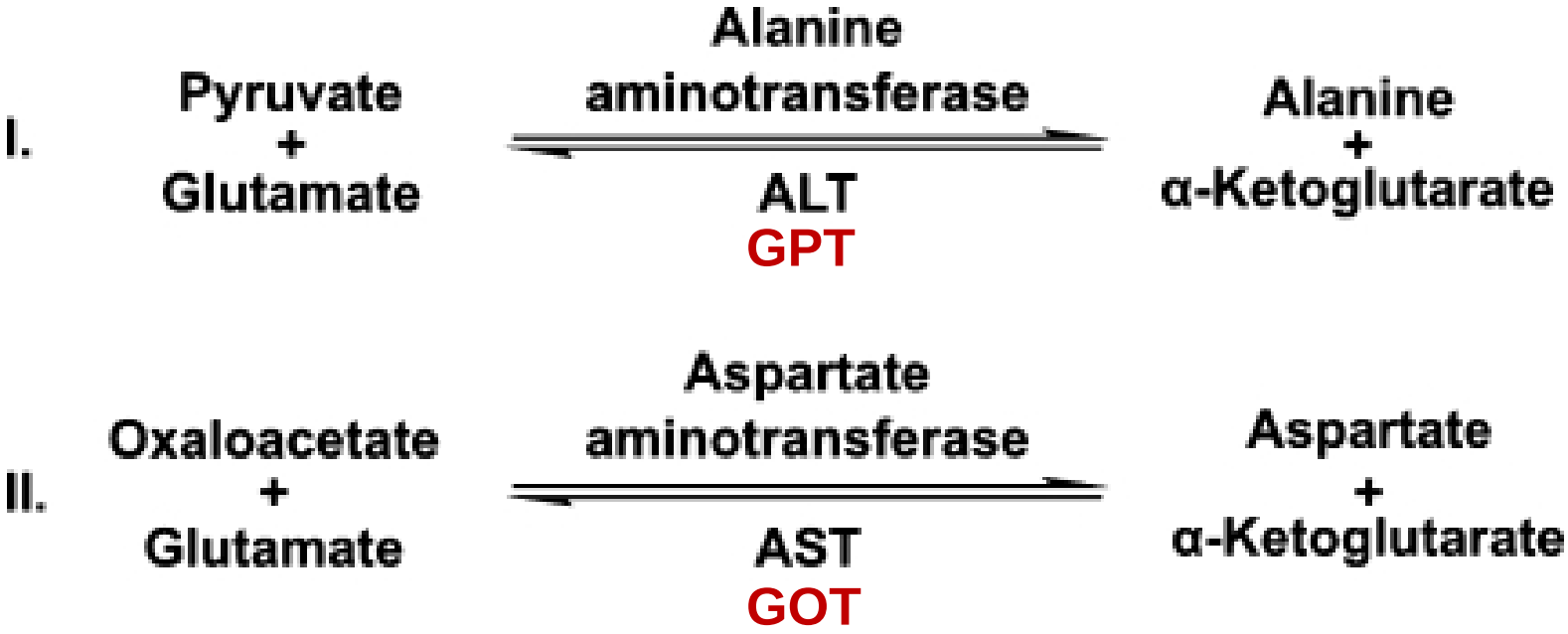
2. **Urea Cycle: Conversion of NH_3 to urea for excretion**

3. **Metabolic break down of carbon skeleton to generate common intermediates that can be catabolized to CO_2 or used in anabolic pathways to be stored as glucose or fat.**

Transamination and Oxidative deamination





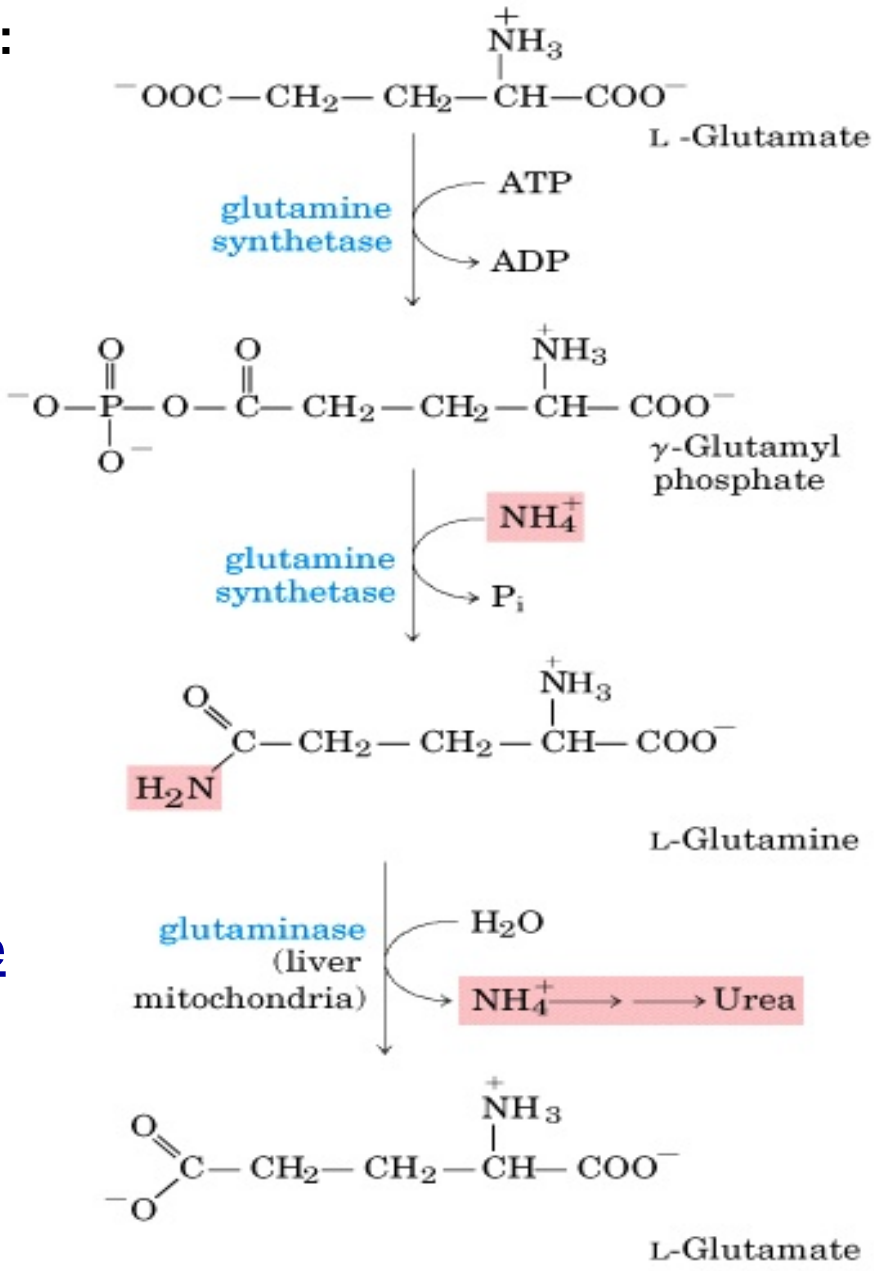

I.
Pyruvate
+
Glutamate
Alanine
aminotransferase
ALT
GPT
Alanine
+
α-Ketoglutarate
II.
Oxaloacetate
+
Glutamate
Aspartate
aminotransferase
AST
GOT
Aspartate
+
α-Ketoglutarate

Transport of excess ammonia by glutamine

- Ammonia is produced as a result of:
  - amino acid catabolism
  - nucleic acid degradation.
- Excess ammonia is toxic to animal tissues.

- Glutamine synthase catalyzes the synthesis of glutamine by adding the ammonia to glutamate at the expense of ATP hydrolysis.
- Glutamine is a non-toxic carrier of ammonia. It is transported to liver or kidney via blood.

- In liver or kidney mitochondria, the glutamine is converted to glutamate and ammonia.
  → Then ammonia is incorporated in urea cycle to be excreted.



Glucose-Alanine cycle:

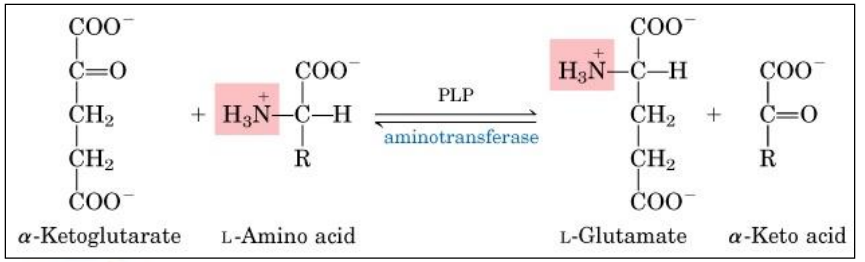
Amino group from excess glutamate produced in muscle as a result of amino acid catabolism, is transferred to pyruvate resulting in the formation of alanine.

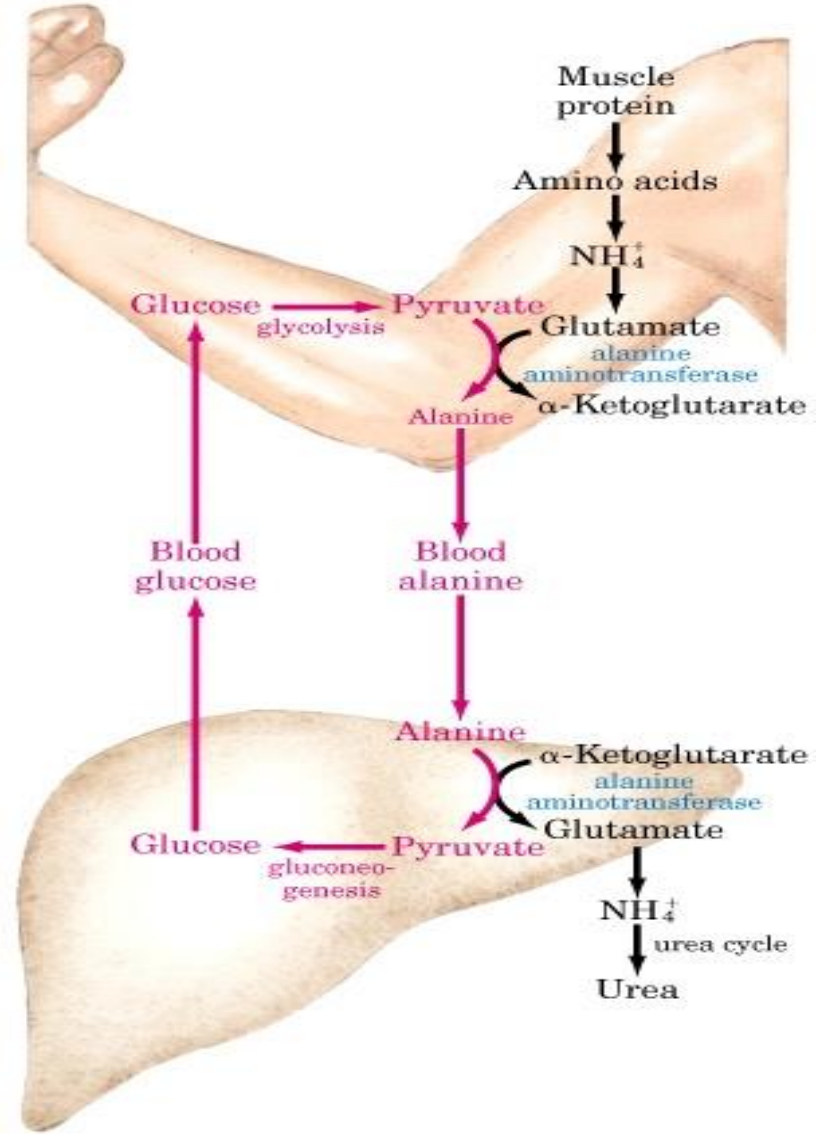
Alanine is another safe way to transport ammonia from muscle to liver via blood.

In liver alanine aminotransferase transfers the amino group to α-ketoglutarate and the pyruvate regenerated is used in gluconeogenesis.

Glucose produced by gluconeogenesis is transported to muscle where it enters glycolysis.

Thus the excess puruvate and ammonia generated in muscle are safely transported to liver.

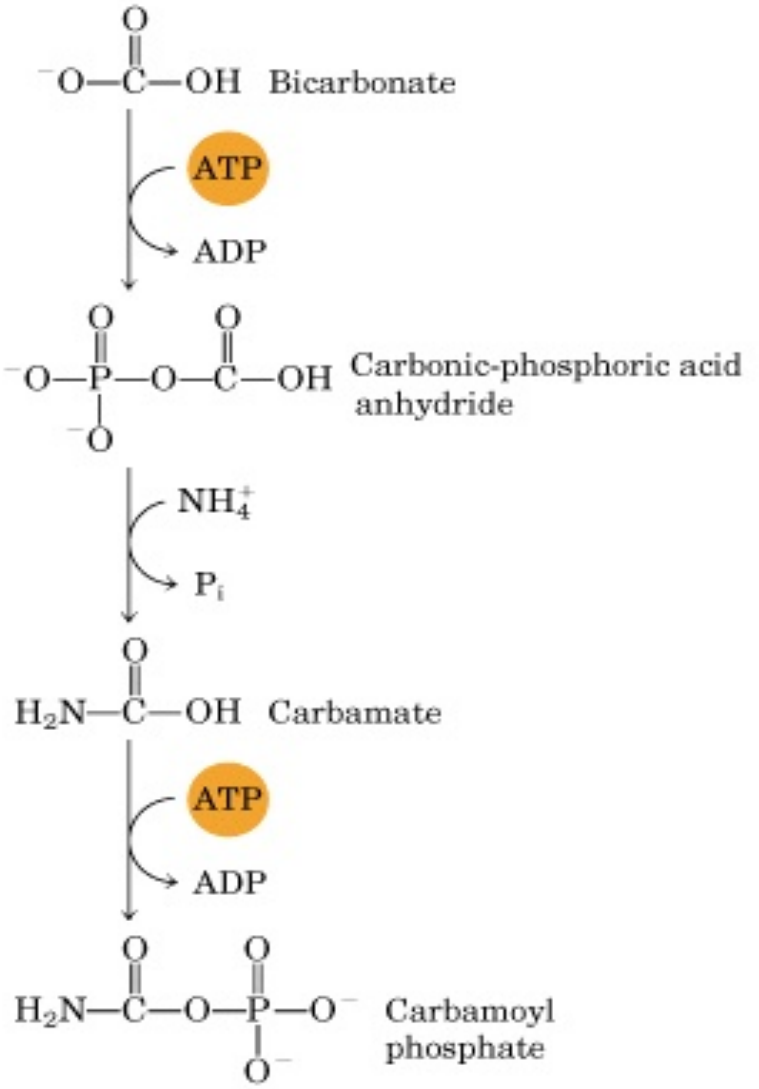


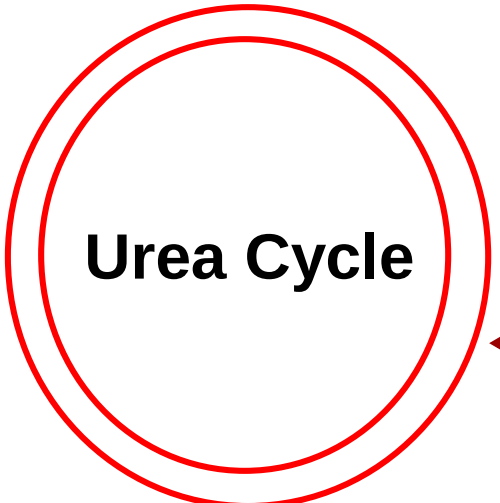


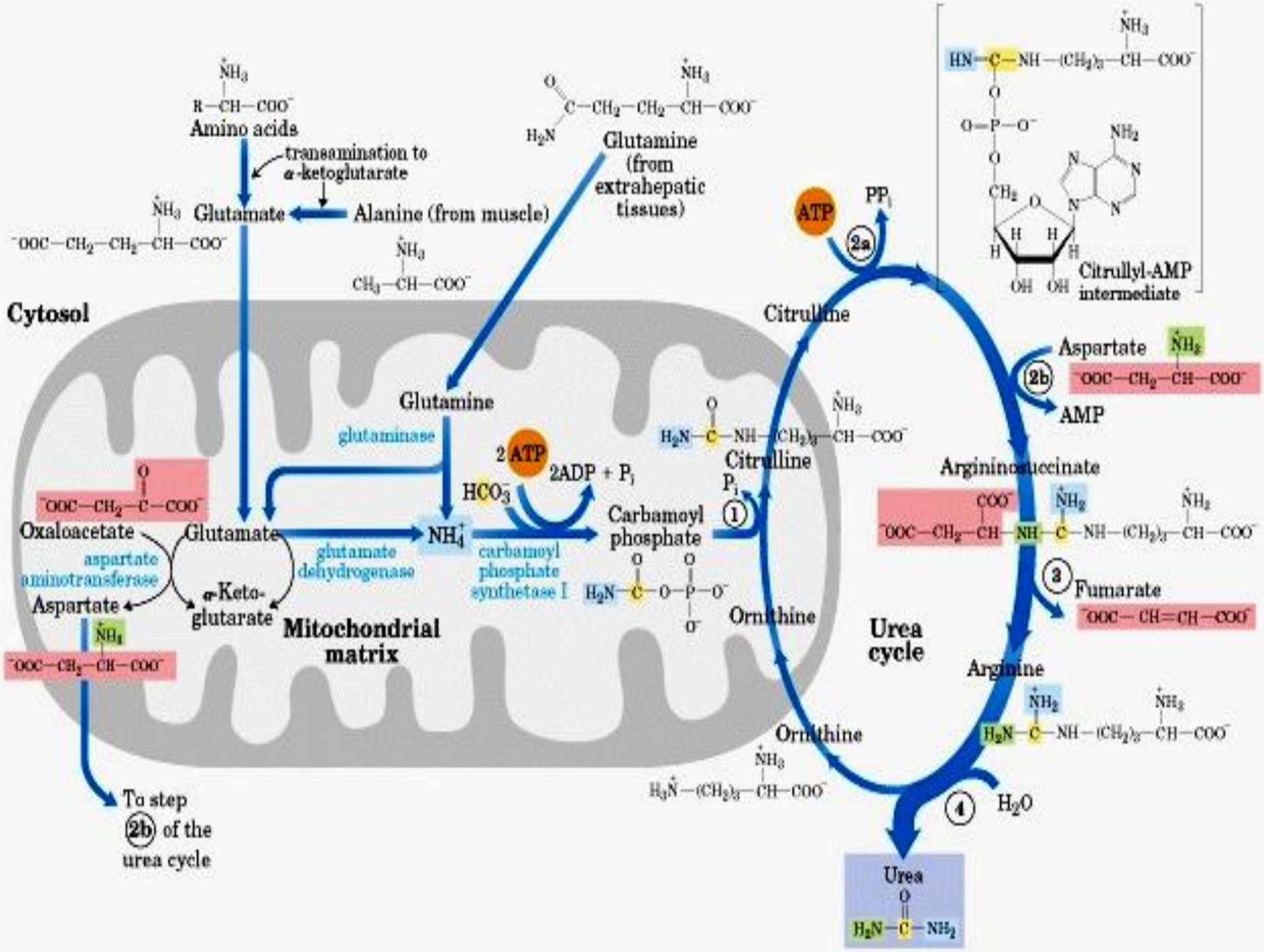
Urea Production

Carbamoyl phosphate synthase-I Reaction

- **Ammonia released from the oxidative deamination is incorporated in: carbamoyl phosphate by using ATP and bicarbonate.**
- **Carbamoyl phosphate enters the urea cycle in the mitochondria.**






Amino acids
transamination to α-ketoglutarate
Glutamate
Alanine (from muscle)
Glutamine (from extrahepatic tissues)
Cytosol
Glutamine
glutaminase
2 ATP
2ADP + Pi
HCO3−
Carbamoyl phosphate
carbamoyl phosphate synthetase I
Citrulline
Pi
1
Ornithine
Urea cycle
ATP
PPi
2a
Citrullyl-AMP intermediate
Aspartate
2b
AMP
Argininosuccinate
3
Fumarate
Arginine
4
H2O
Urea
Oxaloacetate
aspartate aminotransferase
Aspartate
α-Keto-glutarate
glutamate dehydrogenase
Glutamate
NH4+
Mitochondrial matrix
To step 2b of the urea cycle

Regulation of urea cycle

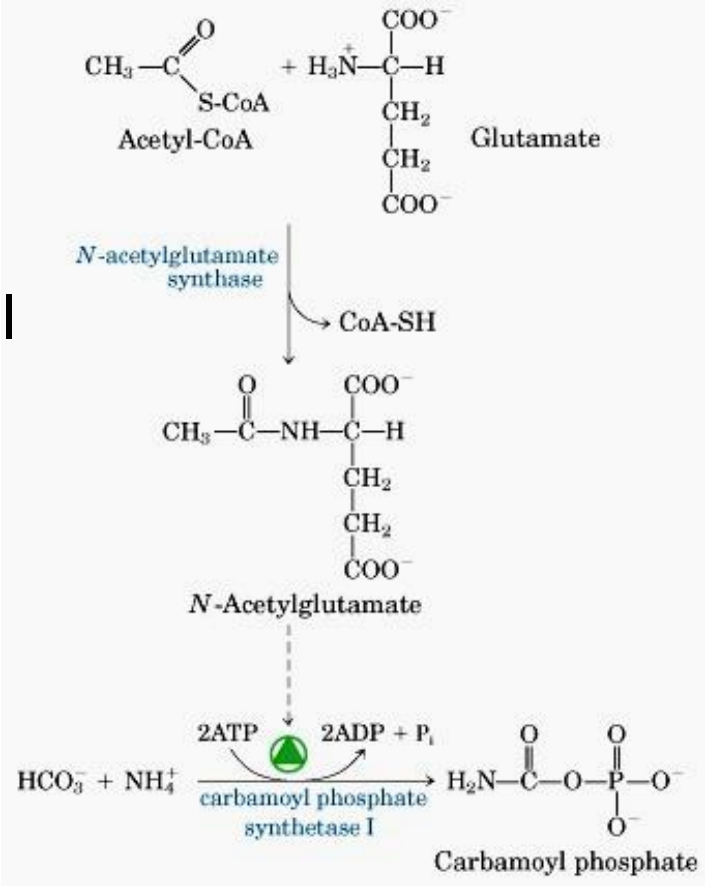
The activity of urea cycle can be regulated at **two levels**:

1. Enzymes involved in urea cycle are synthesized at higher level → proteins are utilized for energy production

When:

- dietary intake is primarily protein
- starvation

2. The carbamoyl phosphate synthetase I is allosterically activated by:
N-acetylglutamate.



Genetic defects in the urea cycle can be life-threatening

- People with genetic defects in any enzyme involved in urea formation cannot tolerate protein-rich diets.

- The absence of a urea cycle enzyme can result in:

1. **hyperammonemia** or
2. the build-up of one or more **urea cycle intermediates**.

- a protein-free diet is not a treatment option ???

Humans are incapable of synthesizing half of the 20 common amino acids…

essential amino acids: must be provided in the diet.

table 18–1

Nonessential and Essential Amino Acids for Humans and the Albino Rat

Nonessential	Essential
Alanine	Arginine*
Asparagine	Histidine
Aspartate	Isoleucine
Cysteine	Leucine
Glutamate	Lysine
Glutamine	Methionine
Glycine	Phenylalanine
Proline	Threonine
Serine	Tryptophan
Tyrosine	Valine

*Essential in young, growing animals but not in adults.

Pathways of amino acid degradation

- Amino acid catabolism pathways account for 10-15% of the human body's energy production.
- Not active as glycolysis and fatty acid oxidation.
- <u>The 20 catabolic pathways converge to form 5 products which enter TCA</u>…

➢ Then diverted to **gluconeogenesis**, **ketogenesis** or **oxidized** to CO_2 & H_2O.

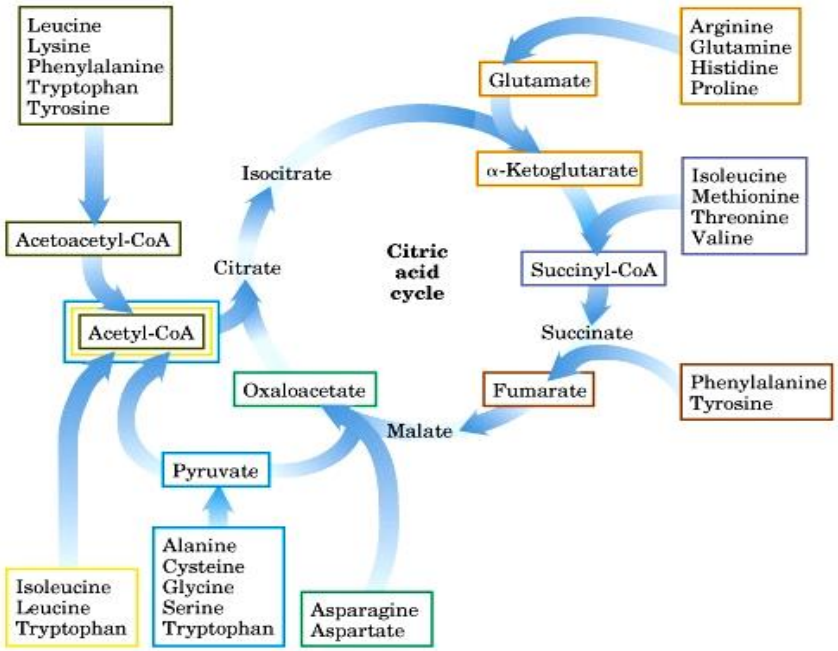


table 22–1

Amino Acid Biosynthetic Families, Grouped by Metabolic Precursor

α-Ketoglutarate
Glutamate
Glutamine
Proline
Arginine*

3-Phosphoglycerate
Serine
Glycine
Cysteine

Oxaloacetate
Aspartate
Asparagine
Methionine†
Threonine†
Lysine†
Isoleucine†

Pyruvate
Alanine
Valine†
Leucine†

Phosphoenolpyruvate and erythrose 4-phosphate
Tryptophan†
Phenylalanine†
Tyrosine‡

Ribose 5-phosphate
Histidine†

*Essential in young animals.

†Essential amino acids.

‡Derived from phenylalanine in mammals.

Glucogenic and Ketogenic amino acids

1. ketogenic amino acids:

Some amino acids can be converted to ketone bodies (liver).

Seven amino acids:

- Phenylalanine, tyrosine, tryptophan, leucine, isoleucine, threonine & lysine.
- are degraded (entirely or in part) to **acetoacetyl-CoA** and/or **acetyl-CoA-**.

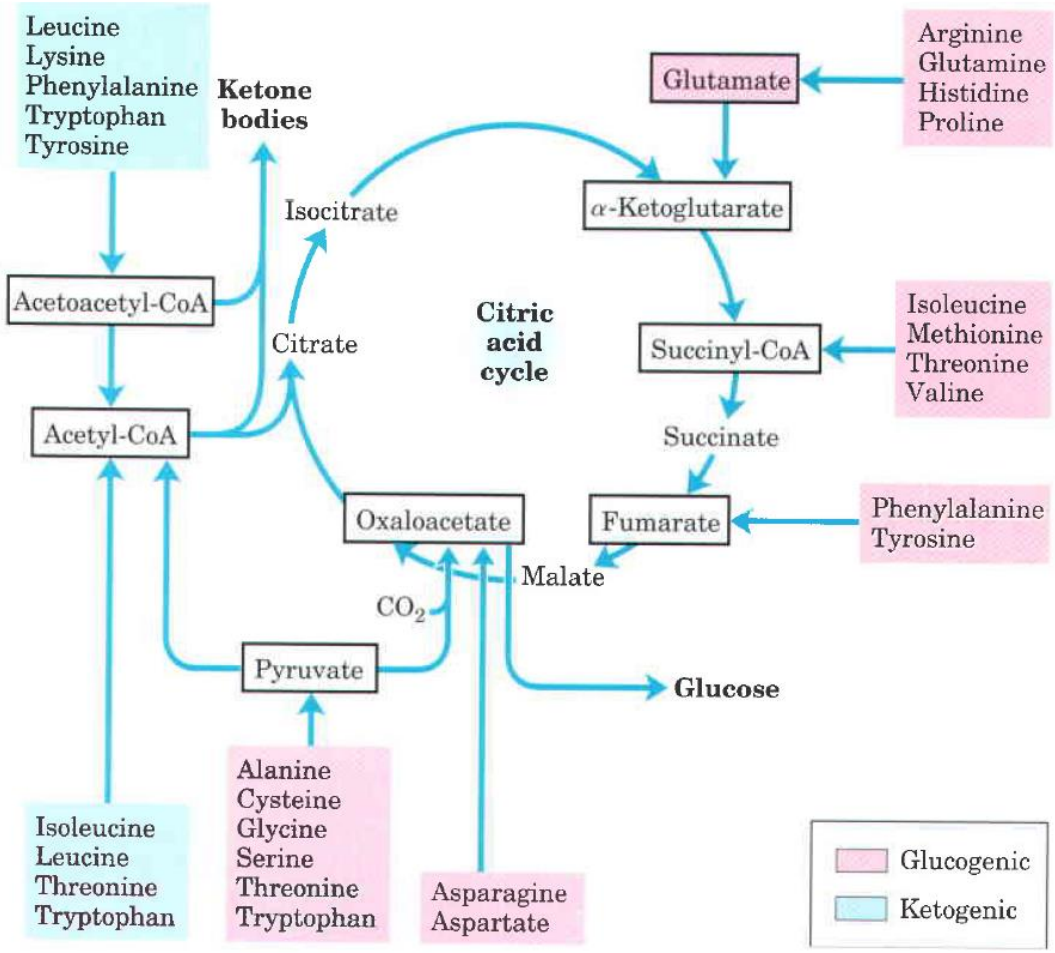
Then acetoacetyl-CoA is converted to **acetoacetate** and then to **acetone** & **β-hydroxybutyrate**.

➢ Particularly in uncontrolled diabetes mellitus:

Liver produces large amounts of **ketone bodies** from fatty acids and the ketogenic amino acids.

➢ Catabolism of amino acids is particularly critical to the survival of animals with high-protein diets or during starvation.

Summary of amino acid catabolism



Glucogenic and Ketogenic amino acids

2. <u>Glucogenic amino acids</u>:
Some amino acids can be converted to glucose.

- are degraded to **pyruvate**, **α-ketoglutarate**, **succinyl-CoA**, **fumarate**, and/or **oxaloacetate**

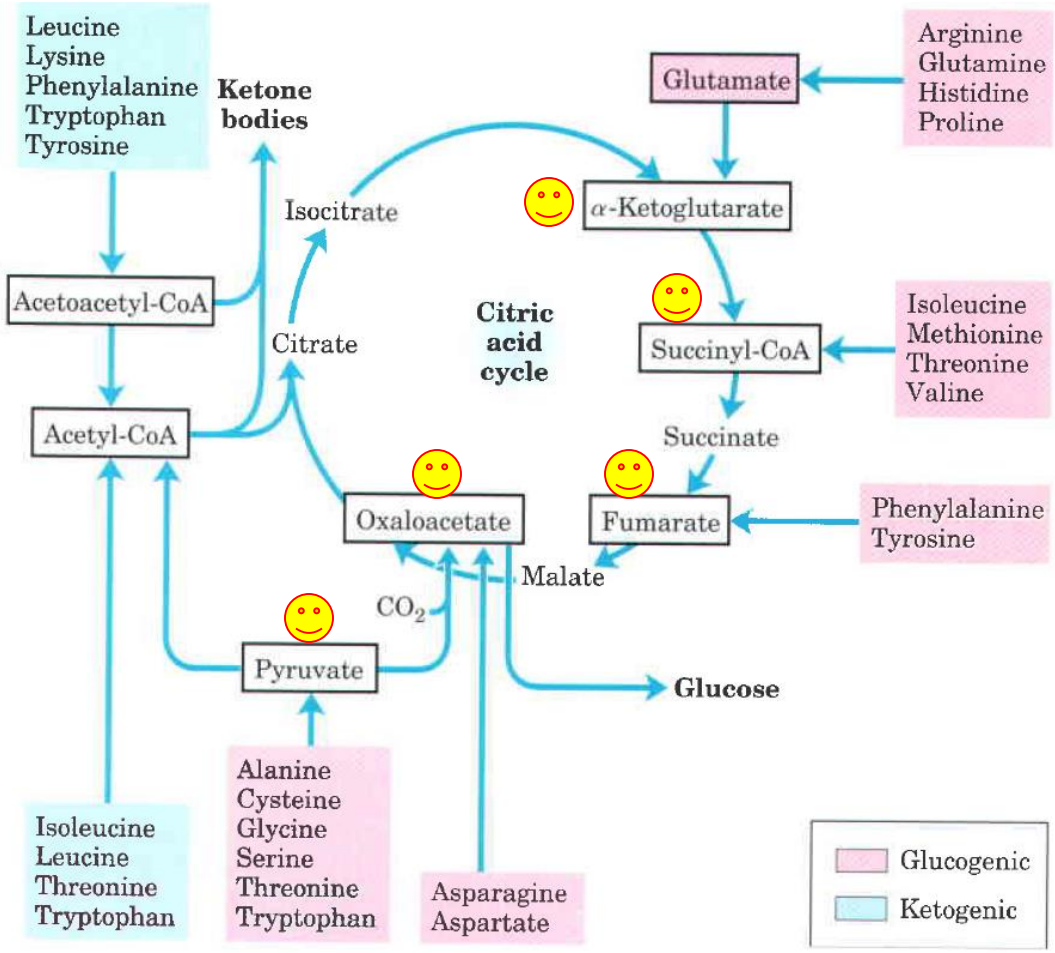
Then can be converted to glucose and glycogen.

Five amino acids:

- tryptophan, phenylalanine, tyrosine, threonine, and isoleucine are both ketogenic and glucogenic.

Leucine and Lysine are exclusively ketogenic amino acids.

Summary of amino acid catabolism




That's it.™