General metabolism of amino acids
Categorized metabolism of amino acids

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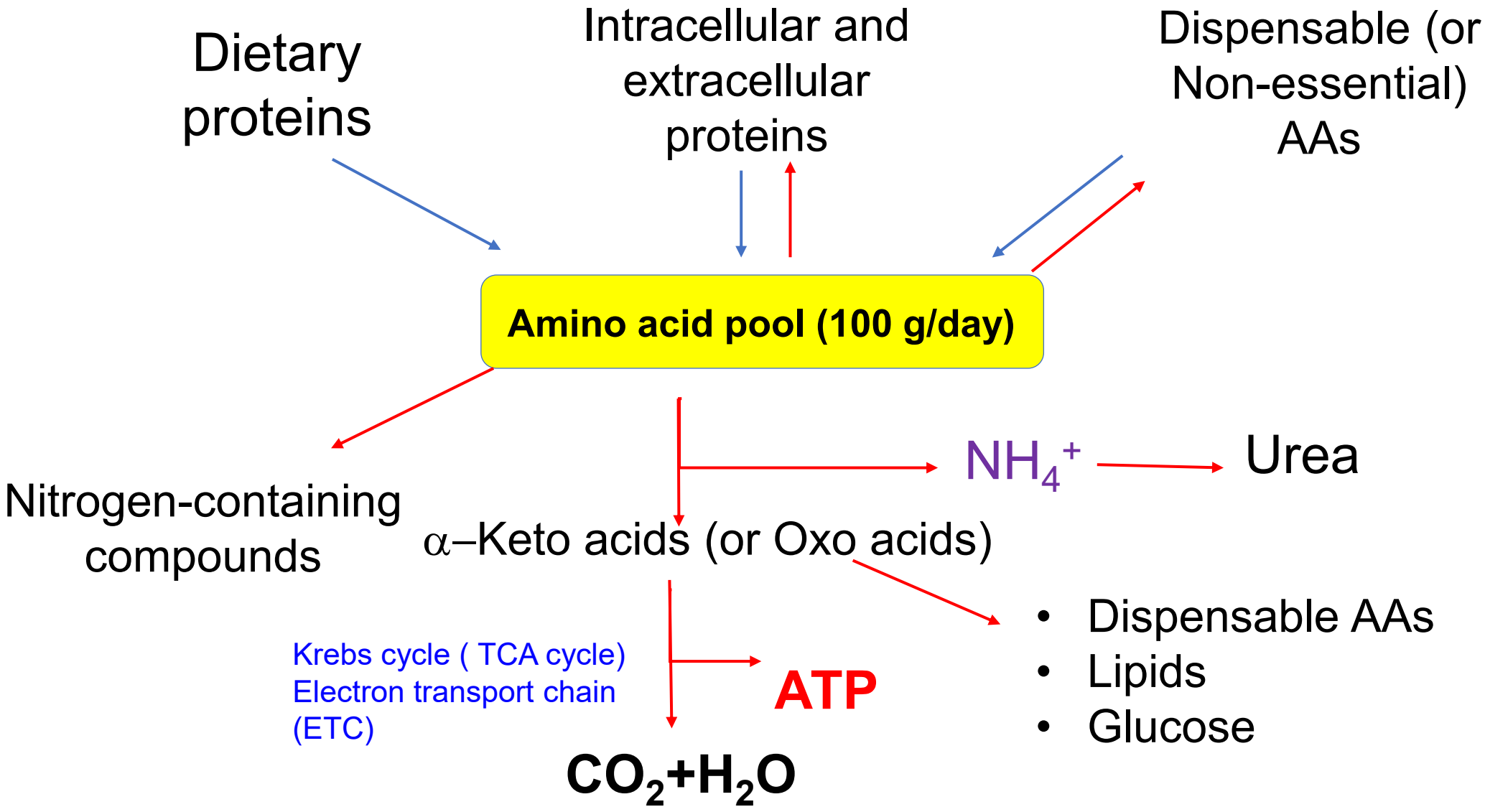
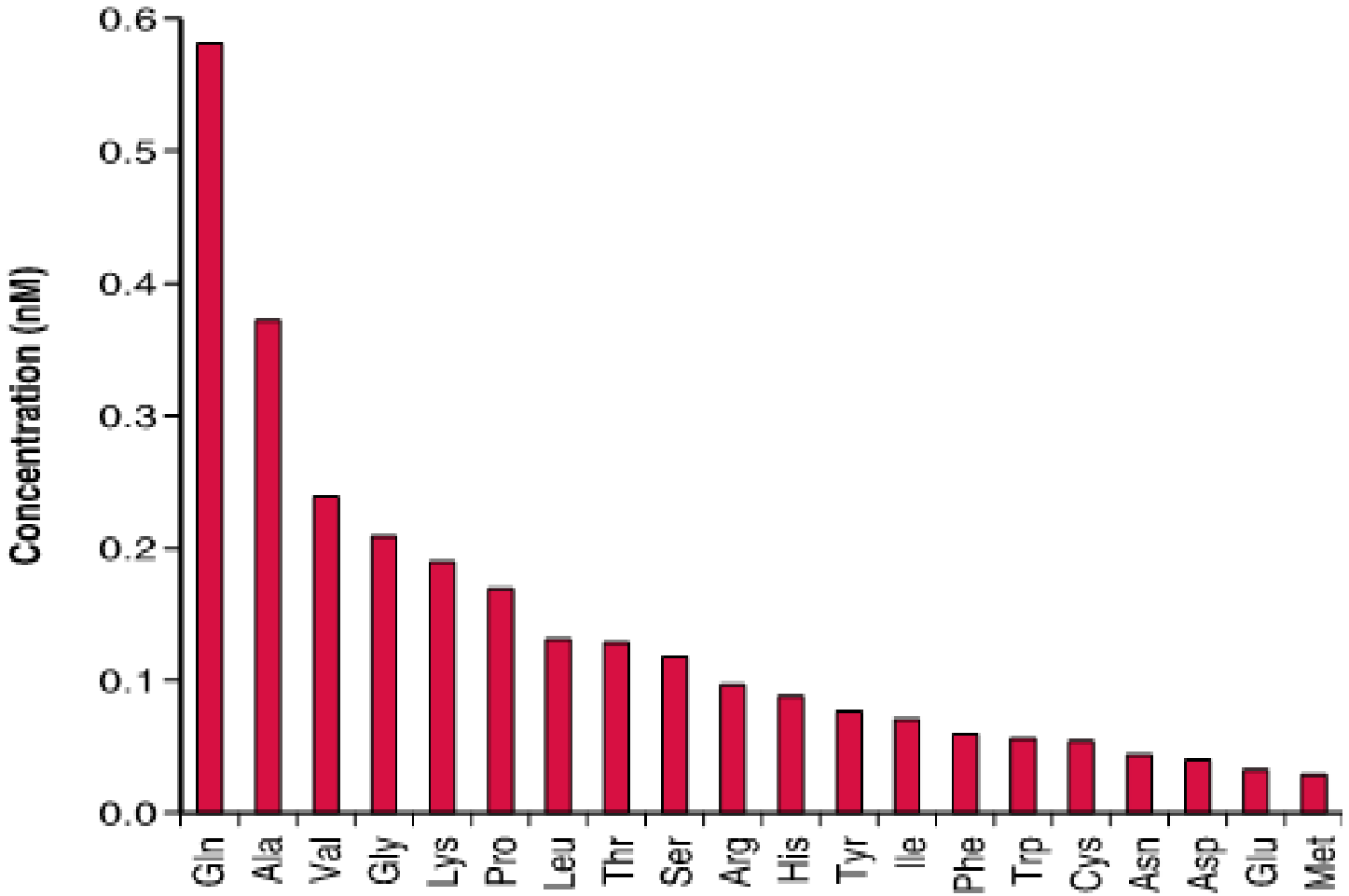
General lecture plan:

- Pathways for the formation and utilization of the amino acid pool in the body
- The essential daily requirement of amino acids
- Pathways of amino acid metabolism
- Reactions of the amino group
- Transamination of terminal amino groups of amino acids
- Use of Aminotransferases in Enzyme Diagnostics
- Deamination of amino acids
- Transdeamination
- Deamination of D-amino acids
- Non-oxidative deamination of amino acids
- Ammonia metabolism in the body
- Transport of Ammonia. Glucose-alanine cycle
- Urea Synthesis. Ornithine cycle
- Regulation of the Urea Cycle
- Disorders of urea synthesis
- Causes of ammonia toxicity
- Urea Level

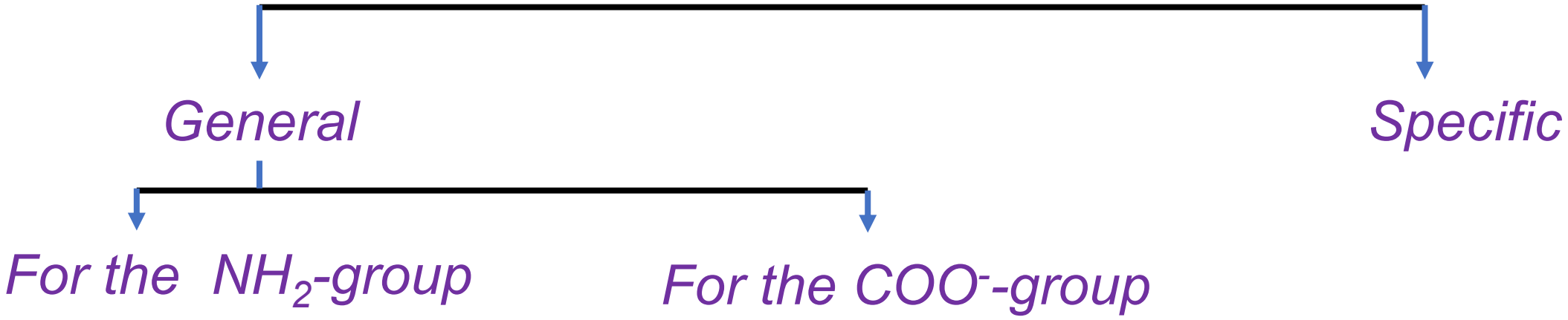
Pathways for the formation and utilization of the amino acid pool in the body



The essential daily requirement of amino acids



Pathways of amino acid metabolism



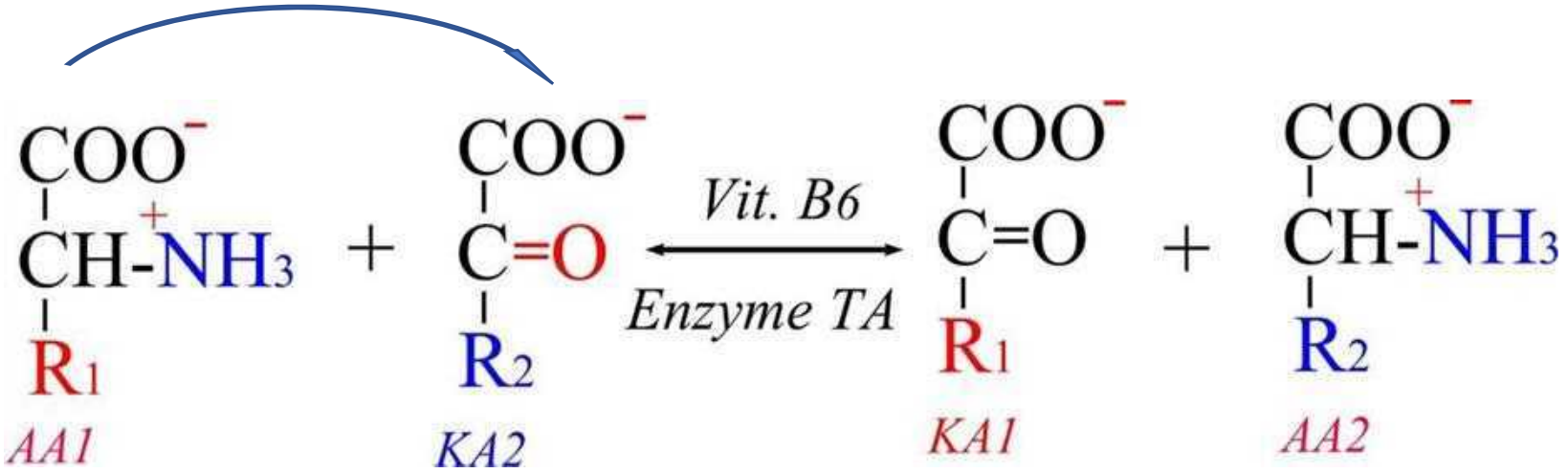
- Transamination
- Deamination
- Transdeamination

Decarboxylation

Reactions of the amino group

Transamination of amino acids (AA's)

Except: Lys, Pro, Thr.

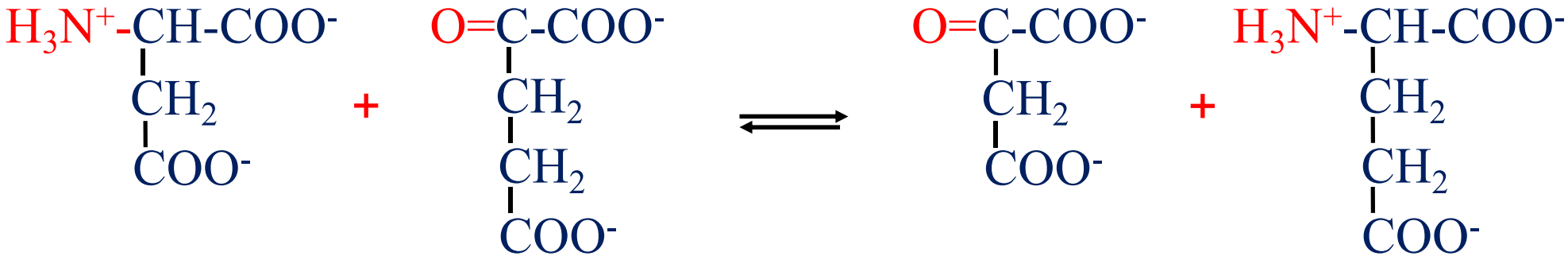


Enzyme name: name of the amino group donor : name of the amino group acceptor (except α-KG) + aminotransferase (transaminase)

The transamination reaction:

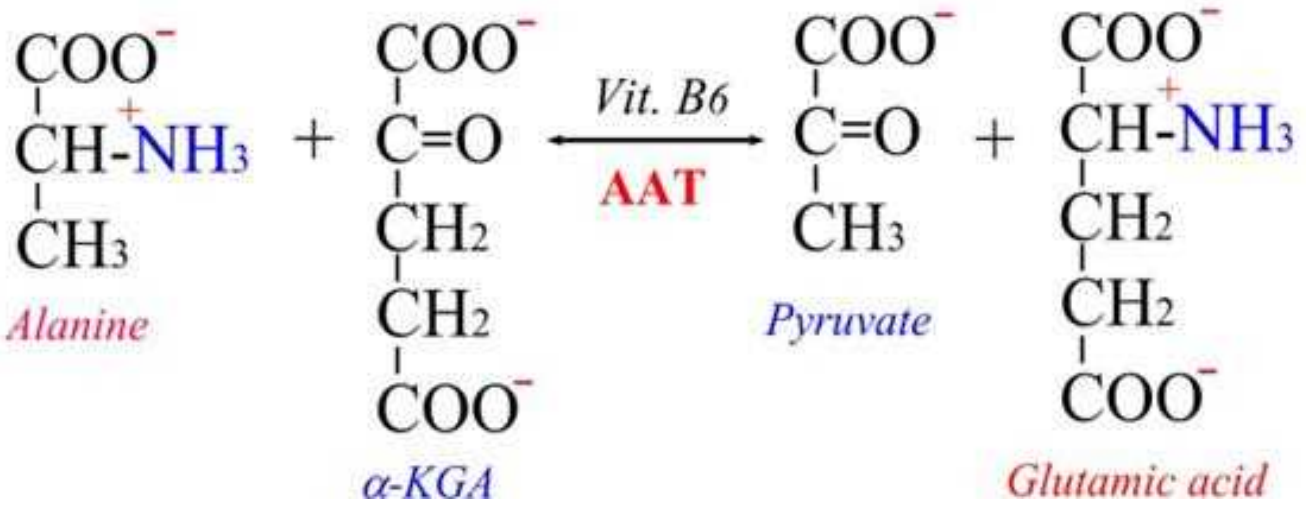
- occurs in the cytosol and mitochondria of cells in almost all organs and tissues;
- is reversible.

Example:



→ Aspartate aminotransferase (AST)

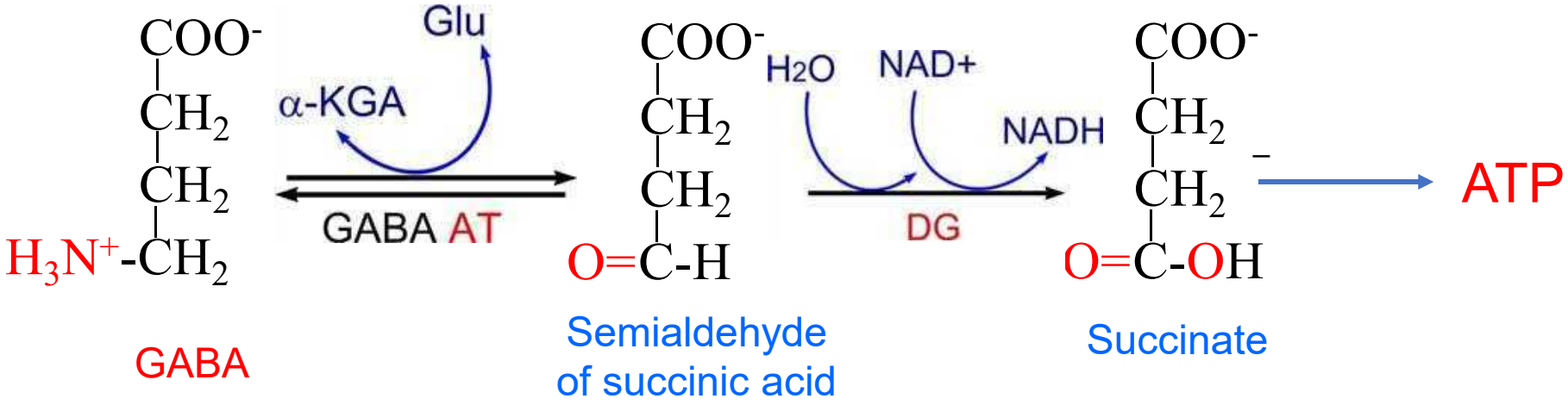
←Glutamate:oxaloacetate aminotransferase (GOAT)



→Alanine aminotransferase (ALT)

←Glutamate:pyruvate aminotransferase (GPAT)

Transamination of terminal amino groups of amino acids



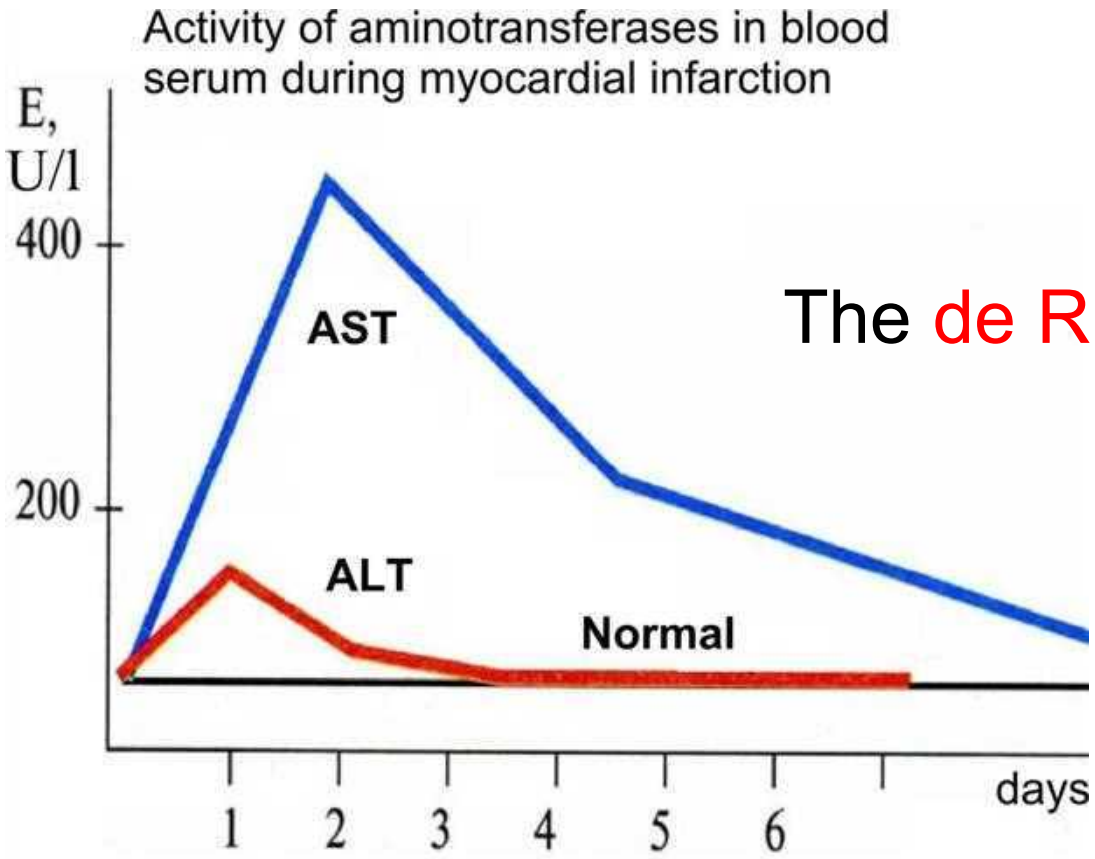
Significance of transamination:

Transamination reactions ensure the redistribution of amino acid nitrogen:

- non-essential (dispensable) amino acids are formed,
- and the concentration of excess amino acids is reduced

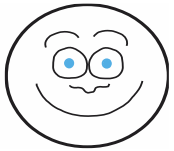
Use of Aminotransferases in Enzyme Diagnostics

AST and ALT show their highest activity in the cytosol of **liver** and **myocardial** cells



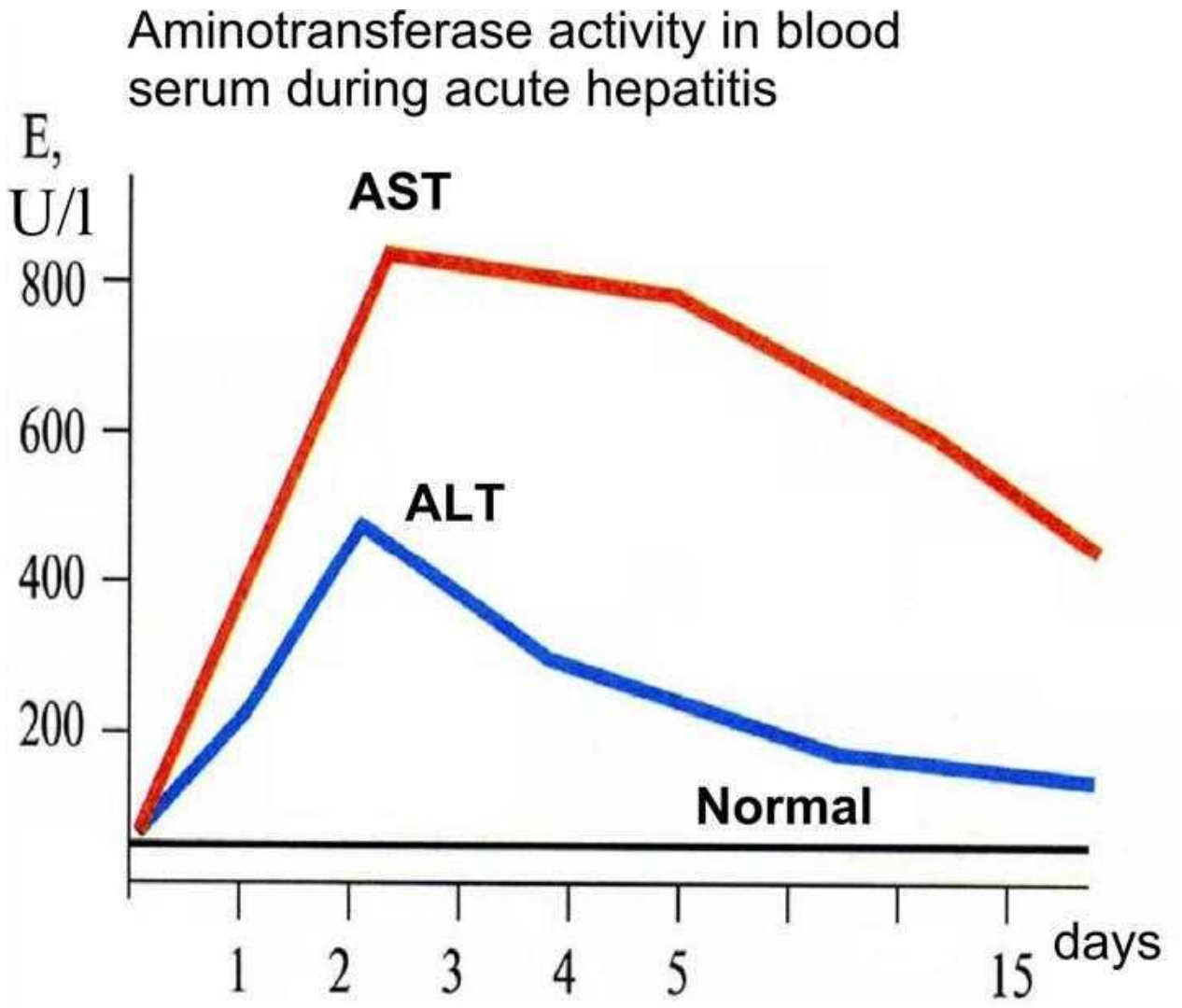
In blood, the normal activity is:

- AST = 8-40 U/L
- ALT = 5-30 U/L



The de Ritis ratio = AST/ALT = 1.33 ± 0.42

During myocardial infarction, the blood activity increases:
AST by 8-10 times, and
ALT by 1.5-2.0 times =>
The de Ritis ratio increases sharply

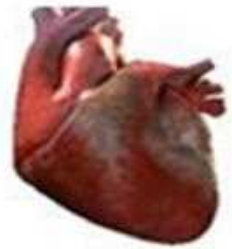


Aminotransferase activity in blood serum during acute hepatitis. In hepatitis, the serum activity increases:

ALT by 8-10 times, and
AST by 2-4 times.

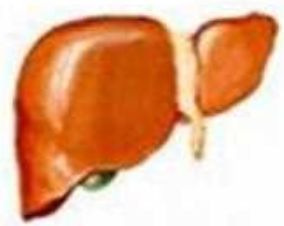
The de Ritis ratio decreases to 0.6.

Myocardial infarction



↑↑↑**AST**

Hepatitis. Cirrhosis



↑↑↑**ALT**

Deamination of amino acids

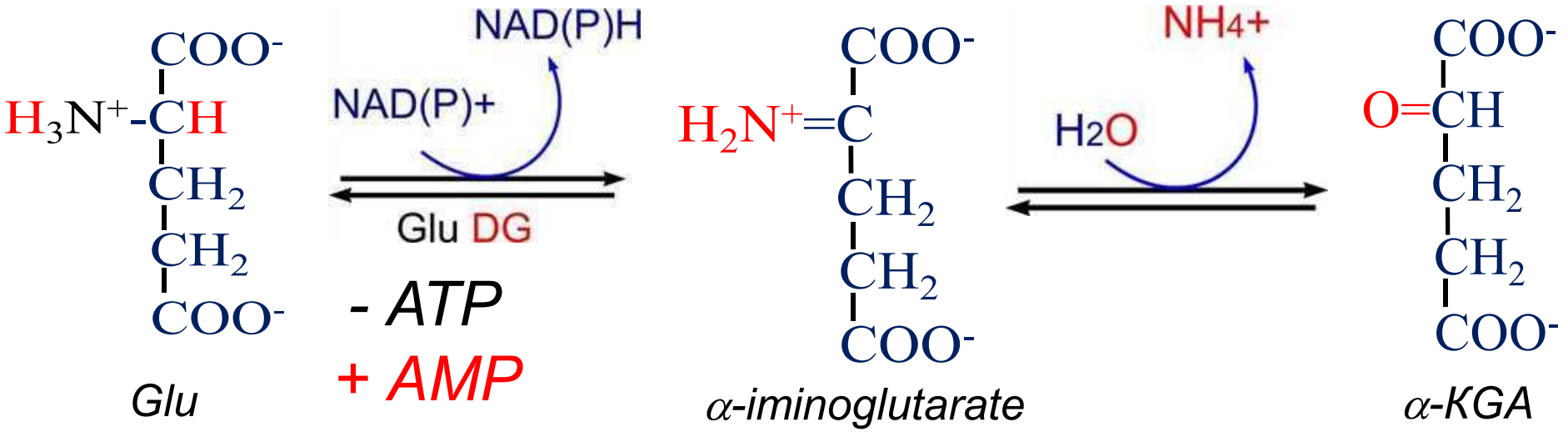
Deamination is the process of removing the α-amino group from an amino acid and releasing it as ammonia/ammonium ion

Oxidative deamination: Glu

Non-oxidative deamination: Ser, Thr, Cys, His

Deamination Glu

Occurs in the cytosol (less frequently in mitochondria) of all cells, particularly hepatocytes



Transdeamination

Indirect oxidative deamination

Transamination: $AA + \text{a-}KGA \longleftrightarrow Glu + Ketoacid\ (KA)$

Oxidative deamination: $Glu + HAD^+ + H_2O \longleftrightarrow \text{a-}KGA + NH_4^+ + HADH + H^+$

Overall: $AA + HAD^+ + H_2O \longleftrightarrow KA + NH_4^+ + HADH + H^+$

Most amino acids do not undergo direct deamination. Initially, they transfer their amino group to alpha-ketoglutarate, and the resulting glutamate then undergoes deamination via oxidative deamination.

Example: $Ala + \text{a-}KGA \longleftrightarrow Glu + pyruvate$

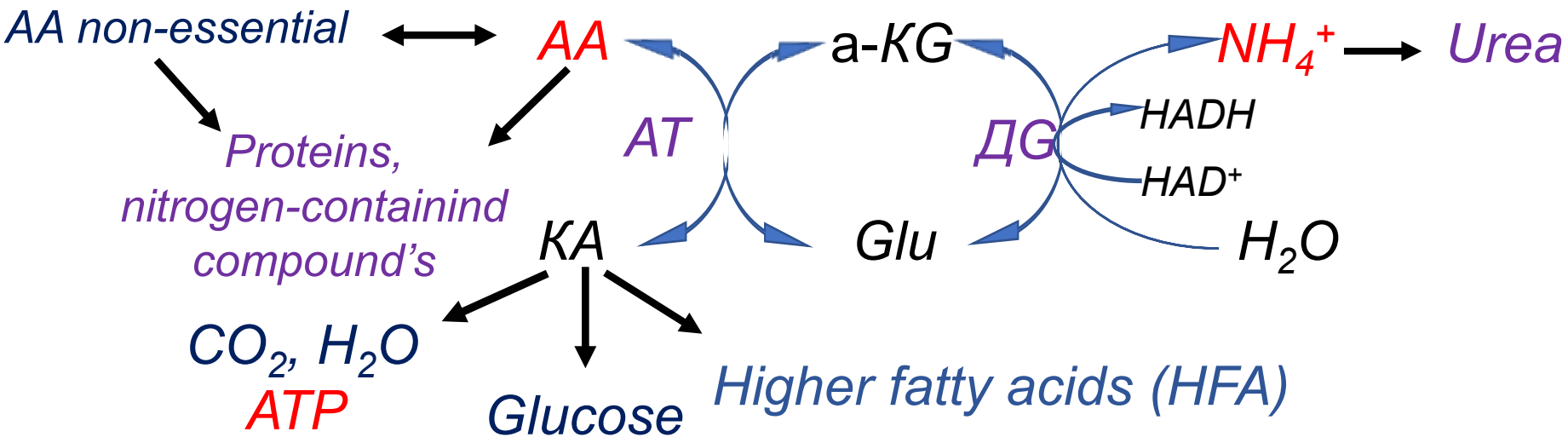
$Glu + HAD^+ + H_2O \longleftrightarrow \text{a-}KGA + NH_4^+ + HADH + H^+$

Overall: $Ala + HAD^+ + H_2O \longleftrightarrow pyruvate + NH_4^+ + HADH + H^+$

Transdeamination

The sequential process of transaminating amino acids with α-ketoglutarate (a-KGA) to form glutamate (Glu), followed by its oxidative deamination, is called transdeamination (or indirect oxidative deamination).

Transdeamination scheme



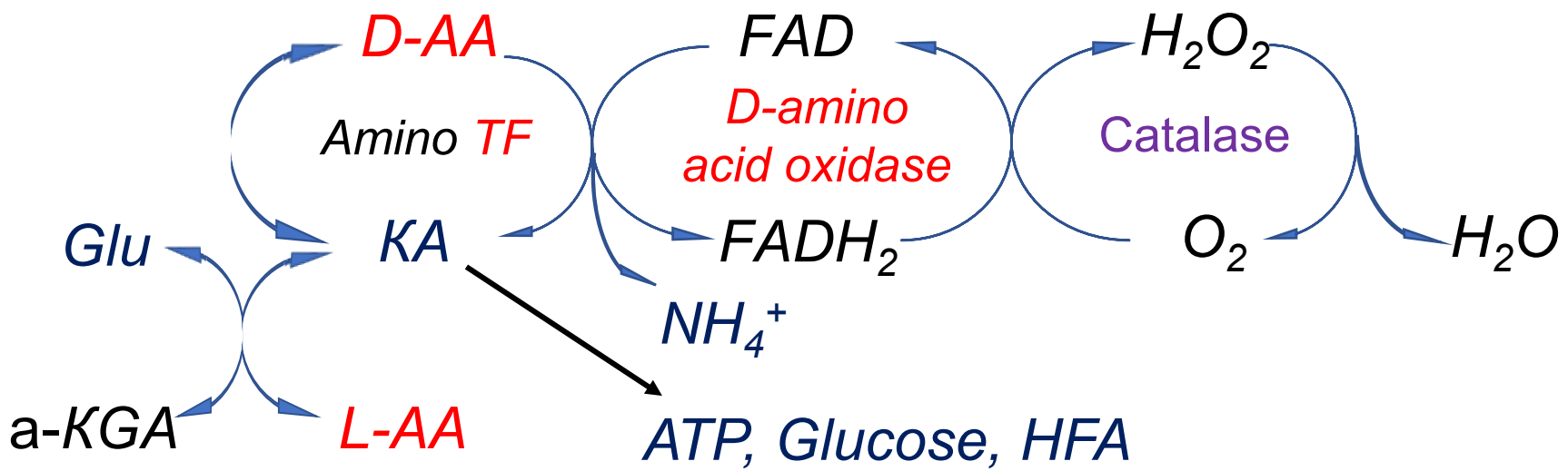
Glutamate dehydrogenase, in combination with the transamination process, plays a major role in the deamination of many amino acids

As a result of transdeamination, liver cells are supplied with:

- ammonium ions/ammonia for urea synthesis;
- and oxoacids (ketoacids) for:
  - energy extraction
  - synthesis of glucose
  - synthesis lipids.

Deamination of D-amino acids

Proceeds most actively in the peroxisomes of the liver and kidneys : D-AA→ L-AA

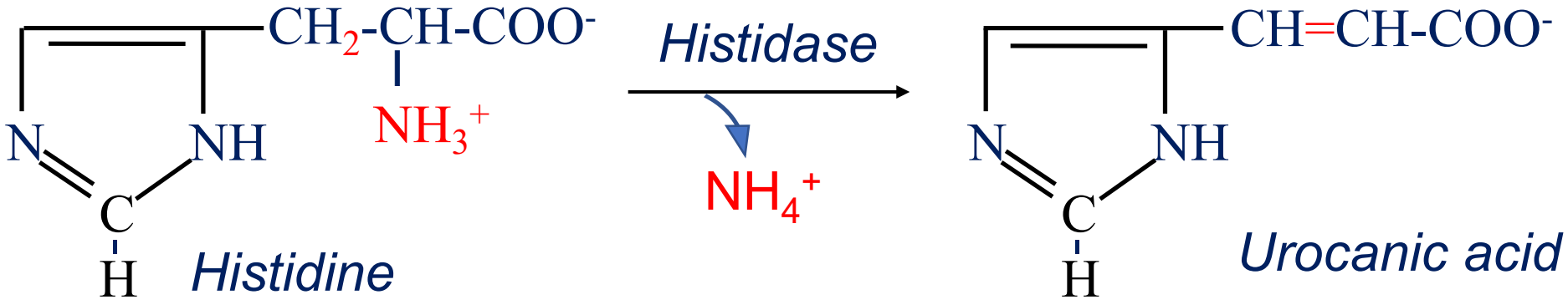


D-AA;s are supplied through plant-based products. They are not directly used in the synthesis of human body proteins but are utilized by the organism after the removal of their amino group.
The enzyme D-amino acid oxidase, present in small quantities in the peroxisomes of the liver and kidneys, catalyzes the oxidative deamination of D-AA's, converting them into the corresponding α-oxoacids.
Flavin adenine dinucleotide (FAD) serves as the coenzyme and oxidizing agent. The resulting reduced flavin ($FADH_2$) is subsequently regenerated through an oxidation reaction involving molecular oxygen. This reaction is accompanied by the formation of hydrogen peroxide (H_2O_2), which is detoxified by the enzyme catalase into oxygen and water.
The resulting ketoacids (KA) can then be converted into L-AA's through transamination reactions.
Thus, D-amino acid oxidase initiates the first step in the conversion of D-AA's into L-AA's.

Non-oxidative deamination of amino acids

Histidine is deaminated in the liver and skin by the enzyme **histidase (histidine ammonia-lyase)**, which removes the amino group from histidine to form trans-urocanic acid (or urocanic acid)

Histidine:

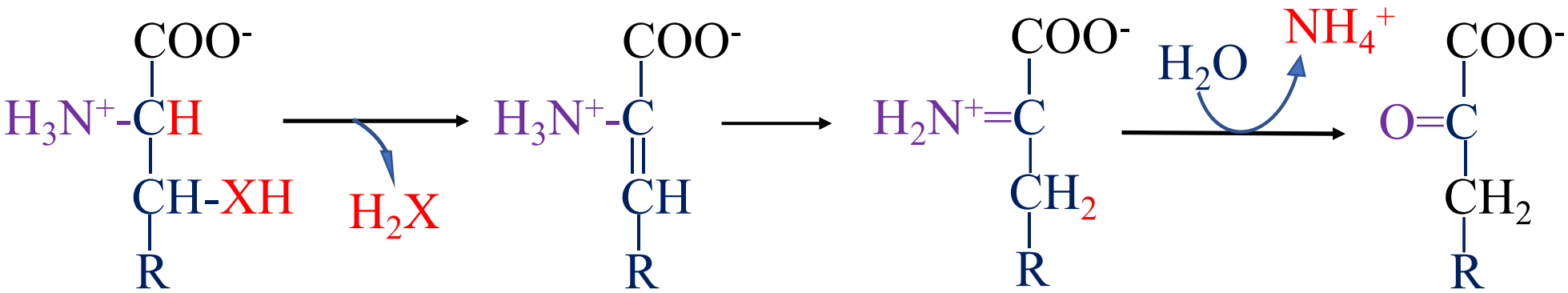


Histidine

Urocanic acid

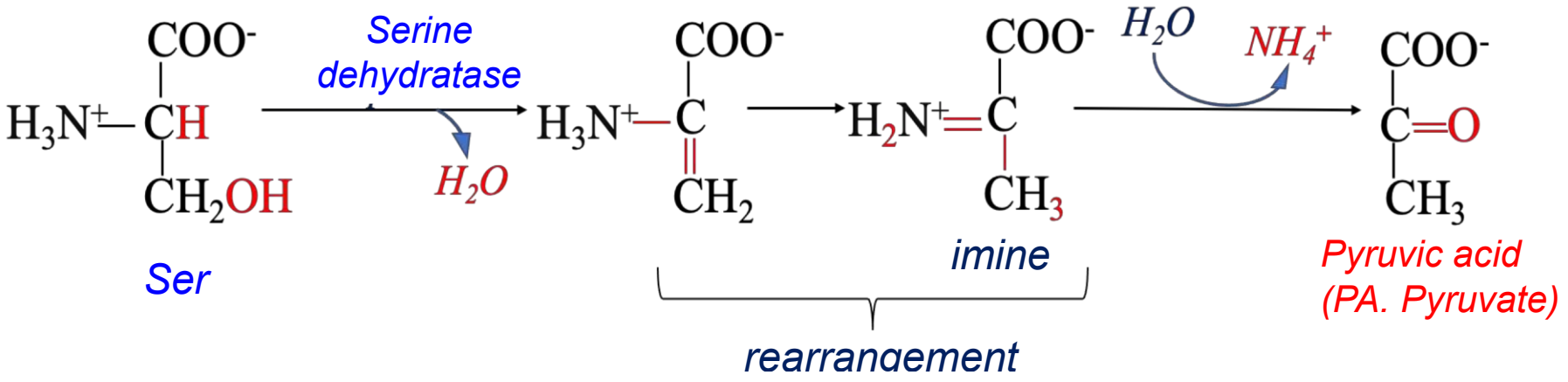
Overall for Ser, Tre, Cis:

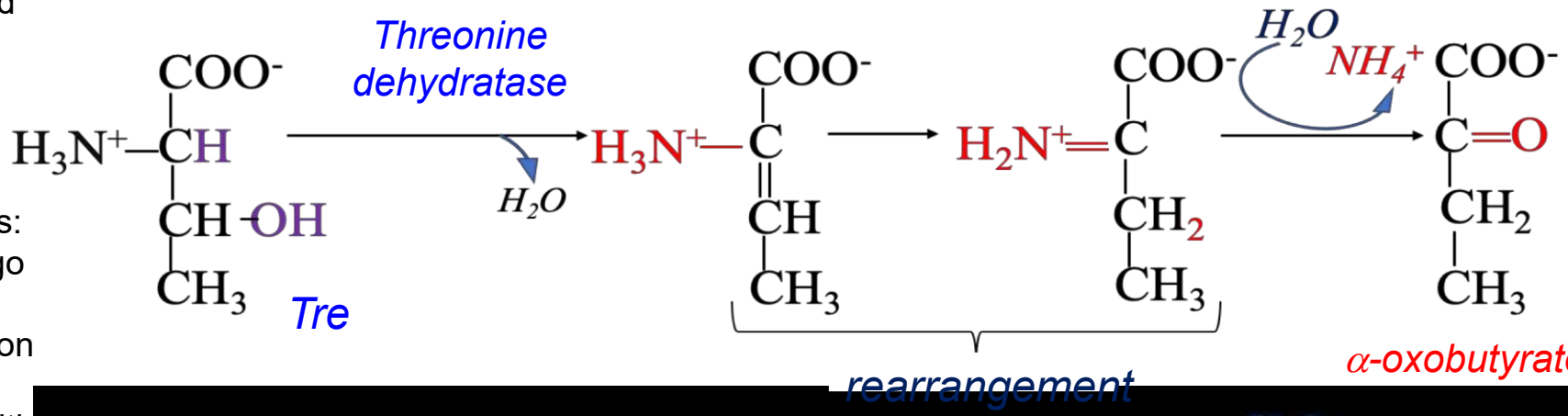
Scheme of the general reaction of non-oxidative deamination of serine, threonine, and cysteine, resulting in the formation of water (Ser, Tre) or hydrogen sulfide (for Cys).



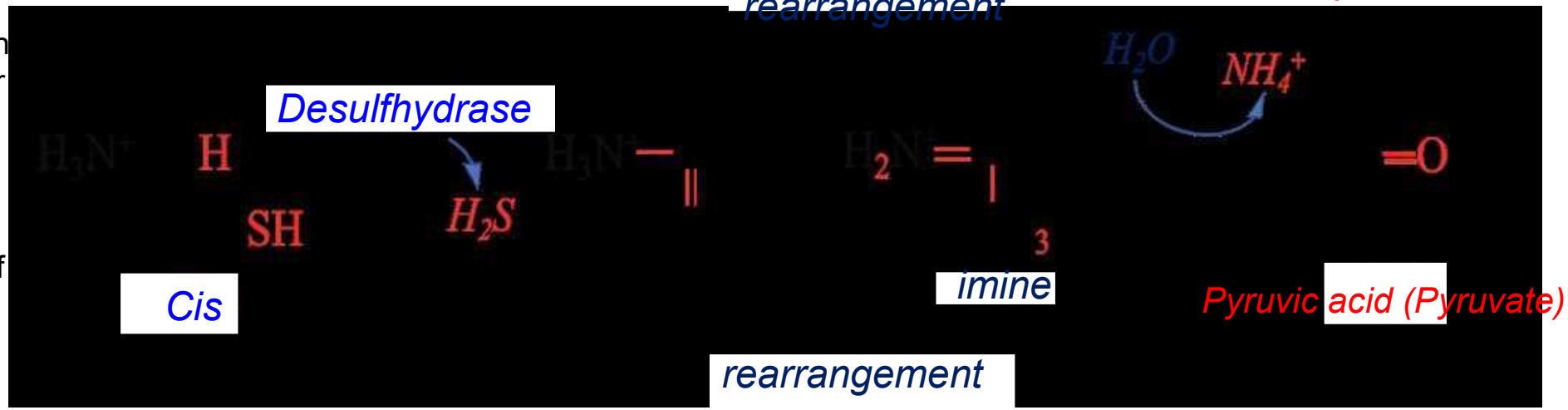
rearrangement

Ser and Tre, with the participation of an enzyme exhibiting group specificity, serine-threonine dehydratase. It catalyzes the elimination of a H2O from Ser and Tre, followed by rearrangement into an imine, which spontaneously hydrolyzes, releasing ammonia/ammonium ion and forming pyruvate/oxobutyrate, respectively.





Sulfur-containing amino acids: Cys or Homocysteine undergo the action of desulfhydrase, which catalyzes the elimination of a hydrogen sulfide (H2S) molecule (desulfhydration) with the formation of an imine (after rearrangement), which undergoes non-enzymatic hydrolysis (similar to Ser). H2S is a signaling molecule. It participates in the regulation of vascular blood flow and blood pressure.



Ammonia metabolism in the body

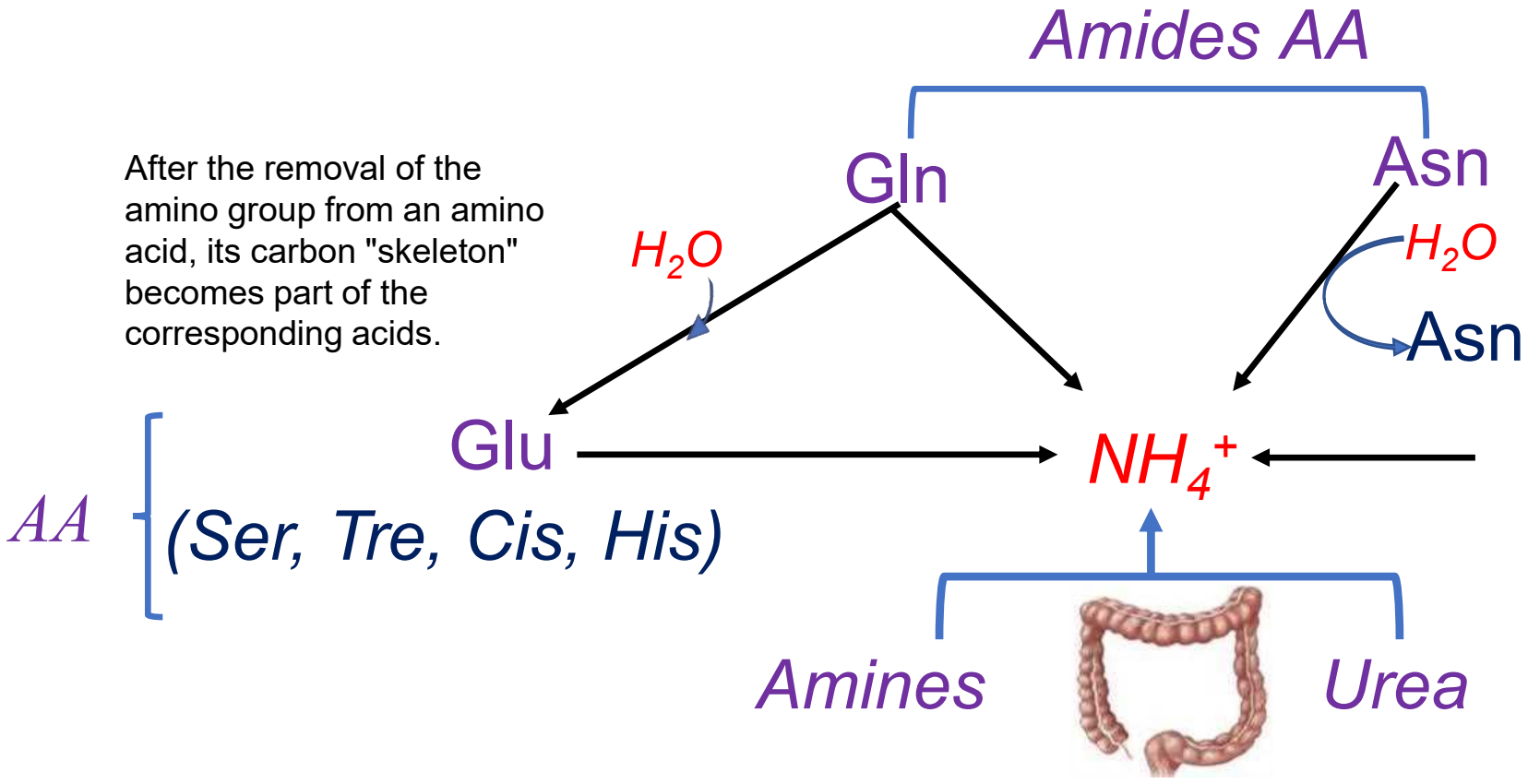
Functions of ammonia:

- participates in the regulation of acid-base balance (ABB) in the body;
- is used in the synthesis of nitrogen-containing compounds: amides, purines...

$H^+ + NH_3 \rightarrow NH_4^+$

Sources of ammonia in the body

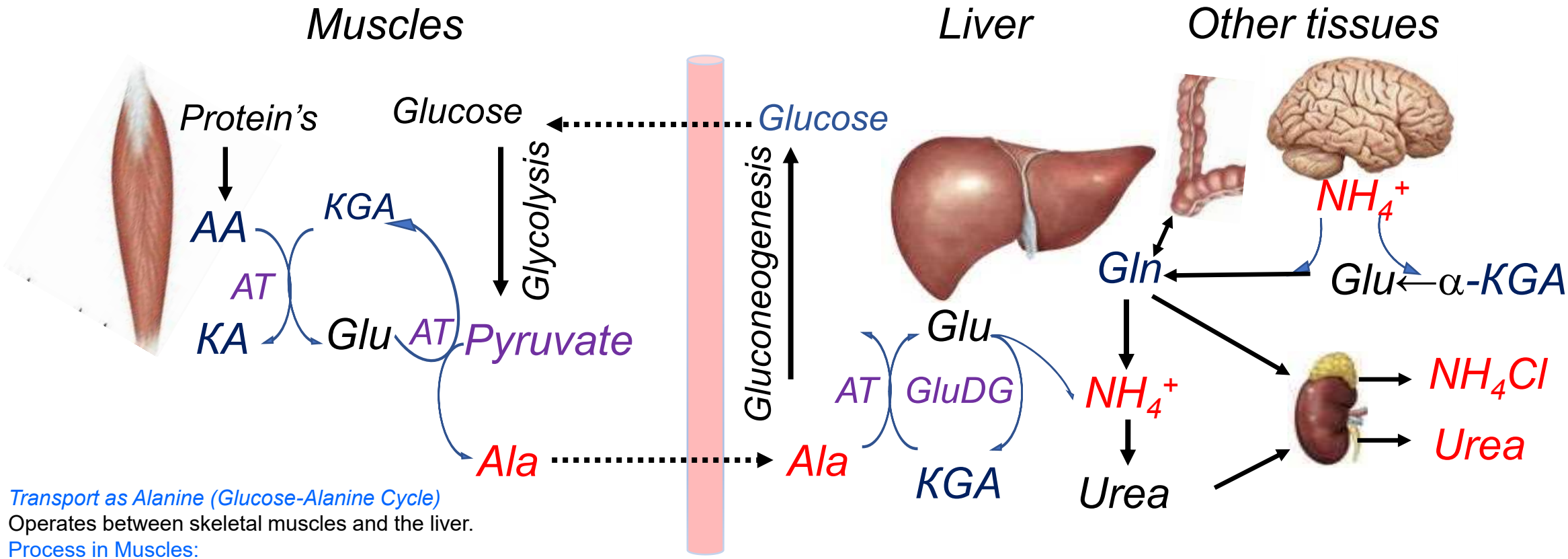
After the removal of the amino group from an amino acid, its carbon "skeleton" becomes part of the corresponding acids.



Nitrogen-containing compounds:

- Purines
- Pyrimidines
- Heme

Transport of Ammonia. Glucose-alanine cycle



Transport as Alanine (Glucose-Alanine Cycle)

Operates between skeletal muscles and the liver.

Process in Muscles:

During muscle activity, pyruvate is generated (the end product of glycolysis).

Pyruvate undergoes transamination with glutamate (which received an amino group from other amino acids).

Alanine is formed.

Transport: Alanine is released into the blood and reaches the liver.

Process in the Liver:

Alanine is transaminated back with α-ketoglutarate.

Pyruvate (which can be used for gluconeogenesis → glucose) and glutamate are formed.

Glutamate undergoes oxidative deamination, releasing ammonia for the urea cycle.

Ammonia: is transported to/from tissues in the form of Gly and Ala is eliminated from the body by the kidneys in the form of:

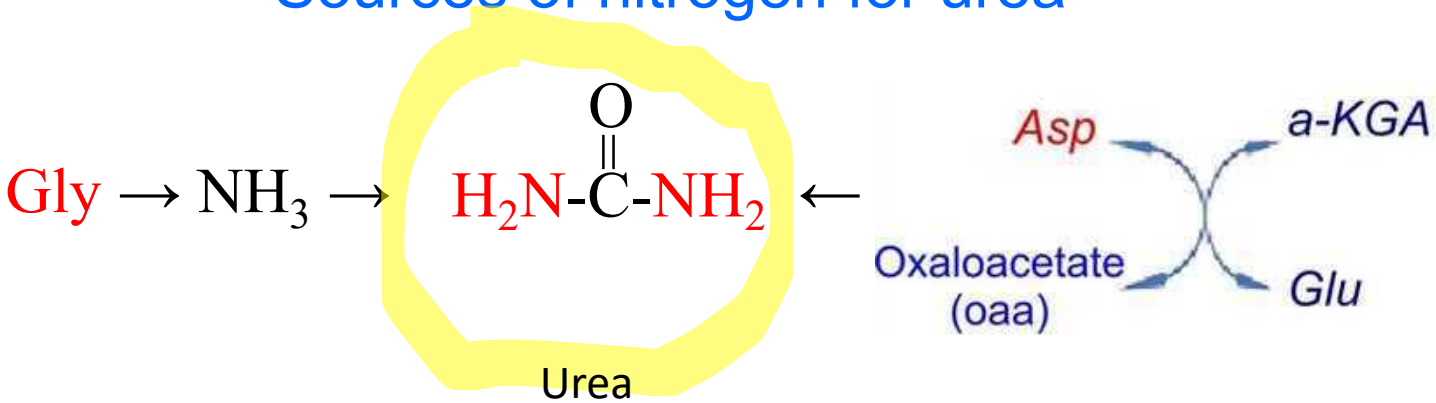
- urea
- ammonium salts

Urea Synthesis

Urea is the final product of the breakdown of proteins and other nitrogen-containing compounds.

Urea is synthesized exclusively in the liver, transported to the kidneys, and excreted in the urine.
Approximately 15-30 g of urea (7-15 g of nitrogen) are excreted in the urine per day.

Sources of nitrogen for urea

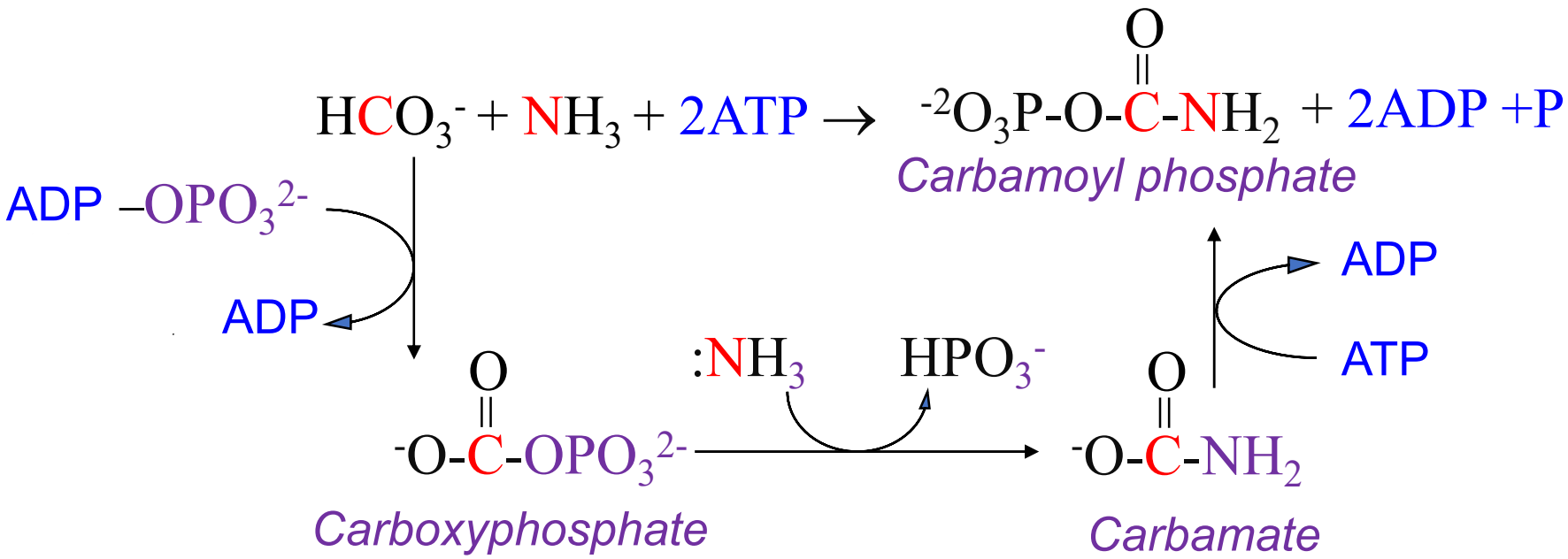


Urea Synthesis. Ornithine cycle

Urea synthesis is a cyclic process occurring:

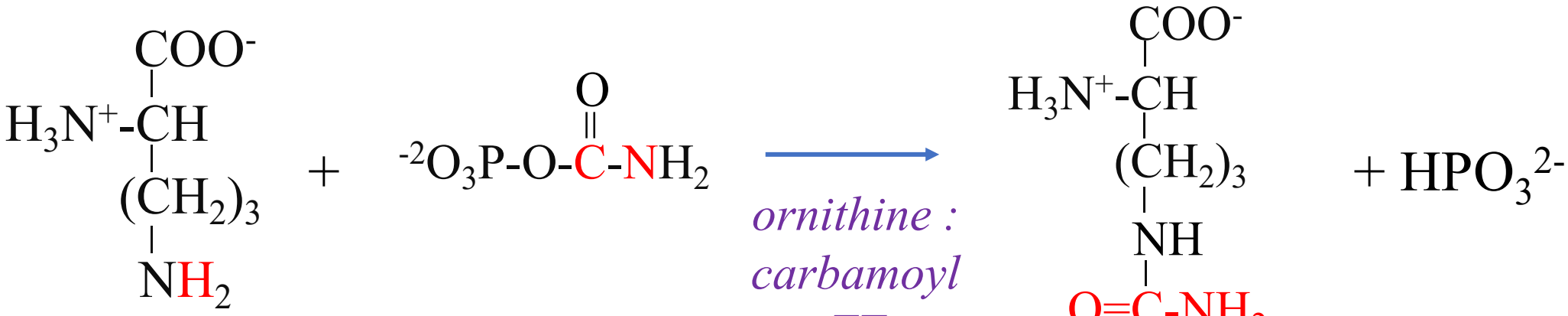
- in the mitochondrial matrix (reactions 1 and 2) and
- in the cytosol of cells (the remaining reactions)

Reaction 1: Synthesis of carbamoyl phosphate in the matrix with the participation of the enzyme **carbamoyl phosphate synthetase I**.



Urea Synthesis. Ornithine cycle

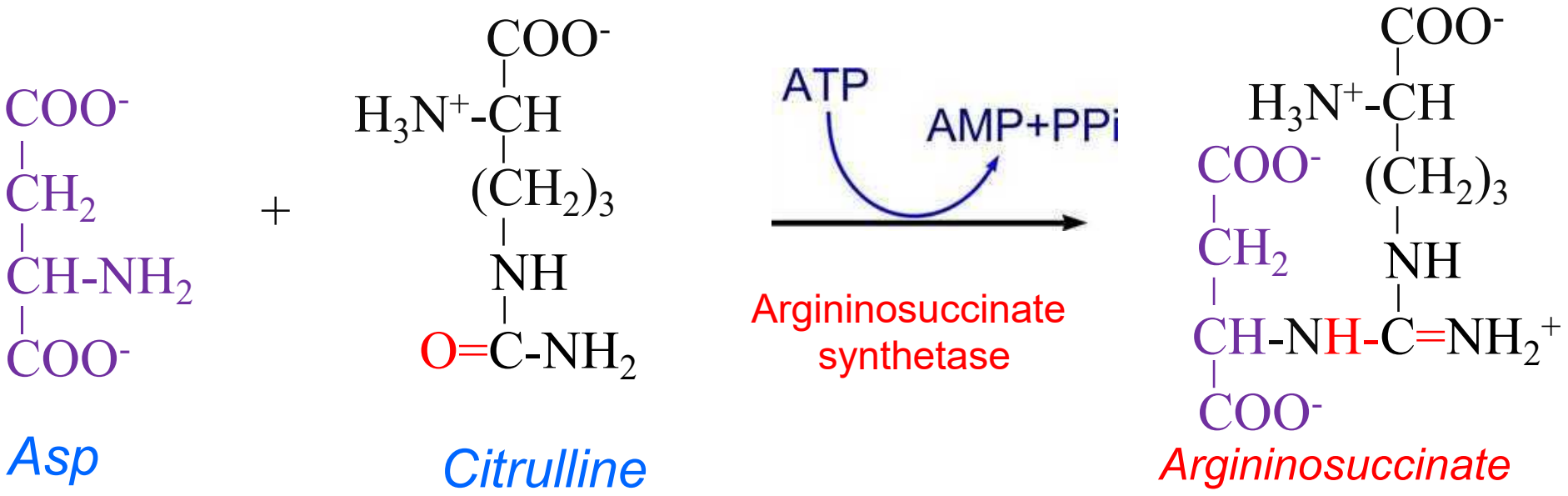
Reaction 2: formation of citrulline from carbamoyl phosphate and ornithine catalyzed by ornithine transcarbamylase (ornithine:carbamoyltransferase)



*Citrulline i*s then transported to the cytosol

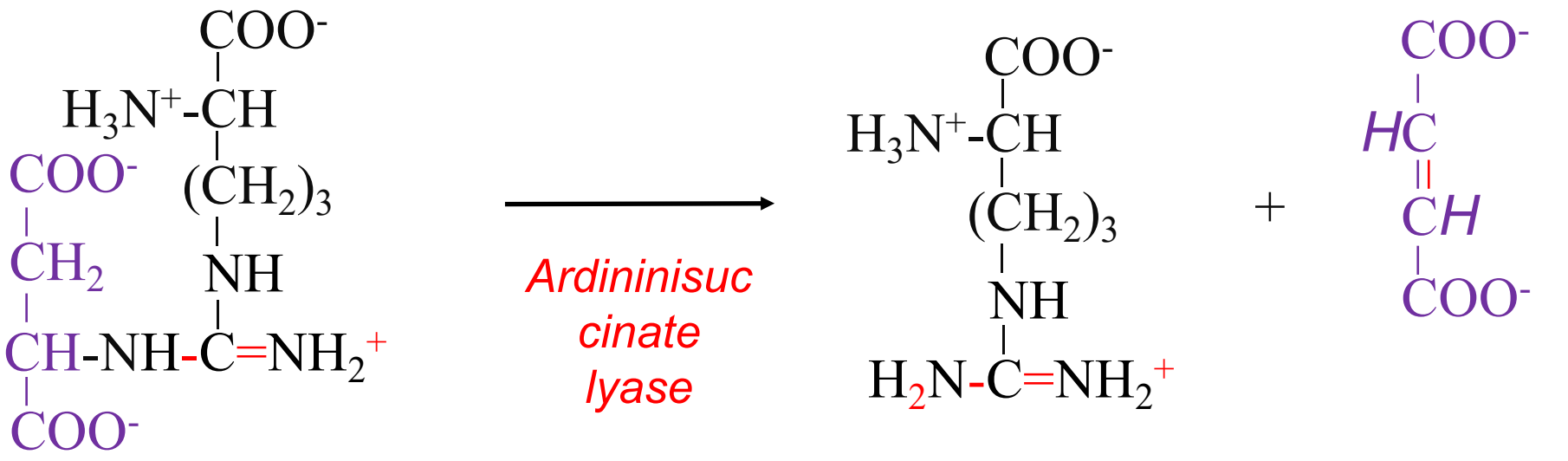
Urea Synthesis. Ornithine cycle

Reaction 3 (cytosol): formation of argininosuccinate through the interaction of *citrulline* with aspartate. Enzyme - argininosuccinate synthetase.



Urea Synthesis. Ornithine cycle

Reaction 4 (cytosol): formation of arginine and fumarate catalyzed by the enzyme *argininosuccinate lyase*.

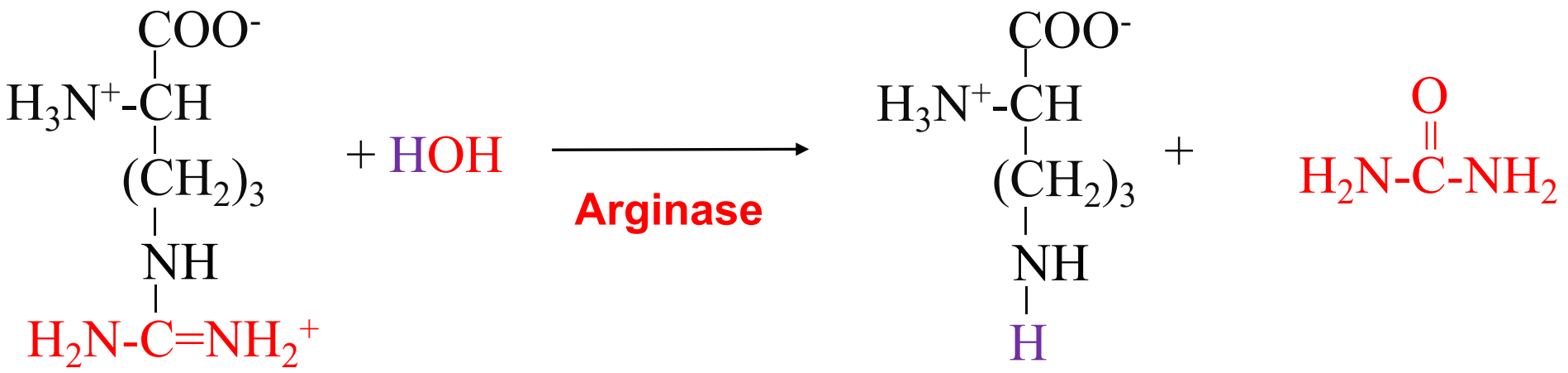


Argininosuccinate *Arginine (Arg)* *Fumarate*

The resulting fumarate links the **urea cycle** and the **tricarboxylic acid cycle (Krebs cycle).**

Urea Synthesis. Ornithine cycle

Reaction 5 (cytosol): formation of ornithine and urea catalyzed by the enzyme **arginase**



Arginine (Arg) *Ornithine* *Urea*

Arginase is activated by calcium and magnesium ions, and its competitive inhibitors are ornithine and lysine.

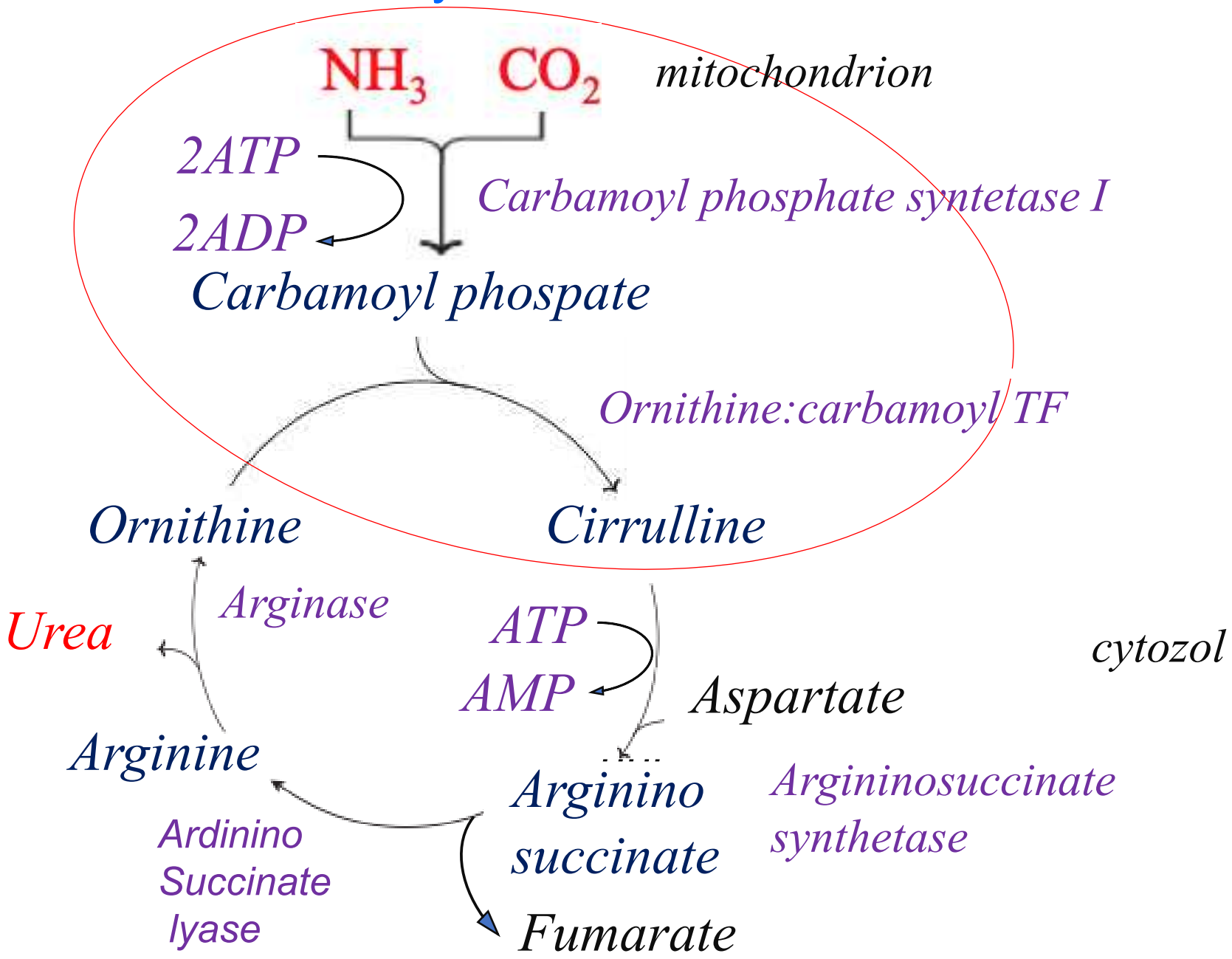
Arginase is found primarily in the liver, whereas the other enzymes of the urea cycle are present in other tissues.

For this reason, arginine synthesis can occur to varying degrees in many tissues, but urea synthesis occurs predominantly in the **liver**.

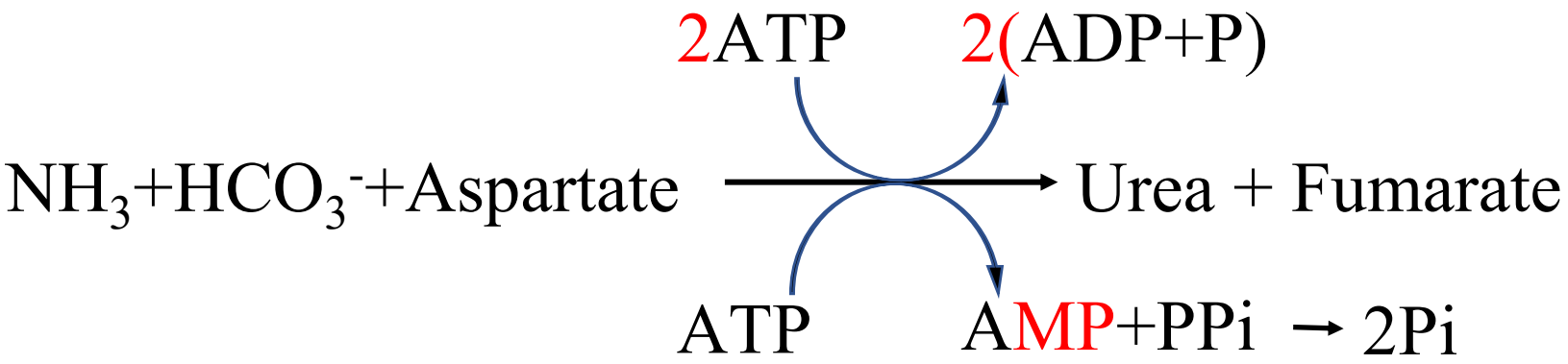
Urea cycle scheme

The first reaction of carbamoyl phosphate synthesis from bicarbonate and ammonia does not actually belong to the urea cycle itself. However, it is precisely this reaction that limits the rate of the entire urea synthesis cycle.

The regenerated ornithine re-enters the mitochondria for reuse in the urea cycle. Thus, ornithine acts as a "platform" upon which the carbon and nitrogen atoms of the future urea molecule are assembled.



Overall equation of urea synthesis:



Energy cost of urea synthesis:
The synthesis of 1 molecule of urea consumes

3 ATP molecules, but 4 high-energy bonds (~4 ATP equivalents)

Biological significance of urea synthesis:

1. Detoxification of ammonia released during the breakdown of nitrogen-containing compounds.
2. Compensation of acid-base balance (ABB) disturbances.
3. Synthesis of arginine – a conditionally essential amino acid

Regulation of the Urea Cycle (Ornithine Cycle)

The rate of the cycle is regulated by:

- Availability of substrates
- Changes in enzyme quantity
- Changes in enzyme activity

Availability of substrates: The higher their concentration, the faster the cycle proceeds.

Ammonia levels and the rate of the cycle increase during *accelerated amino acid degradation*, which can occur due to:

1. High-protein diet: due to deamination of excess amino acids;
2. Initial stage of fasting: amino acids after deamination are used for glucose synthesis

Regulation of the Urea Cycle (Ornithine Cycle)

Ammonia levels and cycle rate decrease due to reduced amino acid degradation during prolonged fasting:

•slowed protein breakdown in tissues;

•decreased glutaminase activity in the liver and increased activity in the kidneys, where the released ammonia binds H^+ and is excreted as salts.

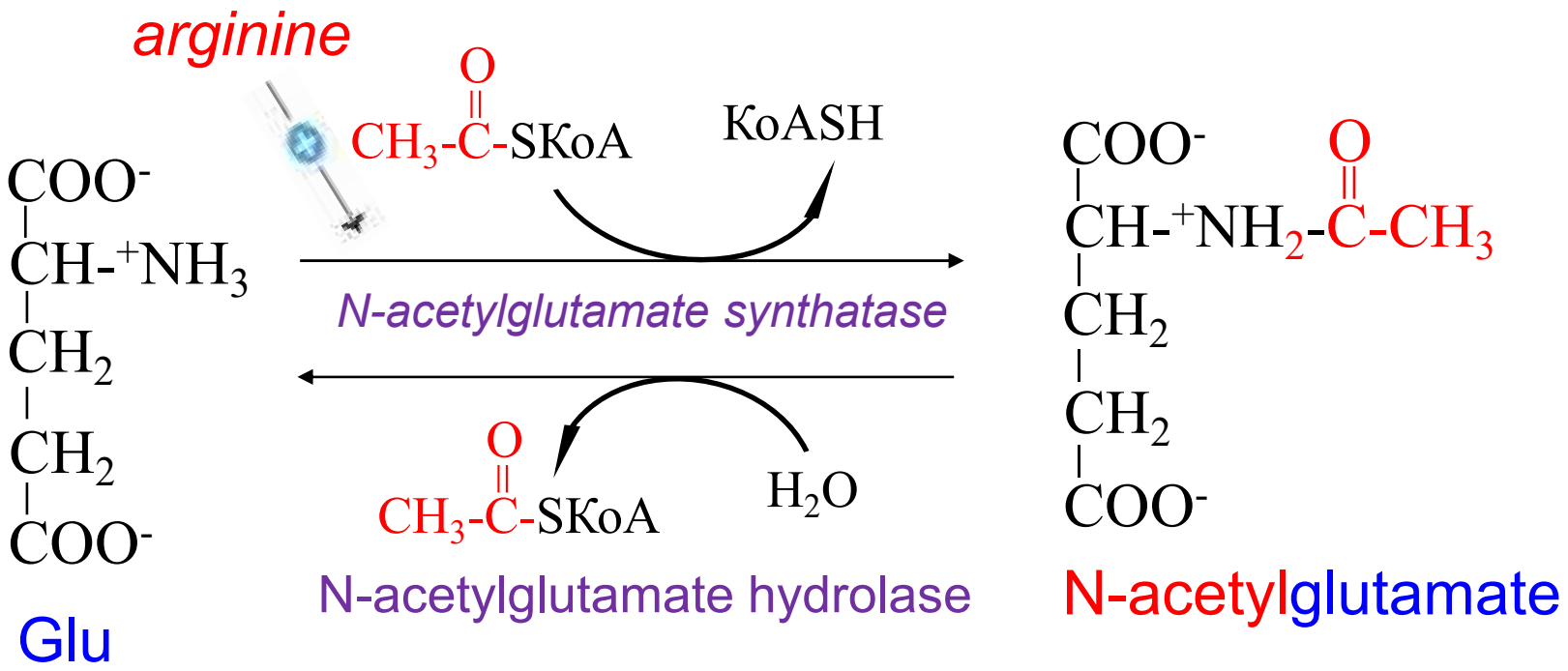
Regulation at the gene expression level:

Cycle enzymes are induced during a high-protein diet and repressed during fasting.

Regulation of the Urea Cycle (Ornithine Cycle)

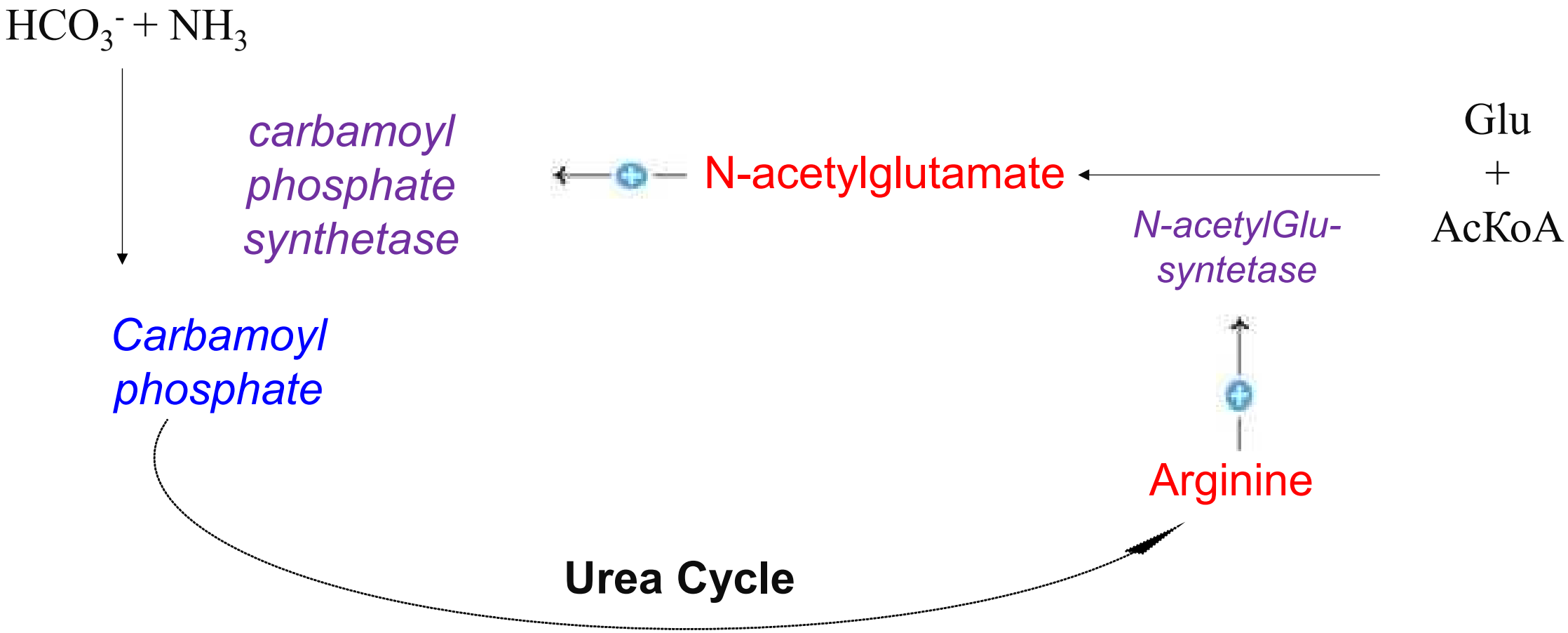
Allosteric regulation

The regulatory enzyme is carbamoyl phosphate synthetase, its activator is N-acetylglutamate, which is formed with the participation of synthetase (activator - arginine)



Regulation of the Urea Cycle (Ornithine Cycle)

Allosteric regulation



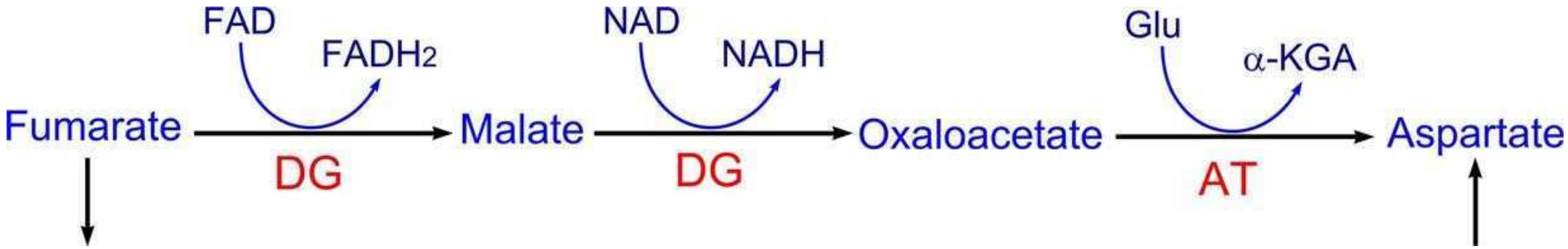
Thus, an increase in arginine levels in the liver accelerates two key reactions: the synthesis of carbamoyl phosphate and the formation of ornithine (substrate availability), leading to a significant acceleration of the urea cycle.

The Interconnection between the Urea Cycle and the TCA Cycle

The Krebs cycle produces compounds utilized in the urea cycle:

- *oxaloacetate*, which is converted to *aspartate*;
- *ATP;*
- CO_2 and H_2O

In the urea cycle, fumarate is produced, which enters the TCA cycle and can be utilized for the formation of aspartate: from the urea cycle it enters the TCA cycle, and from there it can re-enter the urea cycle.



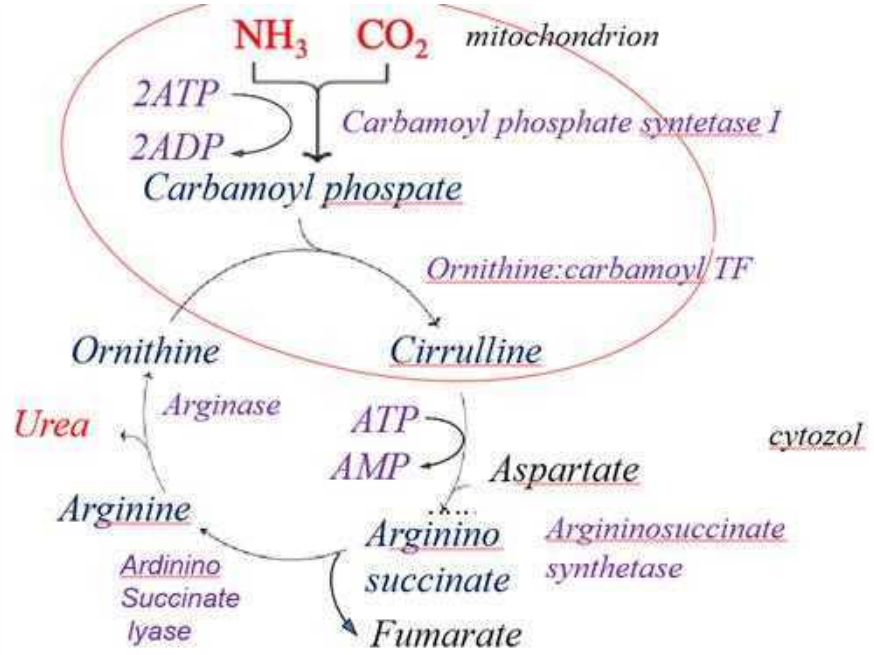
from the urea cycle
it enters the TCA cycle

enters the urea cycle

Disorders of urea synthesis

The absence or reduction in the synthesis of any one of the urea cycle enzymes leads to:

- hyperammonemia,
- hyperglutaminemia,
- accumulation of one or more intermediate products of the urea cycle, depending on which enzyme's activity is impaired



Disorders of urea synthesis

Hyperammonemia. An increase in the level of ammonia in the blood plasma (> 60 μmol/L)

Hereditary:
genetic defects of the ornithine cycle

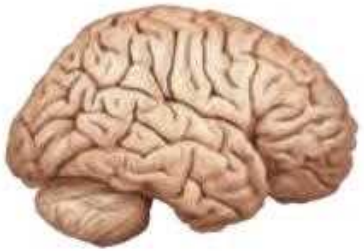
Acquired:
- Severe parenchymal liver damage
- Hepatic-portal insufficiency

Inhibition of the ornithine cycle

↑Blood ammonia → Hepatic coma

↑Urinary ammonia → Ammoniagenesis

Causes of ammonia toxicity



$\uparrow NH_3 + \uparrow H^+ \uparrow \rightarrow$ α-KGA $\xrightarrow{NH_4^+}$ Glu $\xrightarrow{NH_4^+}$ Gln

Metabolic alkalosis

by ↑ NH_4^+ :

- ↓α-*KGA* → *Inhibition TCA and* ↓*ATP*
- ↓Glu → ↓GABA — Inhibitory neurotransmitter
- ↑ Gln
  - → ↓*NO* *(vasodilator)* → ↓entry *Glucose, O_2…*
  - → ↑*entry* Ca^{2+} *and* Na^+ *, but* ↓K^+ → *Edema, change* $\Delta\varphi$

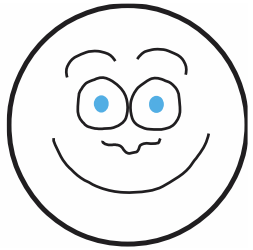
Impaired brain function

Ammonia readily crosses brain cell membranes and sequentially undergoes reactions:
with a-KGA to form Glu, and with Glu to form Gln. As a result, the concentrations of oxoglutarate (α-KGA) and Glu decrease, while the level of Gln increases.

Deficiency of:
Oxoglutarate slows down the tricarboxylic acid cycle, impairing ATP production;
Glu reduces the level of GABA, the main inhibitory neurotransmitter of the CNS.

Ammonia depletes protons by binding them into ammonium ions, leading to metabolic alkalosis; ammonium ions activate membrane channels through which calcium and sodium ions enter neurons in exchange for potassium ions, resulting in brain cell swelling and their death.

Urea Level



Normal range:

- in blood serum: 2.5 – 3.3 (8.3) mmol/L;
- in daily urine: 24-40 g/day

The blood urea level reflects:

- the excretory function of the kidneys,
- liver function

Urea Level

More N

Less N

Uremia: an increase in blood urea level (> 9 mmol/L).

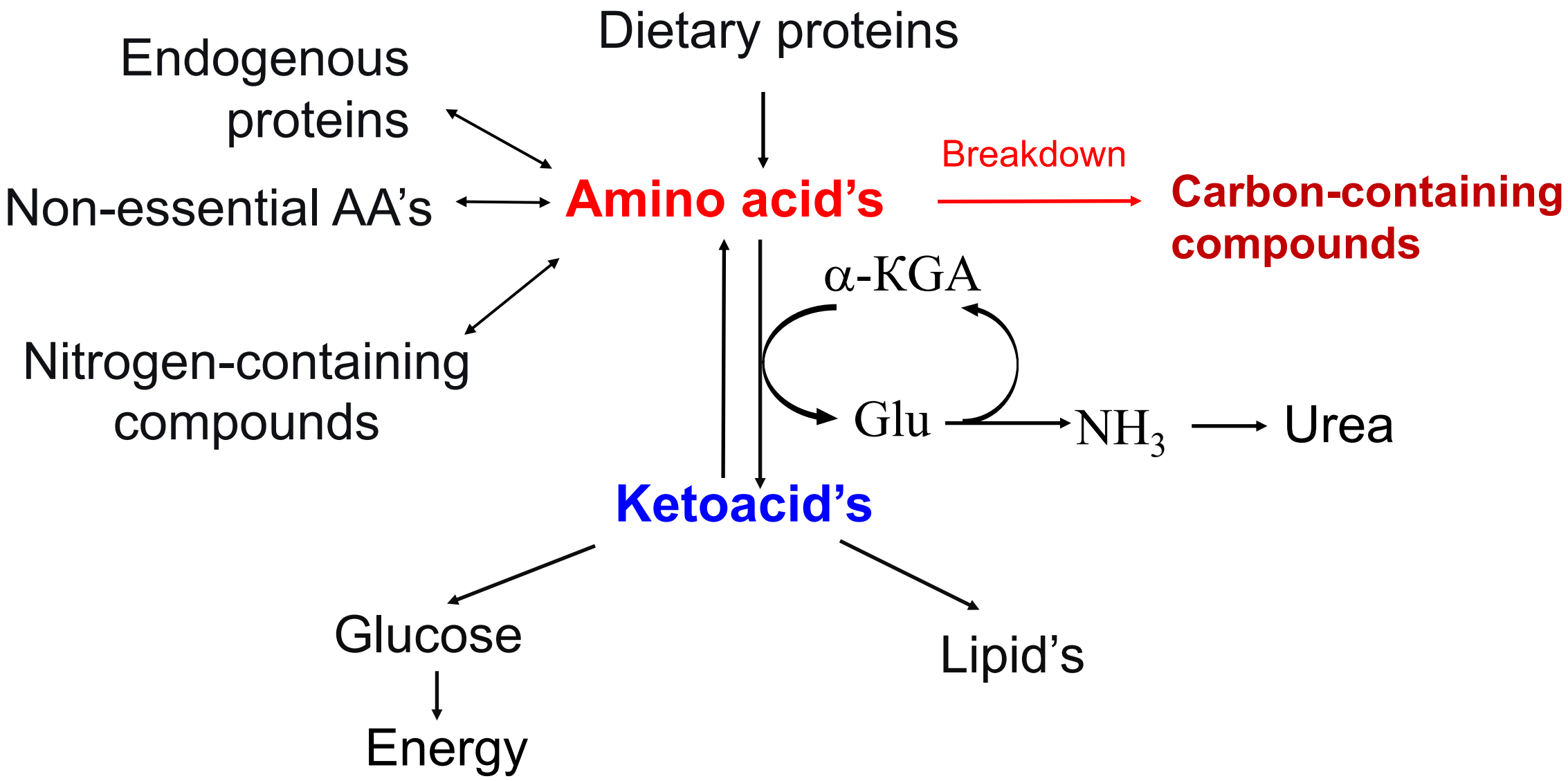
Causes of Increased Urea (Azotemia):

- Excessive protein intake;
- Starvation, dehydration, burns;
- Renal failure.

Causes of Decreased Urea:

- Liver failure;
- Starvation;
- Low protein diet;
- Impaired intestinal absorption.

Pathways of Formation and Utilization of the Amino Acid Pool



Breakdown of Amino Acids

Amino acid breakdown is enhanced under the following conditions:

- Excessive protein intake: enzymes of degradation are induced;
- Various physiological states:
  - intense physical exertion;
  - stress;
  - trauma;
  - cancer (oncological conditions).

Amino acids are degraded to:

Pyruvate and/or TCA cycle intermediate → Glucose

Acetyl-CoA and/or acetoacetate → Ketone bodies

Acetyl-CoA and/or acetoacetate, Pyruvate and/or TCA cycle intermediate

Amino acid's:

Glucogenic:

Ala, Cys, Ser, Gly; Arg, His, Pro, Glu, Gln; Met, Val; Asp, Asn

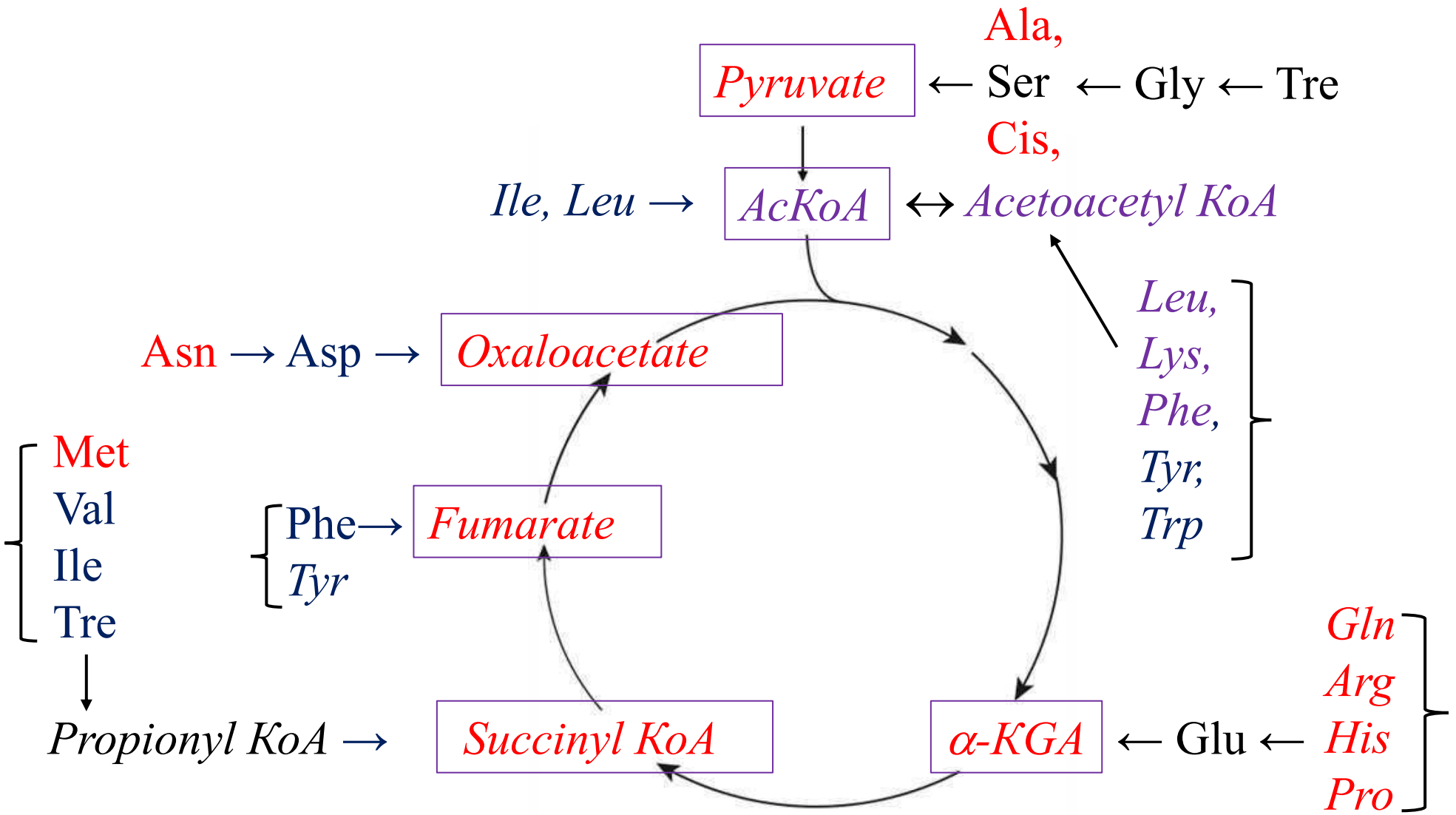
Ketogenic:

Lys, Leu

Gluco- and ketogenic:

Phe, Ile, Tyr, Trp, Thr

Amino Acid Degradation Pathway:



Thank you for your attention!