Biosynthesis of non-essential amino acids

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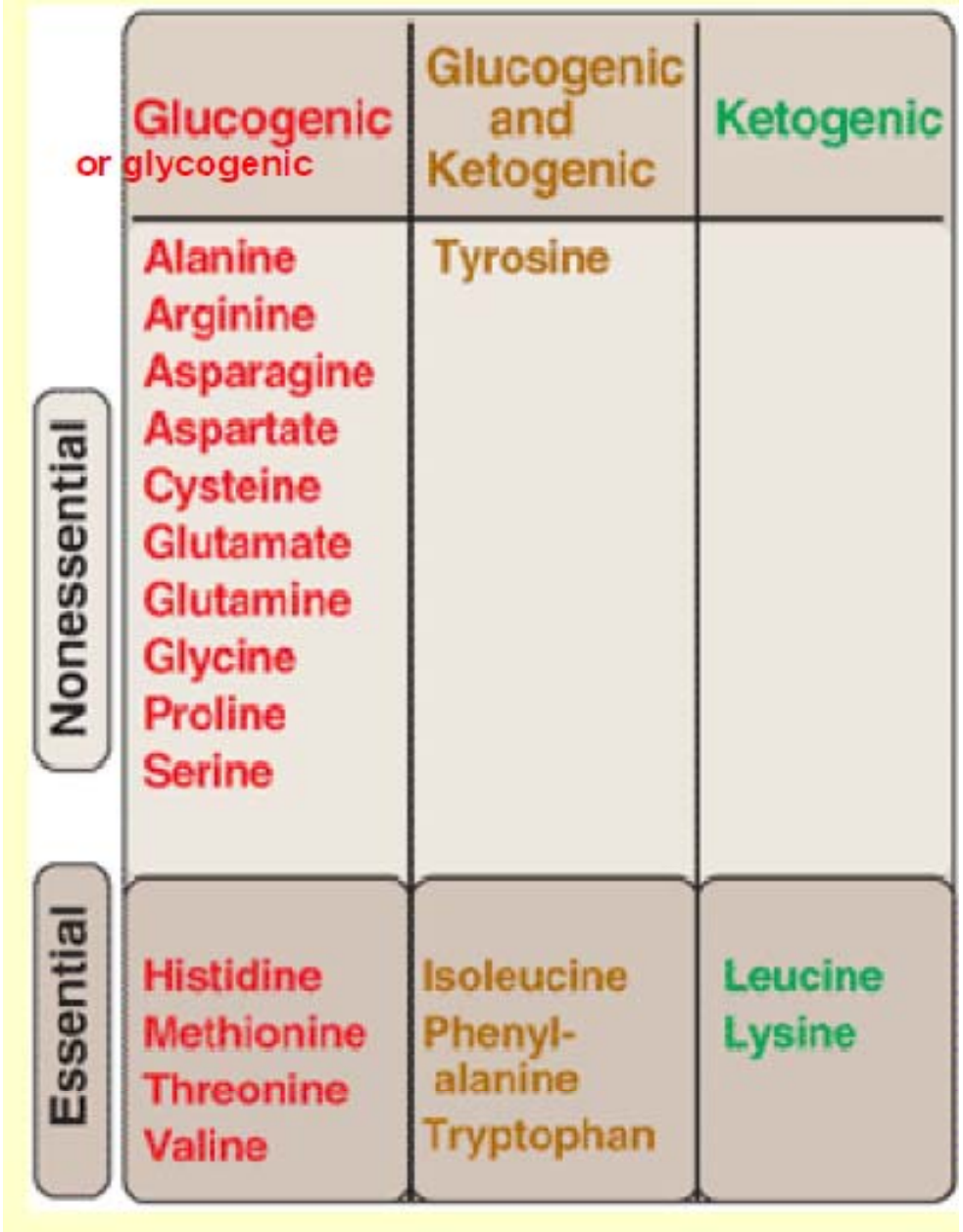
Essential and Non-essential Amino acids



	Glucogenic or glycogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Proline Serine	Tyrosine	
Essential	Histidine Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

You can remember the essential amino acids by using a mnemonic: Very Many Hairy Little Pigs Live In The Torrid *Argentine

which translates to: Valine Methionine, Histidine, Leucine, Phenylalanine, Lysine, Isoleucine, Threonine Tryptophan

***Arginine:-** **NB: Arginine is non-essential but is essential only in children and infants**

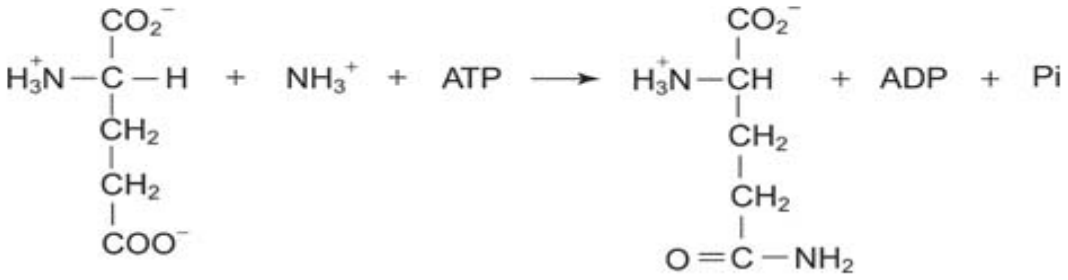
Non essential amino acids are synthesized from intermediates of metabolism or, from essential amino acids.

Nonessential amino acids

Many of the nonessential amino acids are derived directly from intermediate products of the TCA cycle or glycolysis. The key reactions include:

- Transamination, as in the synthesis of alanine from pyruvate.

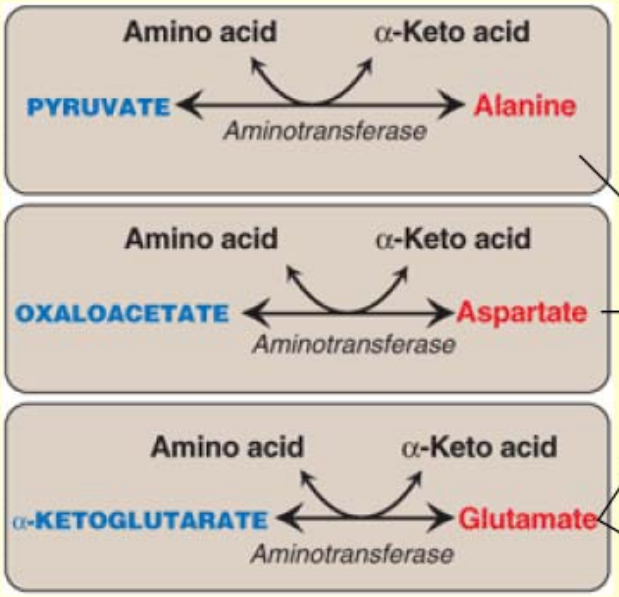
- Amidation via amidotransferases, as in glutamine synthetase:



A more complex series of reactions synthesizes other nonessential amino acids. For example, the carbon chain of cysteine derives from serine and the sulfur derives from homocysteine (which results after methyl donation from S-AdoMet).

Non essential amino acids are synthesized from intermediates of metabolism or, from essential amino acids.

Synthesis from α-keto acids

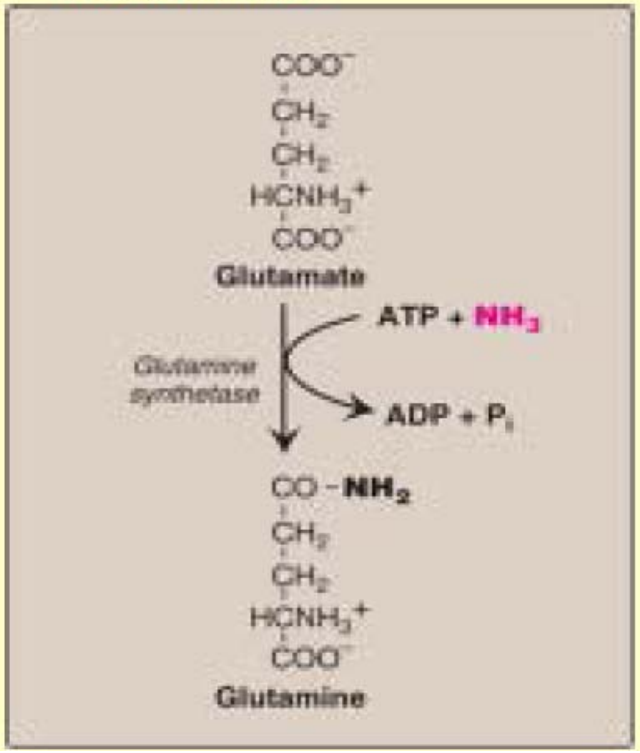


Ala, Asp and Glu are synthesized by transfer of an amino group to the α-keto acids pyruvate, oxaloacetate, and a-ketoglutarate respectively.

Glutamate can also be synthesized by Reverse of oxidative deamination, catalyzed by glutamate dehydrogenase.

Synthesis by amidation

Glutamine:



Aspargine:

Aspargine:

- contains an amide linkage with ammonia at the β-carboxyl
- Is formed from Aspratate
- Reaction is driven by asparagine synthatase using glutamine as a amide donor.
- Requires ATP

Glutamine:

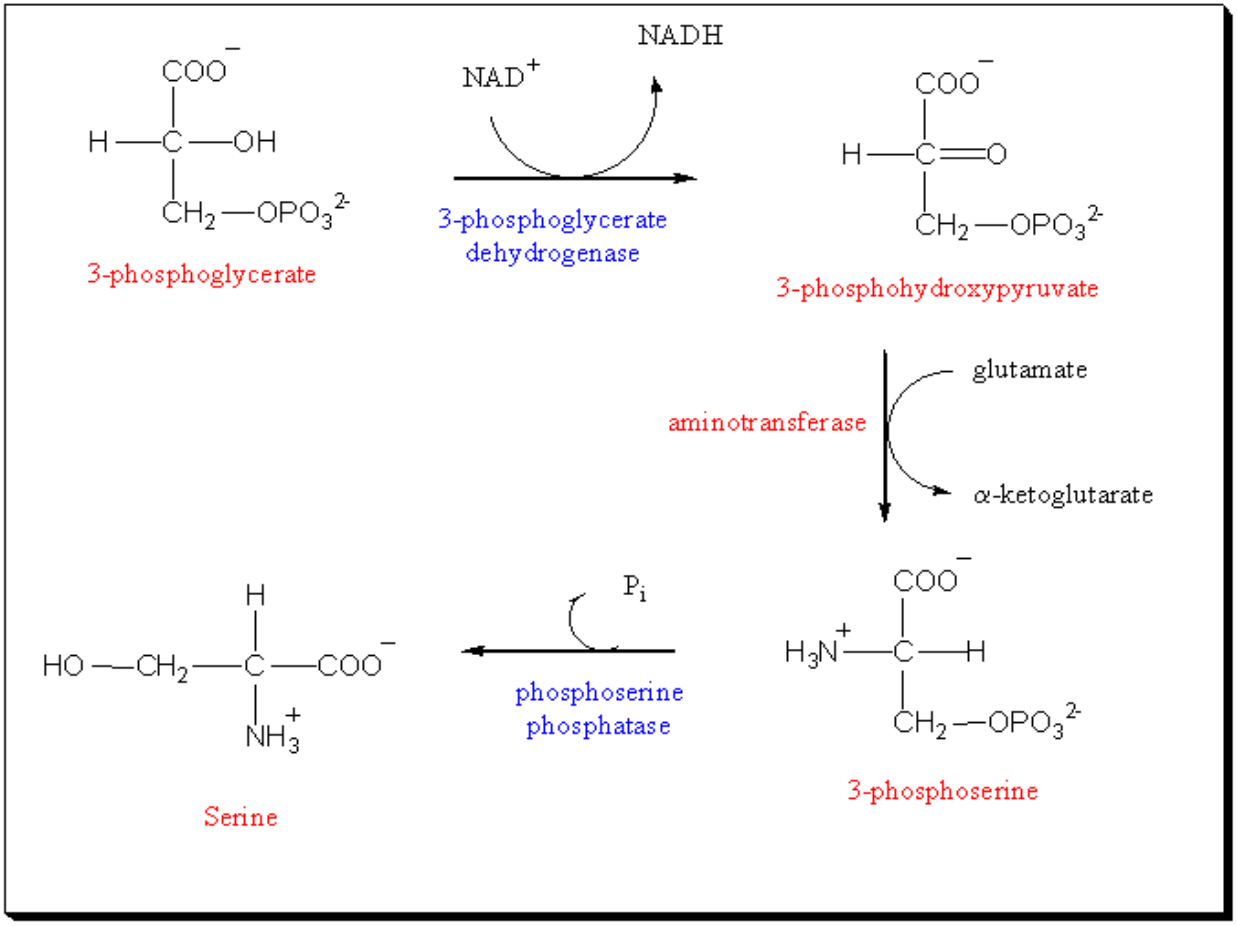
- contains an amide linkage with ammonia at the γ-carboxyl
- Is formed from glutamate
- Reaction is driven by glutamine synthetase
- Requires ATP
- Reaction serves as a major step for detoxification of ammonia in addition to the synthesis of Glutamine for protein synthesis.

Proline:

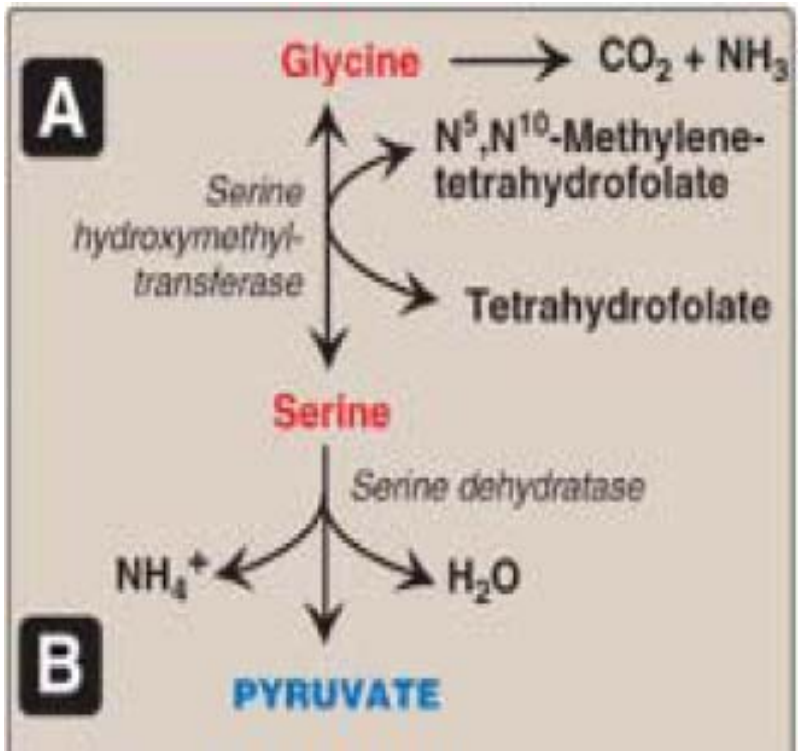
Glutamate is converted to proline by cyclization and reduction reactions.

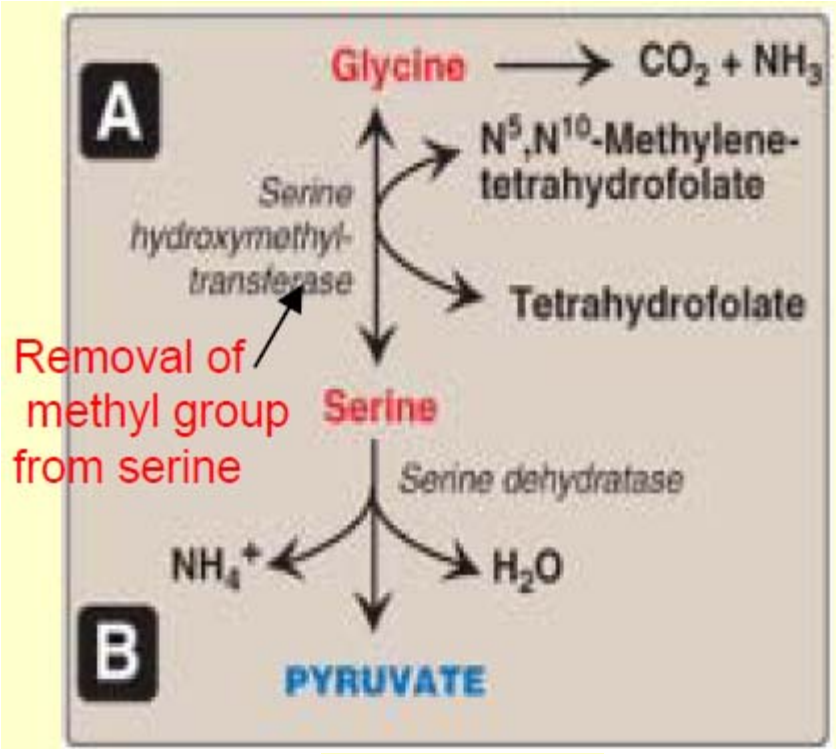
Serine:

Synthesized from glycolysis intermediate 3-phosphogylcerate.



Glycine: Synthesized from Serine

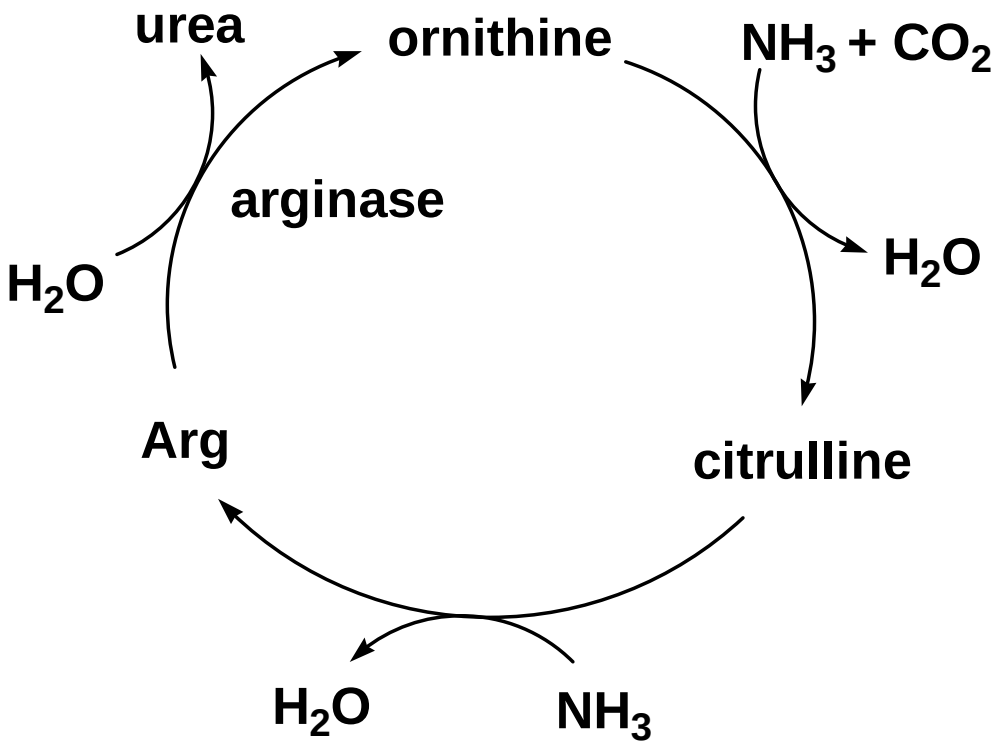


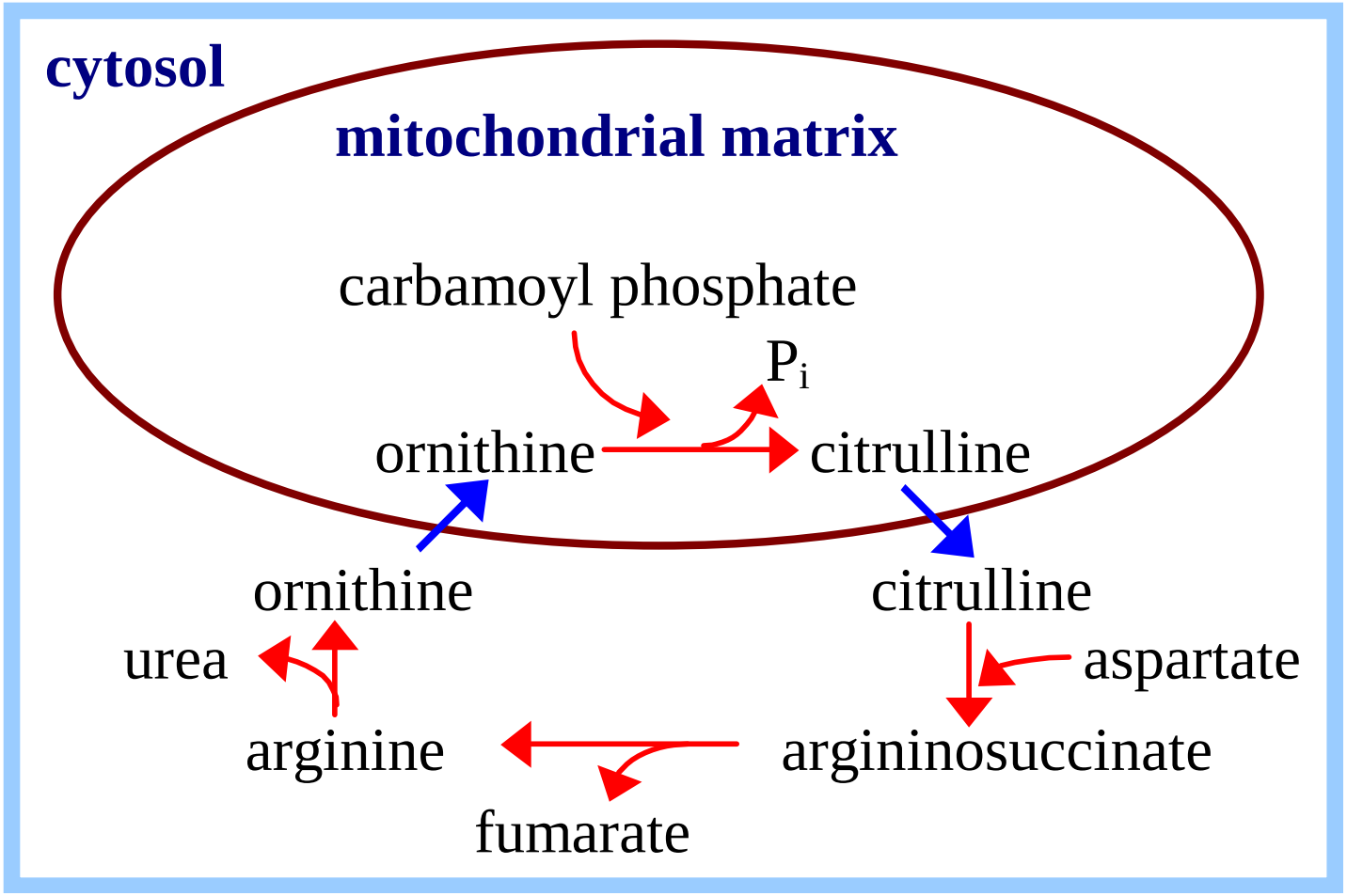


Glycine

Biosynthesis of Arginine: Urea cycle/Ornithine Cycle

1. Site: liver (mitochondria and cytosol)
2. Process urea cycle also called ornithine cycle
3. Produces urea from ammonia and arginine is synthesized



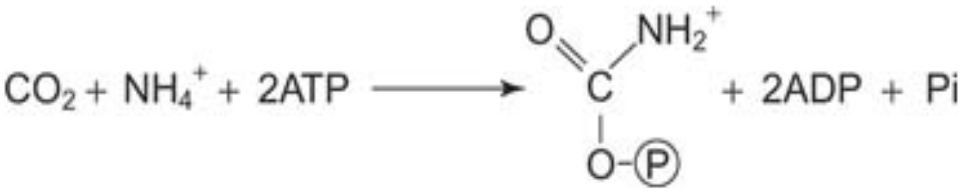


- For each cycle, **citrulline** must leave the mitochondria, and **ornithine** must enter the mitochondrial matrix.
- An **ornithine/citrulline transporter** in the inner mitochondrial membrane facilitates transmembrane fluxes of citrulline & ornithine.
- A complete **Krebs Cycle** functions only within mitochondria.
- But cytosolic isozymes of some Krebs Cycle enzymes are involved in regenerating **aspartate** from **fumarate**.

Biochemistry of the urea cycle

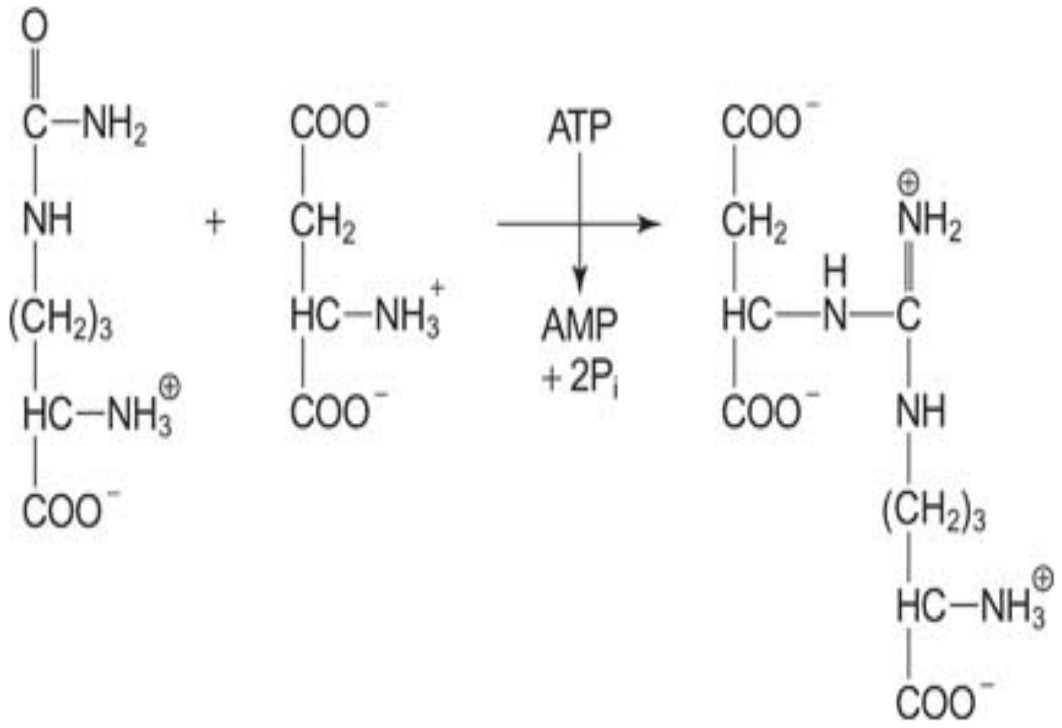
1. First the ammonium ions must be activated through conversion to carbamoyl phosphate by the **mitochondrial form** of carbamoyl phosphate synthetase.

$$NH_4^+ + HCO_3^- + 2\ ATP \rightarrow \text{Carbamoyl Phosphate} + 2\ APP + P_i$$

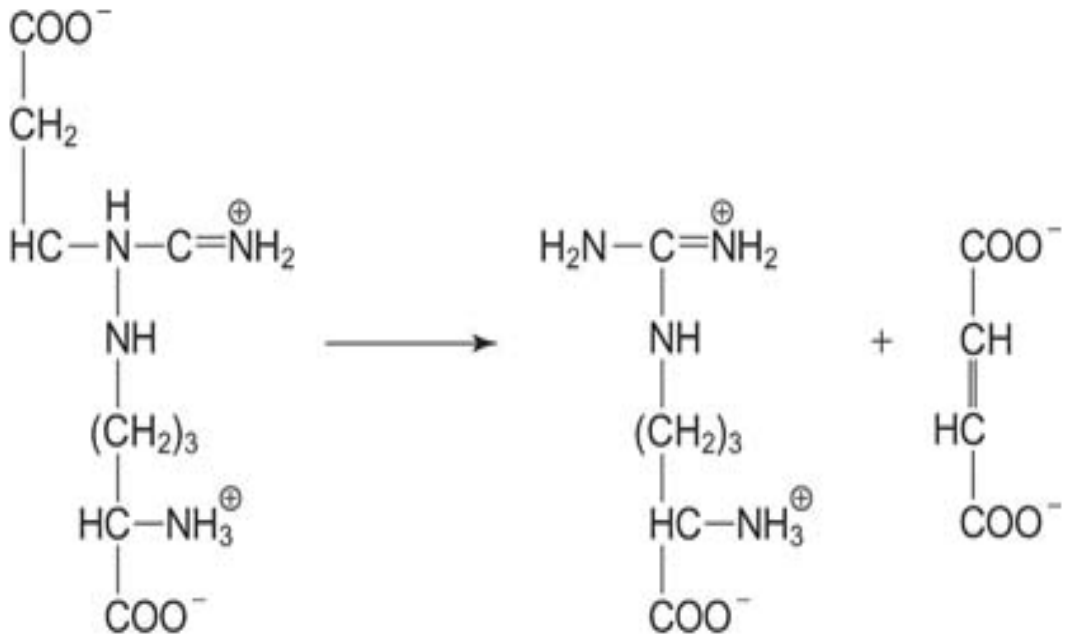


2. The entry of activated ammonia into the urea cycle occurs by the ornithine transcarbamoylase reaction where the carbamoyl group is transferred to the side chain amino group of the non-protein amino acid, **ornithine**. Ornithine has five carbons; its carbon chain therefore has the same length as that of arginine. The product of the ornithine transcarbamoylase reaction is the amino acid **citrulline**.

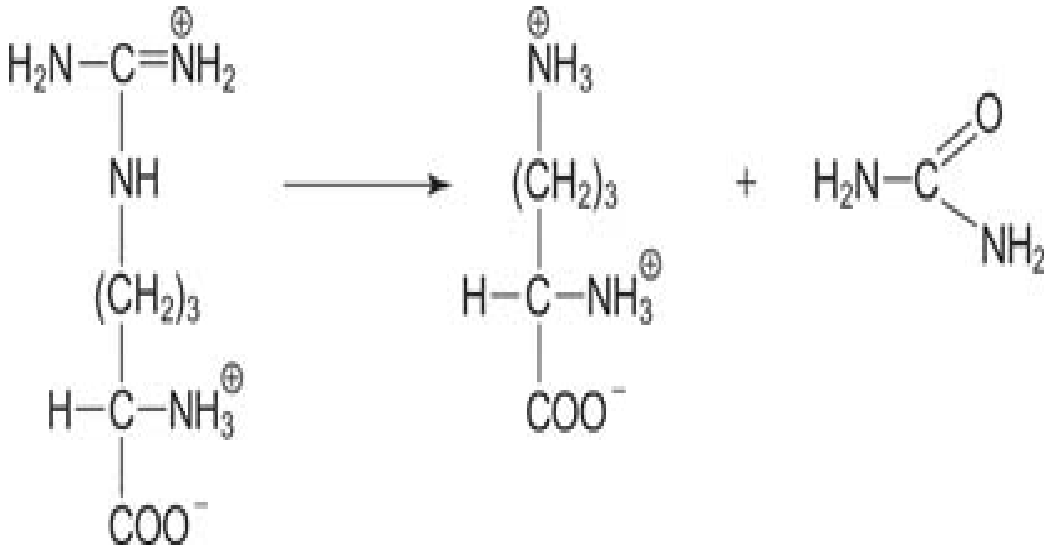
3. The addition of the second ammonia to the backbone involves the joining of the carbamoyl group of citrulline to the χ-amino group of aspartate, leading to a complex compound, arginosuccinate. ATP is hydrolyzed in this step.



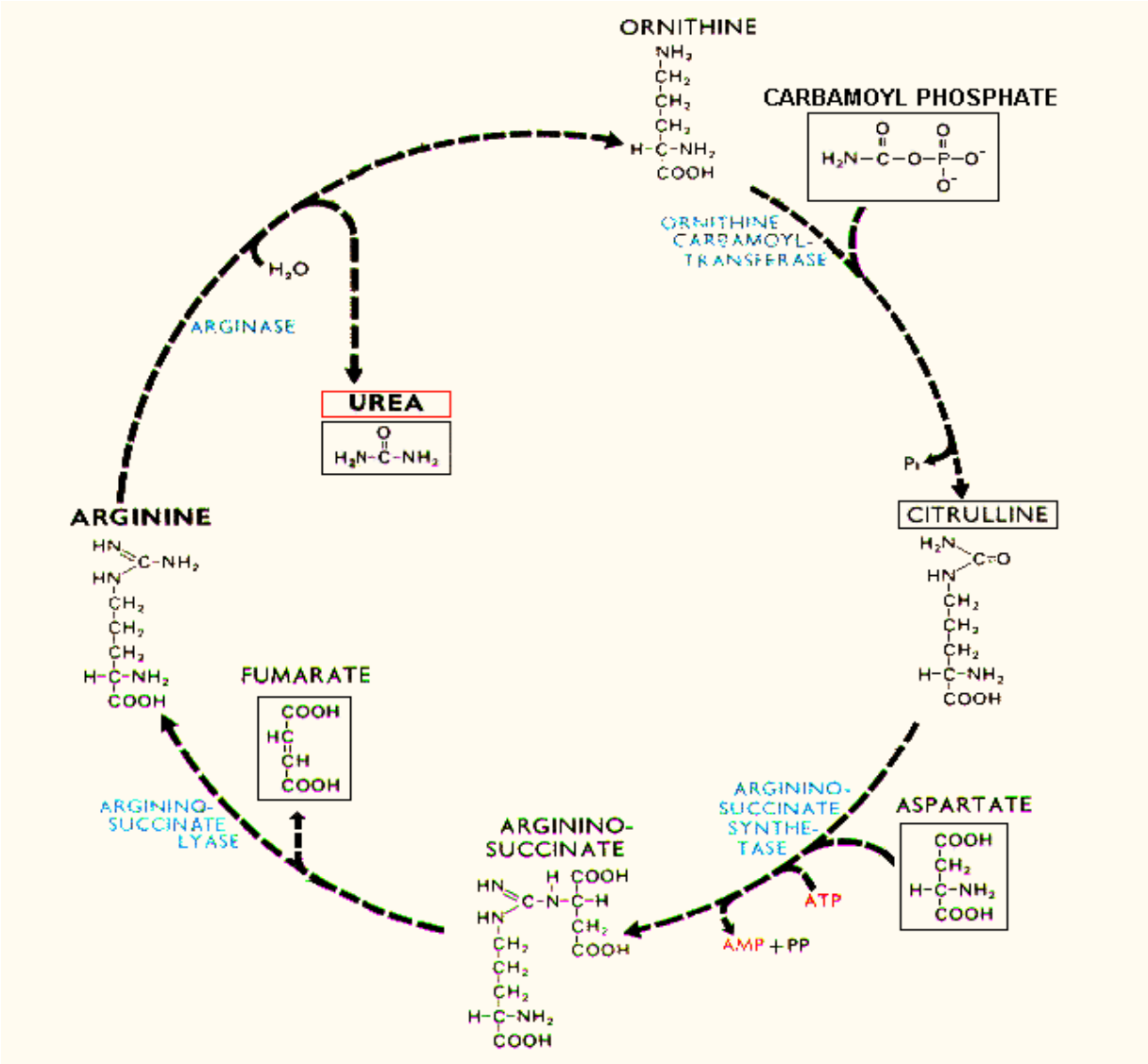
4. The next step is cleavage of arginosuccinate to arginine and fumarate by the enzyme arginosuccinate lyase. Lyases cleave bonds with the creation of a double bond in one of the products. In this case, the double bond is the carbon-carbon double bond of fumarate.



5. The final step is the release of urea by the enzyme arginase, which regenerates ornithine.

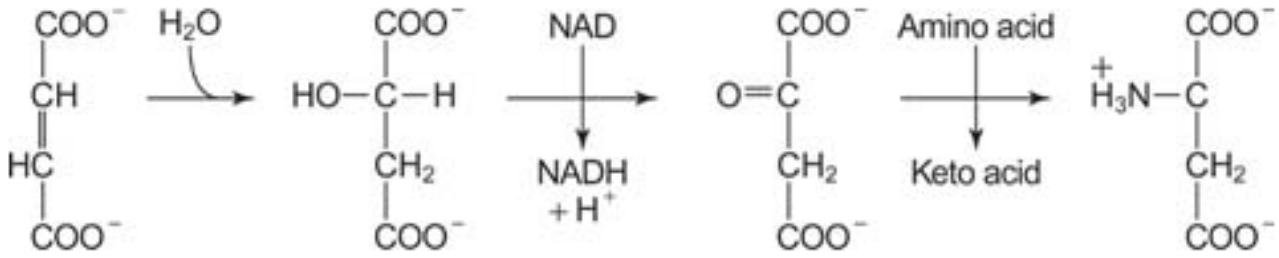


Urea cycle-Summary

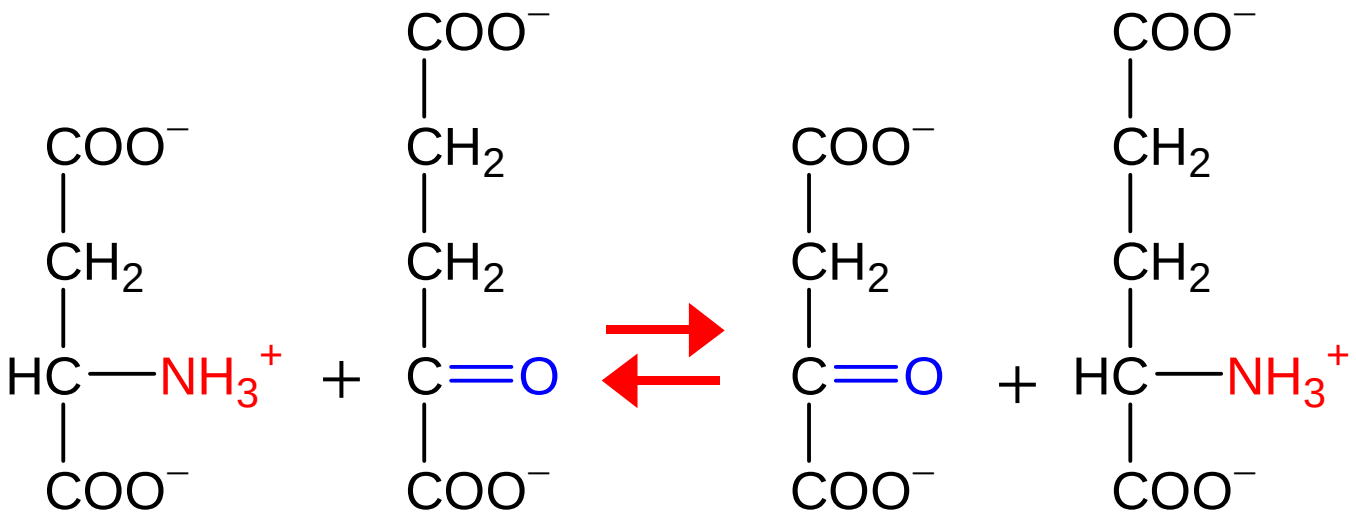


Link: Urea cycle and TCA cycle

The other part of the urea cycle that has occurred is the conversion of the carbons of aspartate to fumarate. The fumarate is recycled back to oxaloacetate through TCA cycle reactions in the mitochondrion. Transamination with glutamate regenerates aspartate. The glutamate comes from the glutamate dehydrogenase reaction.



The urea is excreted through the kidneys and broken down to carbon dioxide and ammonia by plants and microorganisms. The enzyme **urease** causes this conversion.



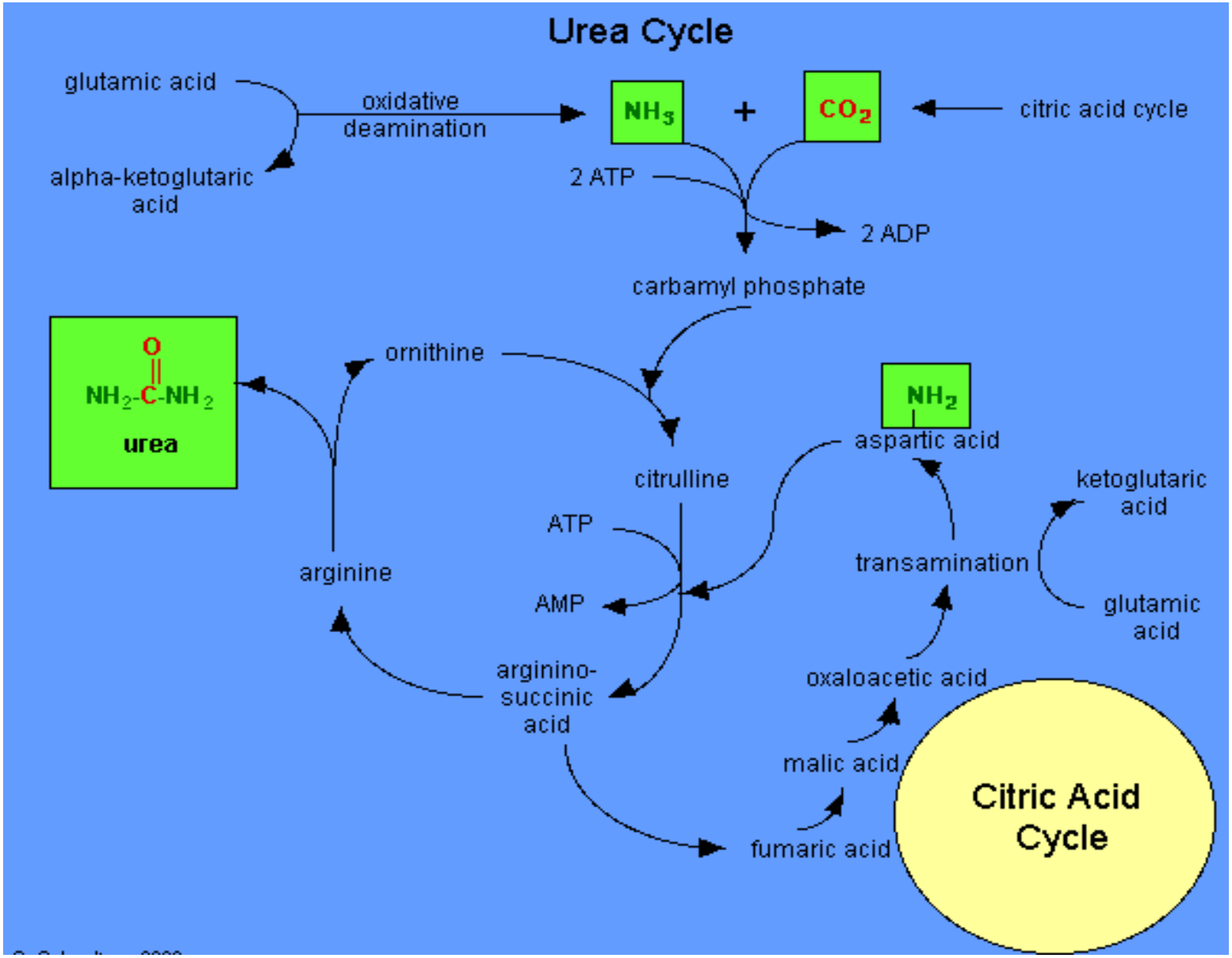
Aminotransferase (Transaminase)

Fumarate is converted to **oxaloacetate** via Krebs Cycle enzymes Fumarase & Malate Dehydrogenase.

Oxaloacetate is converted to **aspartate** via transamination (e.g., from glutamate).

Aspartate then re-enters Urea Cycle, carrying an amino group derived from another amino acid.

Link: Urea cycle and TCA cycle



Urea cycle enzyme defects:

Hereditary deficiency of any of the Urea Cycle enzymes leads to **hyperammonemia** - elevated [ammonia] in blood.

Total lack of any Urea Cycle enzyme is lethal.

Elevated ammonia is toxic, especially to the brain.

If not treated immediately after birth, severe mental retardation results.

Renal Kidney Failure:

- **Urea is routinely measured in the blood as: Blood Urea Nitrogen (BUN). BUN levels may be elevated (a condition called uremia) in both acute and chronic renal (kidney) failure.**
- **Various diseases damage the kidney and cause faulty urine formation and excretion.**
- **Congestive heart failure leads to a low blood pressure and consequent reduced filtration rates through the kidneys, therefore, BUN may be elevated.**
- **Urinary tract obstructions can also lead to an increased BUN. In severe cases, hemodialysis is used to remove the soluble urea and other waste products from the blood.**
- **Waste products diffuse through the dialyzing membrane because their concentration is lower in the dialyzing solution.**
- **Ions, such as Na^+ and Cl^- which are to remain in the blood, are maintained at the same concentration in the dialyzing solution - no net diffusion occurs.**

Cysteine: Is synthesized by two consecutive reactions

1) Homocysteine + serine ⟶ Cystathionine

2) hydrolysis ↓

α-ketobutyrate + cysteine

- **The carbon chain of Cysteine derives from Serine and the sulfur derives from homocysteine (which results after methyl donation from S-Adenosyl Methionine**

Tyrosine

Phenylalanine —(Phenylalanine hydroxylase)→ Tyrosine

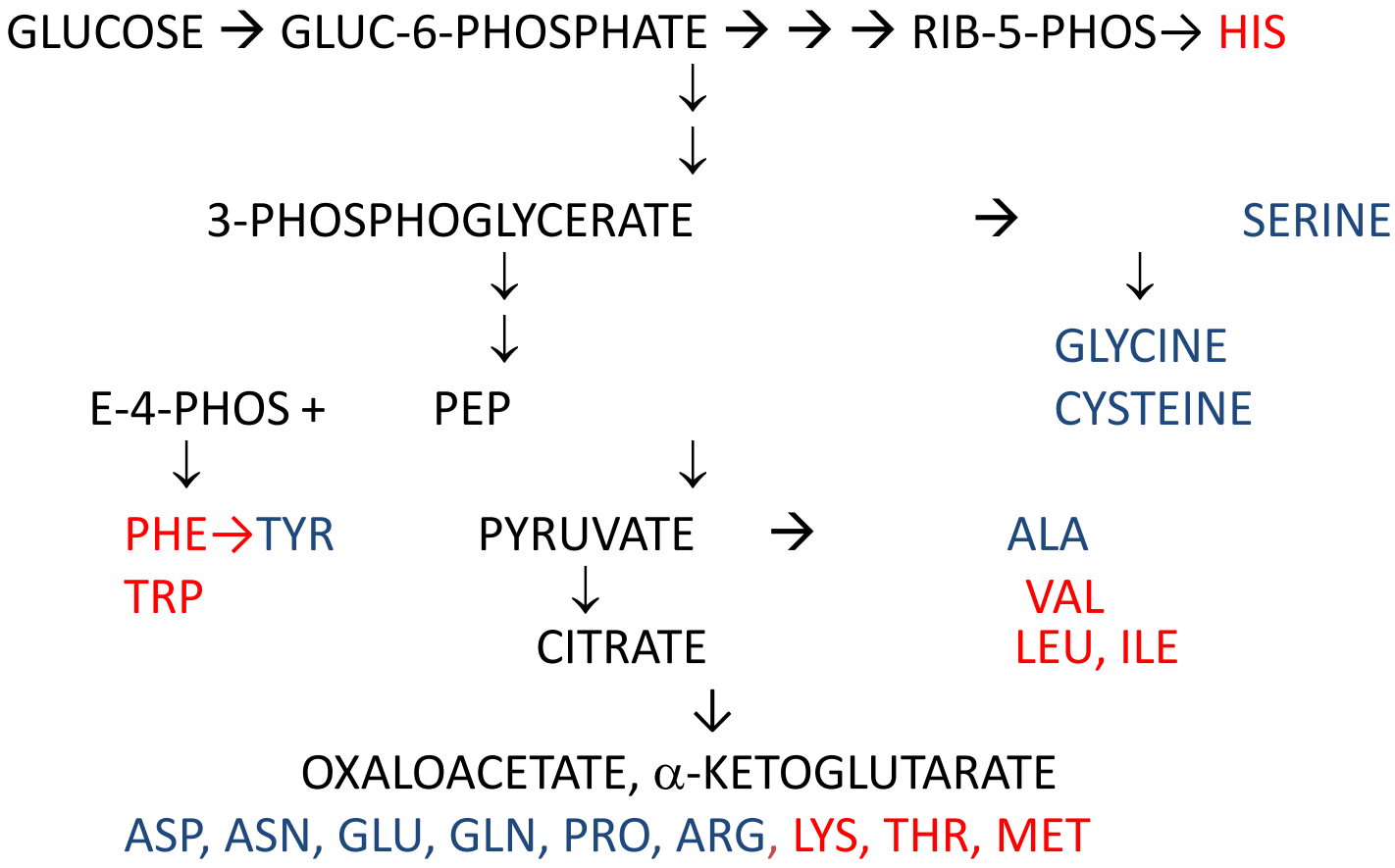
Tyrosine and Cysteine are non essential AA. But there synthesis is dependent on the essential AAs phenylalanine and methionine resp.

NON-ESSENTIAL AMINO ACID SYNTHESIS

- ***SUMMARY POINT:***
  - **ALL NONESSENTIALS (EXCEPT TYR) ARE DERIVED FROM ONE OF THE FOLLOWING COMMON INTERMEDIATES:**
    - **PYRUVATE**
    - **OXALOACETATE**
    - **α-KETOGLUTARATE**
    - **3-PHOSPHOGLYCERATE**

AMINO ACID BIOSYNTHESIS OVERVIEW

(USE OF COMMON INTERMEDIATES)



IN-CLASS EXERCISE

- **WHICH OF THE 4 AMINO ACID INTERMEDIATES OF THE UREA CYCLE IS ESSENTIAL IN CHILDREN?**

- **OUTLINE A PATHWAY BY WHICH ADULTS CAN SYNTHESIZE THIS AA FROM 1 GLUCOSE MOLECULE.**
  - **HINTS: YOU WILL NEED TO CONSIDER THE FOLLOWING METABOLIC PATHWAYS:**
    - **GLYCOLYTIC**
    - **GLUCONEOGENIC**
    - **CITRIC ACID CYCLE**
    - **GLUTAMATE DEHYDROGENASE REACTION**
      - **ASSUME IT CAN GO IN REVERSE DIRECTION**
    - **ORNITHINE PRODUCTION**
    - **UREA CYCLE**