Faculty of Pharmacy
Biochemistry-2

Edited By:

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Lecturer of Biochemistry

Lecture 6

Amino acid degradation

Metabolism of the carbon skeleton

Removal of amino group

Excretion of Nitrogen

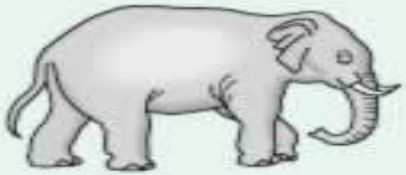
Proteins

Nucleic acids

Amino acids

Nitrogenous bases

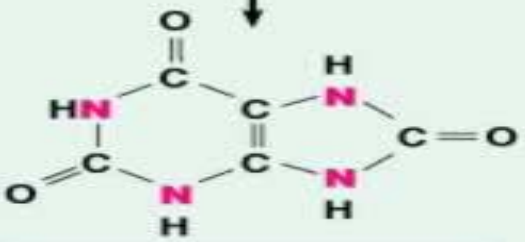
$-NH_2$
Amino groups



Most aquatic animals, including many fishes

Mammals, amphibians, sharks, some bony fishes

Birds, insects, many reptiles, land snails



Ammonia

Urea

Uric acid

Metabolism of ammonia

Although free ammonia is involved in the liver, the level of ammonia in the blood must be kept low because even slightly elevated concentrations are toxic to CNS.

Formation of urea in the liver is quantitatively the most important disposal route for ammonia.

Sources of Ammonia

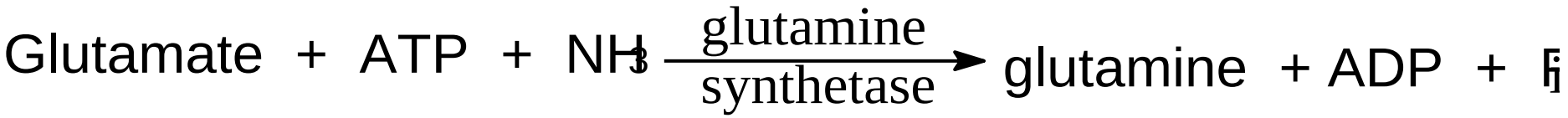
1. From amino acids by transamination and oxidative deamination.
2. Intestinal mucosa hydrolysis of glutamine by intestinal glutaminase.
3. The intestinal lumen by the bacterial degradation of urea by urease.
4. Ammonia absorbed by the portal vein and is almost quantitatively removed by the liver.

Sources of Ammonia

1. Kidneys glutamine by the action of renal glutaminase.
2. Amines obtained from the diet and monoamines that serve as hormones or neurotransmitters give rise to ammonia by the action of monoamine oxidase enzyme (MAO).
3. In both purine and pyrimidine catabolism, the amino groups attached to the rings are released as ammonia.

Transport of Ammonia in the Circulation

- Although ammonia is constantly produced in the tissues, it is present at very low levels in blood.
- This is due to rapid removal of ammonia from blood by liver as well as many tissues, particularly muscle, in the form of glutamine or alanine, rather than as free ammonia.

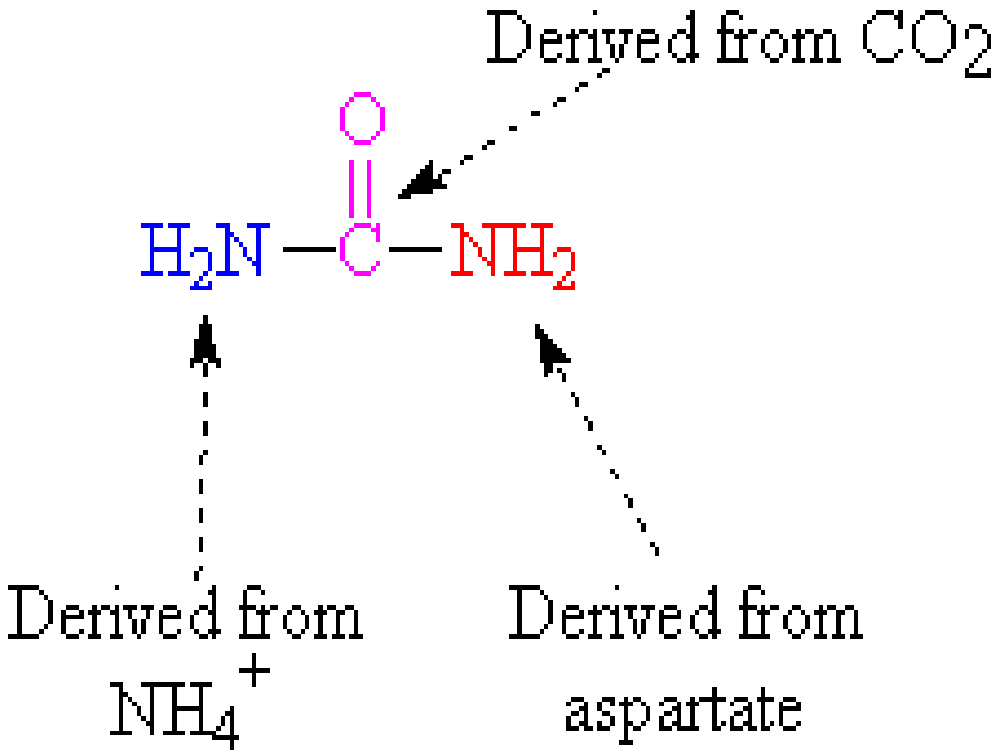


What is urea?

Urea is the major disposal form of amino acids.

Accounts 90% of the nitrogen containing components of urine.

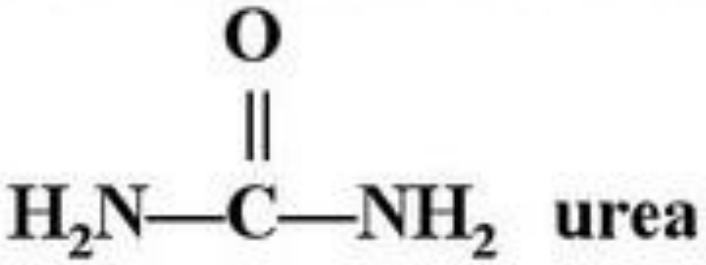
One nitrogen of urea molecule is supplied by free NH_3 and other nitrogen by aspartate.



Urea Cycle (Krebs-Henseleit Cycle)

The urea cycle:

- **Detoxifies ammonium ion from amino acid degradation.**
- **Converts ammonium ion to urea in the liver.**



- **Provides 25-30 g urea daily for urine formation in the kidneys.**

- Urea is synthesized in the liver and then transported in the blood to the kidneys for excretions in urine.

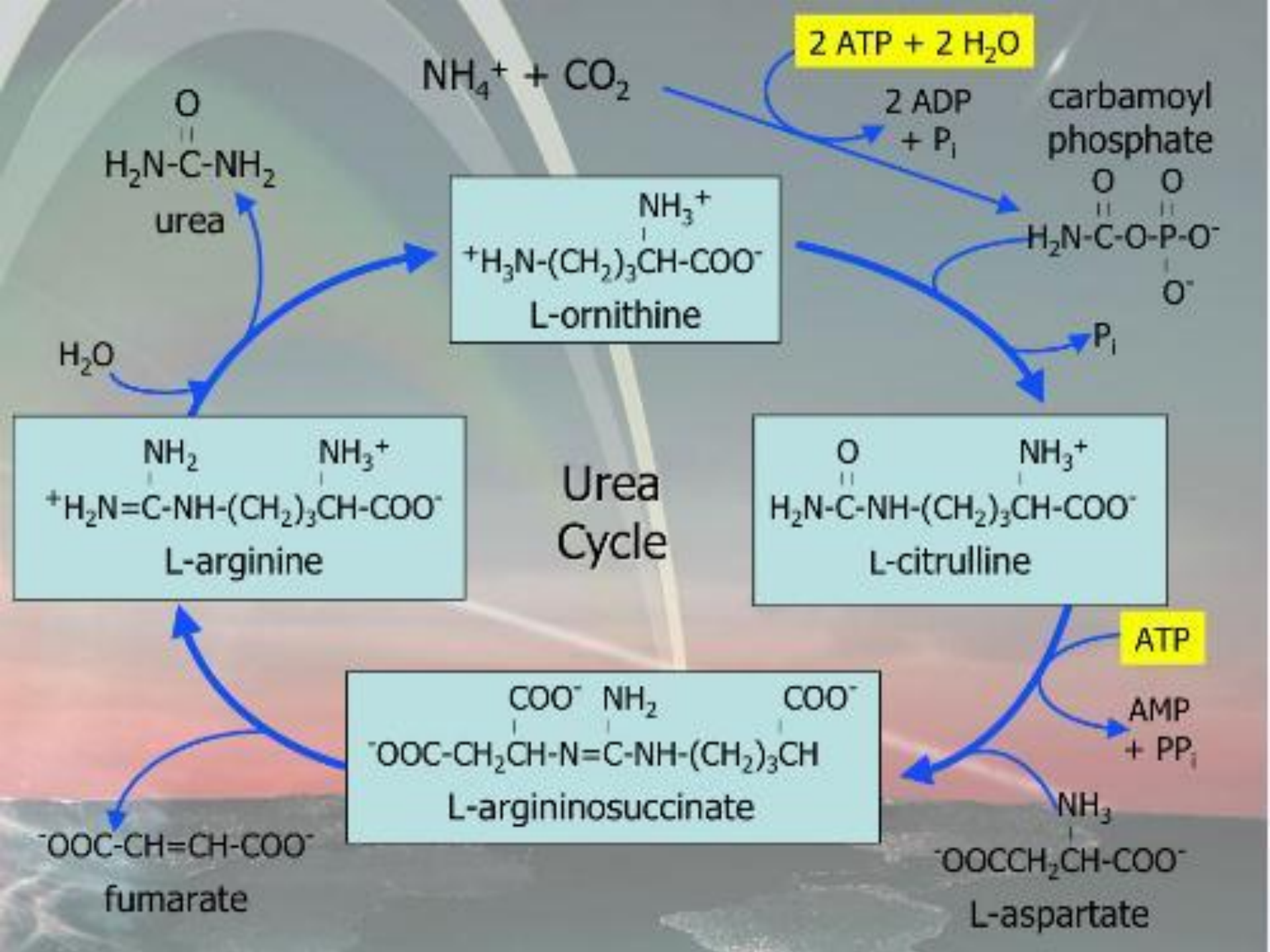
The urea cycle

All excess amino acids are deaminated.

Results in the production of ammonium which is toxic and must be eliminated.

The urea cycle serves this purpose.

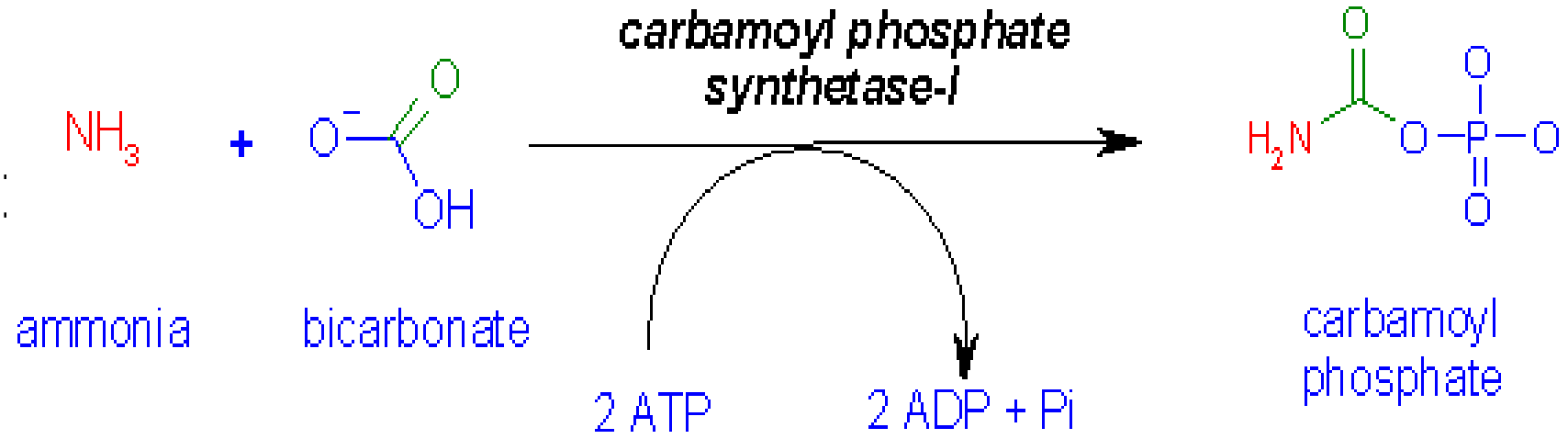
- Occurs in the liver.
- Results in the formation of urea.
- Urea is eliminated by excretion (urine).


Urea Cycle
$NH_4^+ + CO_2$
2 ATP + 2 H_2O
2 ADP + P_i
carbamoyl phosphate
$H_2N-C(=O)-O-P(=O)(O^-)-O^-$
$H_2N-C(=O)-NH_2$
urea
$^+H_3N-(CH_2)_3CH(NH_3^+)-COO^-$
L-ornithine
P_i
H_2O
$^+H_2N=C(NH_2)-NH-(CH_2)_3CH(NH_3^+)-COO^-$
L-arginine
$H_2N-C(=O)-NH-(CH_2)_3CH(NH_3^+)-COO^-$
L-citrulline
ATP
AMP + PP_i
$^-OOC-CH_2CH(COO^-)-N=C(NH_2)-NH-(CH_2)_3CH(COO^-)$
L-argininosuccinate
$^-OOC-CH=CH-COO^-$
fumarate
$^-OOCCH_2CH(NH_3)-COO^-$
L-aspartate
NH_3

Reactions of Urea cycle

- **First two reactions occur in the mitochondria and the remaining steps in the cytosol.**

1- formation of carbamoyl phosphate:



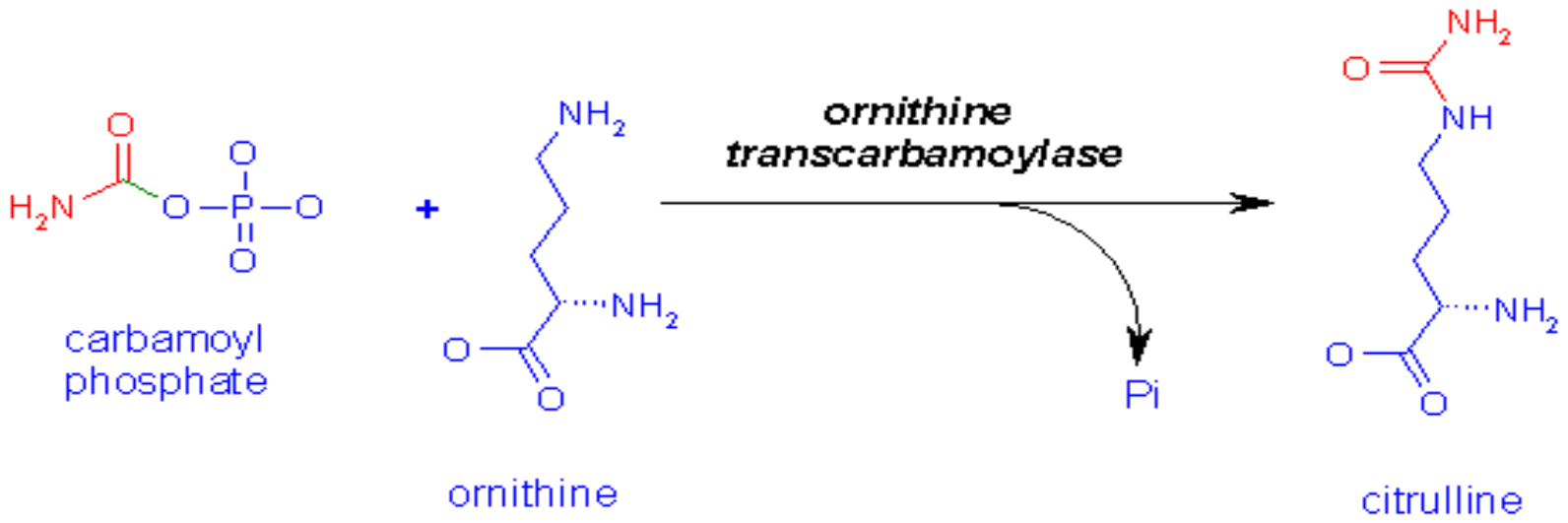
$HCO_3^- + NH_3 + 2\,ATP$

(1) ↓ Carbamoyl Phosphate Synthase

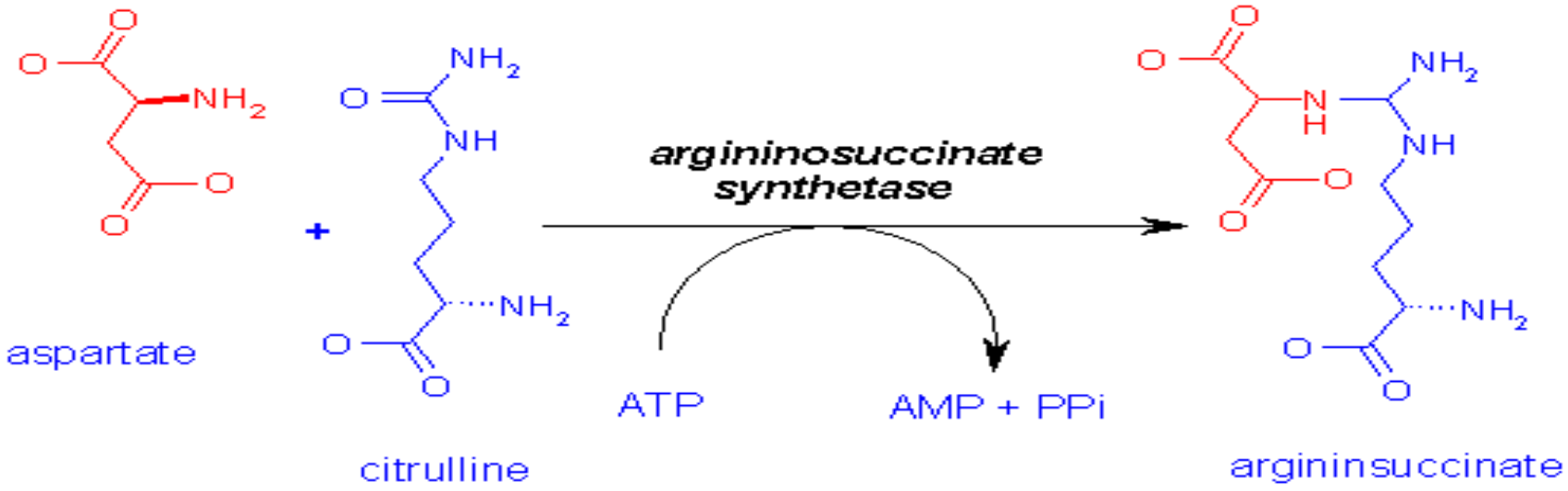
$H_2N-C(=O)-OPO_3^{2-} + 2\,ADP + P_i$

carbamoyl phosphate

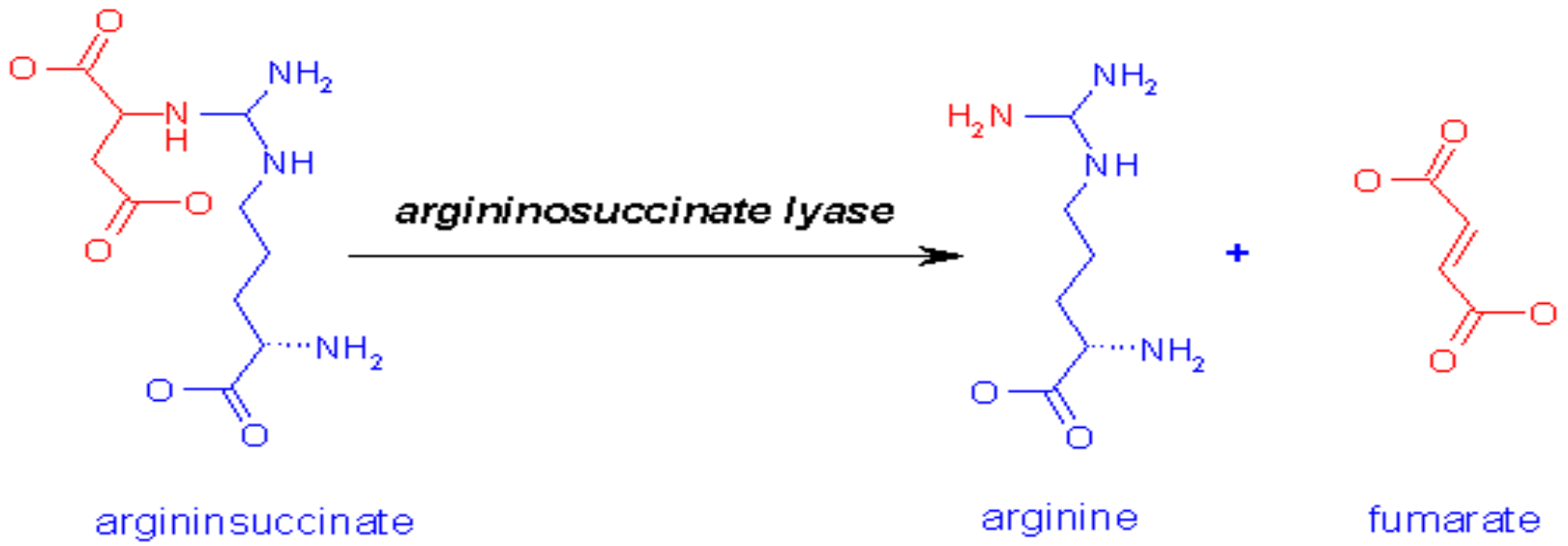
2- Formation of citrulline:



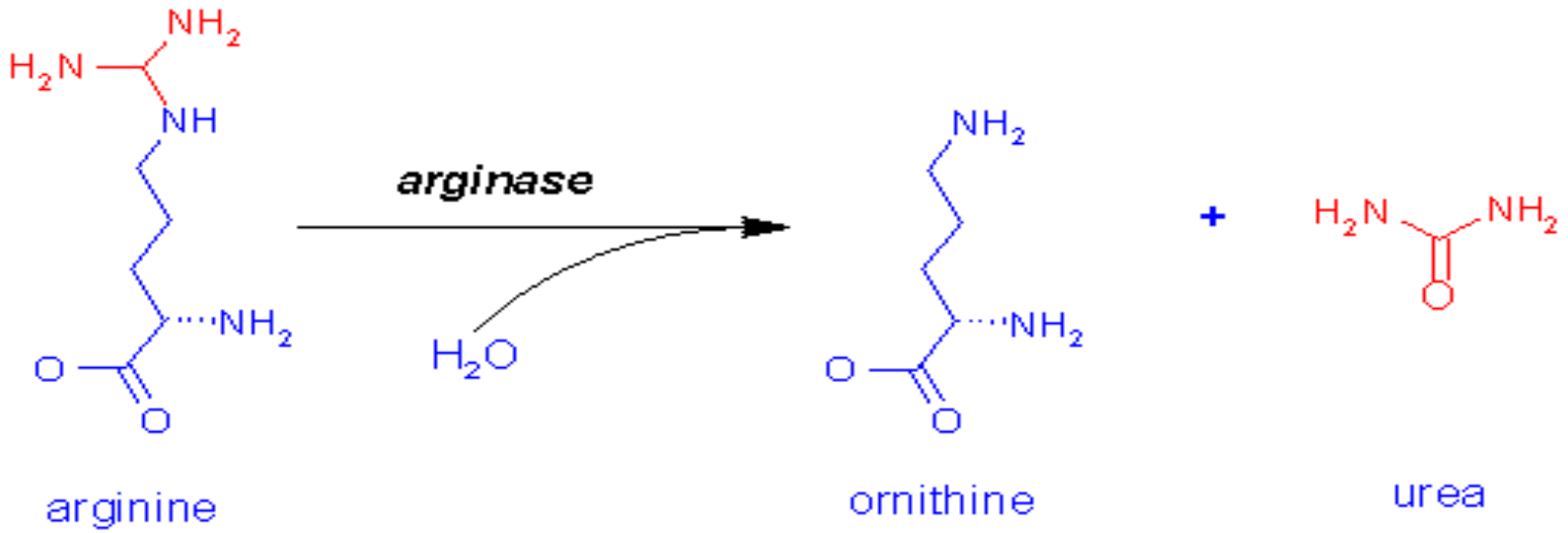
3- Synthesis of argininosuccinate:

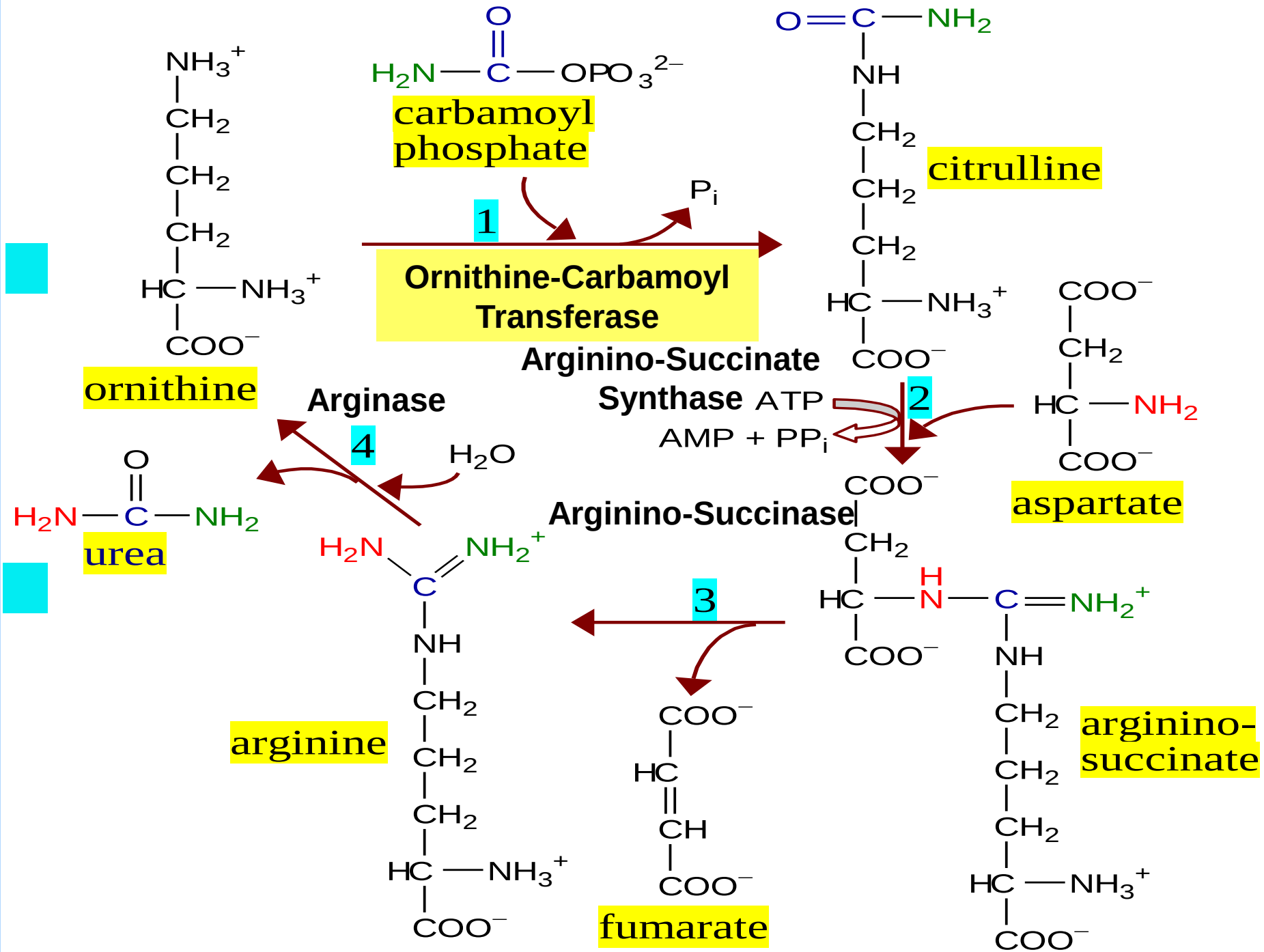


4- Cleavage of argininosuccinate:



5- Cleavage of arginine to ornithine & urea:

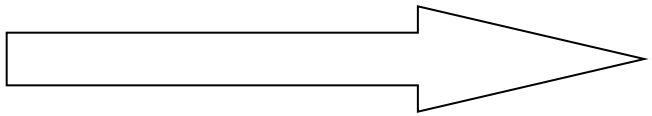



carbamoyl phosphate
Pi
1
Ornithine-Carbamoyl Transferase
citrulline
ornithine
Arginino-Succinate Synthase
ATP
AMP + PPi
2
aspartate
Arginase
4
H2O
urea
Arginino-Succinase
3
arginine
fumarate
arginino-succinate

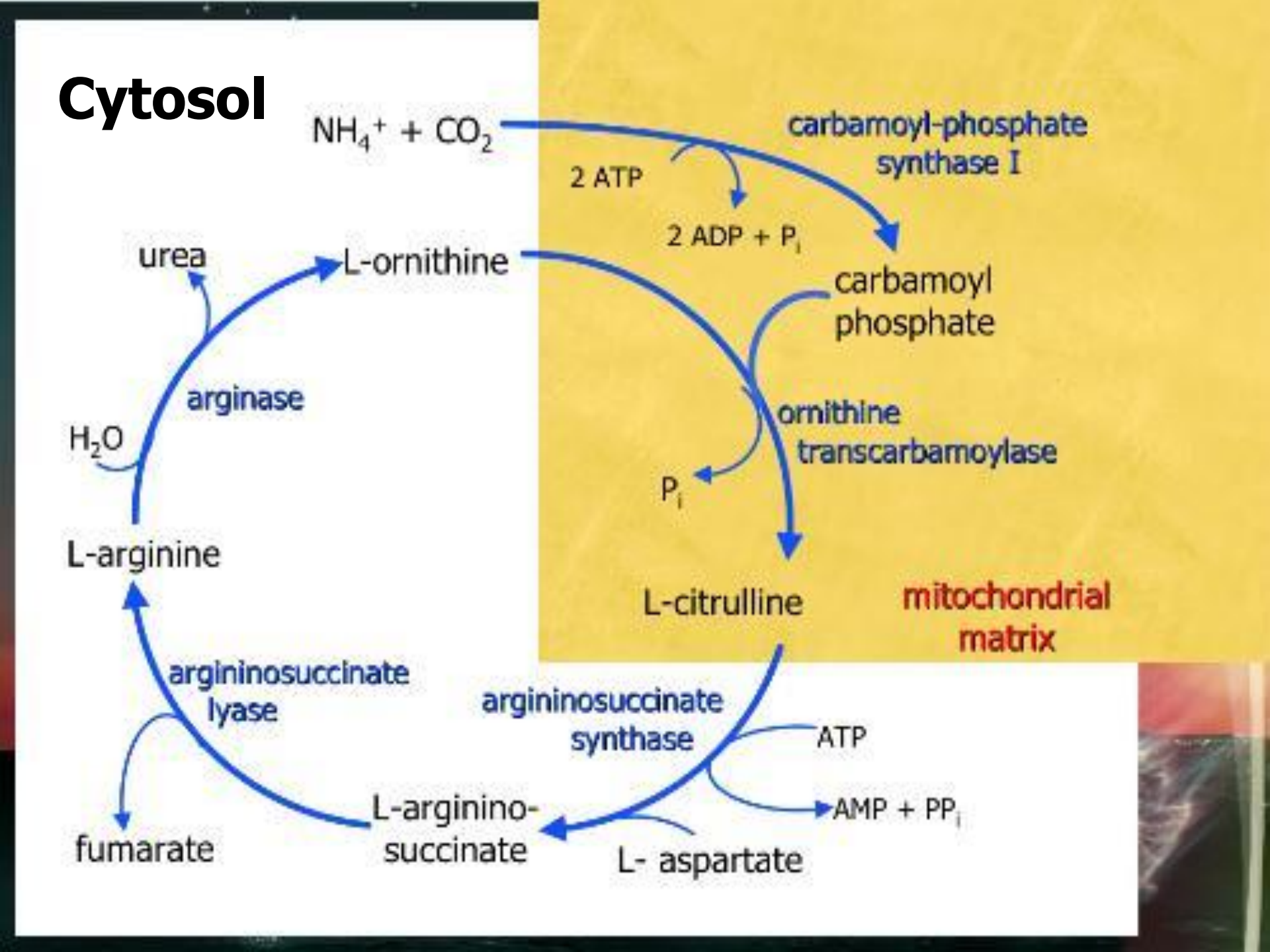
Urea Cycle

- Ø Enzymes in Mitosol:
  - Carbamoyl Phosphate Synthase I.
  - Ornithine-Carbamoyl Transferase Enzymes.
- Ø Enzymes in Cytosol:
  - Arginino-Succinate Synthase
  - Arginino-succinase
  - Arginase

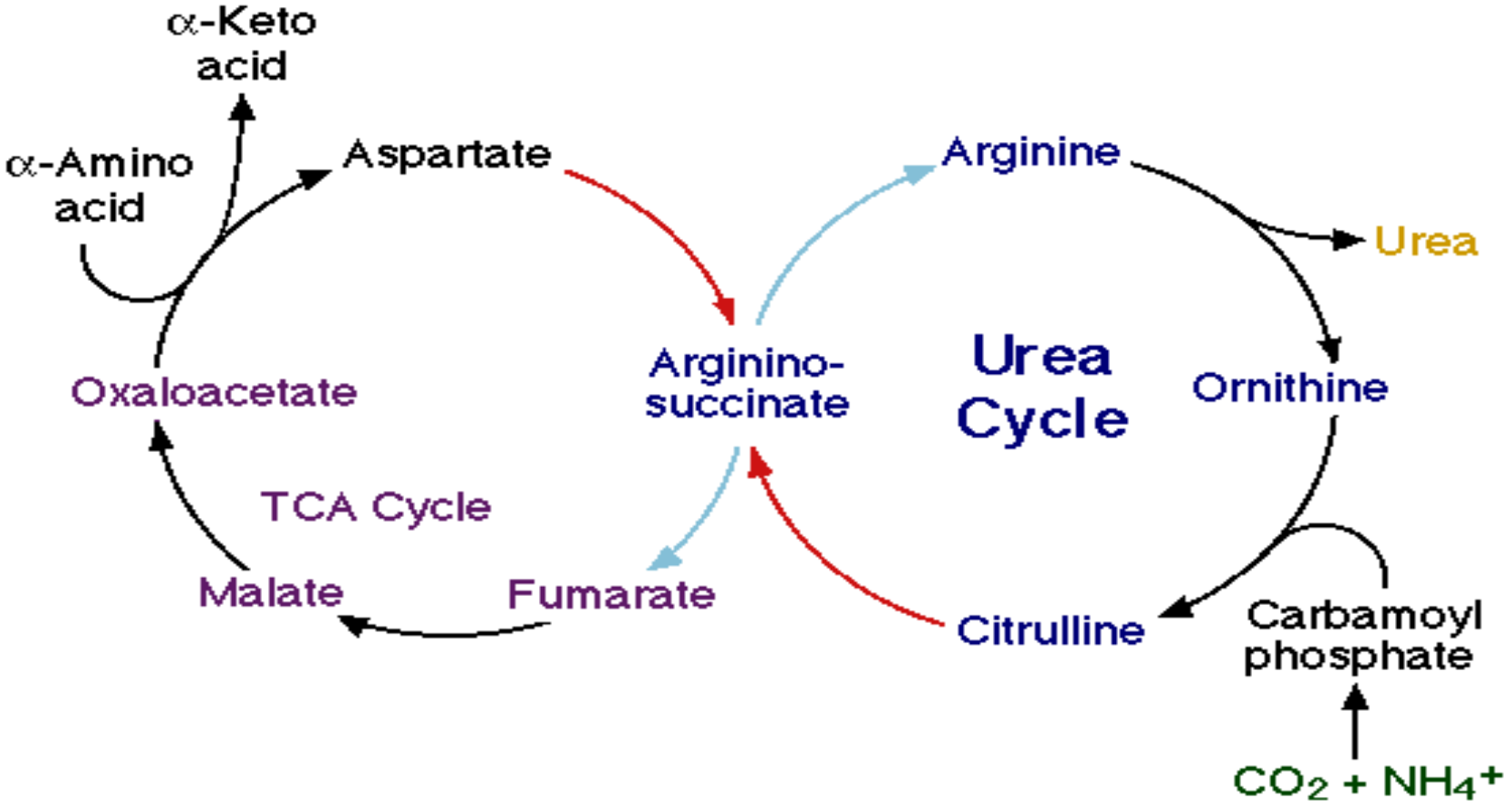
Overall Reaction of Urea Formation

$NH_4+ + HCO_3^- + H_2O + 3\ ATP + Aspartate$ 

$Urea + 2\ ADP + AMP + 2\ Pi + PPi + Fumarate$


Cytosol
$NH_4^+ + CO_2$
2 ATP
2 ADP + P_i
carbamoyl-phosphate synthase I
carbamoyl phosphate
ornithine transcarbamoylase
P_i
L-ornithine
urea
arginase
H_2O
L-arginine
L-citrulline
mitochondrial matrix
argininosuccinate synthase
ATP
AMP + PP_i
L- aspartate
L-arginino-succinate
argininosuccinate lyase
fumarate

Fate of formate produced by urea cycle



- Fumarate is converted to oxaloacetate via Krebs Cycle enzymes Fumarase & Malate Dehydrogenase.
- Aspartate then reenters Urea Cycle, carrying an amino group derived from another amino acid.

Types of Hyperammonemia

- ***Acquired hyperammonemia:***
  - High plasma urea (or BUN) values "azotemia" occurs due to:
  - 1. Glomerulonephritis, Diabetes & high blood pressure.
  - 2. Dehydration, shock or heart failure (Decreased blood flow to kidneys).
  - 3. Obstruction of urinary tract by kidney stone or tumor.
  - 4. Eating unusually-high protein foods

Inherited hyperammonemia (Urea Cycle Defects)

- A complete lack of any one of the enzymes of urea cycle
- All inherited deficiencies of the urea cycle enzymes result in mental retardation.

Inherited hyperammonemia (Urea Cycle Defects)

- Symptoms of UCDs usually arise at birth
- Characterized by:
    1. Aataxia.
    2. Convulsions.
    3. Lethargy.
    4. Coma.
    5. Death.

TREATMENT OF UCDs

In general, the treatment has as common elements:

a) The reduction of protein in the diet.

b) Removal of excess ammonia.

c) Replacement of intermediates missing from the urea cycle.

TREATMENT OF UCDs

1. Administration of levulose:

- Levulose reduces ammonia absorption through its action of acidifying the colon. Bacteria metabolize levulose to acidic byproducts which promotes excretion of ammonia in the feces as ammonium ions, NH_4^+.

2. Oral Antibiotics can be administered to kill intestinal ammonia-producing-bacteria.
3. Dietary supplementation with arginine or citrulline can increase the rate of urea production in certain UCDs.

Clinical significance

High plasma urea (or BUN) values "azotemia" occurs due to:

1. Glomerulonephritis, Diabetes & high blood pressure.

2. Dehydration, shock or heart failure (Decreased blood flow to kidneys).

3. Obstruction of urinary tract by kidney stone or tumor.

4. Eating unusually-high protein foods

Clinical significance

Low plasma urea (or BUN) values occurs due to:

1. A very low-protein diet & malnutrition.

2. Severe liver damage.

3. Overhydration due to drinking excessive amounts of liquid.

4. Third trimester of pregnancy

The carbon skeleton of Amino acids