# Biochemistry (Renal module)

- ❑ Urea cycle
- ❑ Creatine & Creatinine metabolism

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# Urea cycle

- **Ammonia is highly toxic** to the CNS; it is converted to non toxic urea in the liver only.
- **Urea is water soluble easily excreted by the kidneys in urine**.
- Urea is the main end product of protein (amino acids) metabolism.
- Plasma urea is 15-45 mg/dl, it is formed in the liver and transported in blood to the kidney to be excreted in urine (urinary urea is 25-30 g/day).
- Urea cycle occurs in **five steps**, the first 2 steps in mitochondria and the last 3 steps in cytoplasm. It utilizes 3 ATP and 4 high energy phosphate bonds.
- The five steps catalyzed by 5 enzymes, any defect in these enzymes leads to **ammonia intoxication**.

# Urea cycle

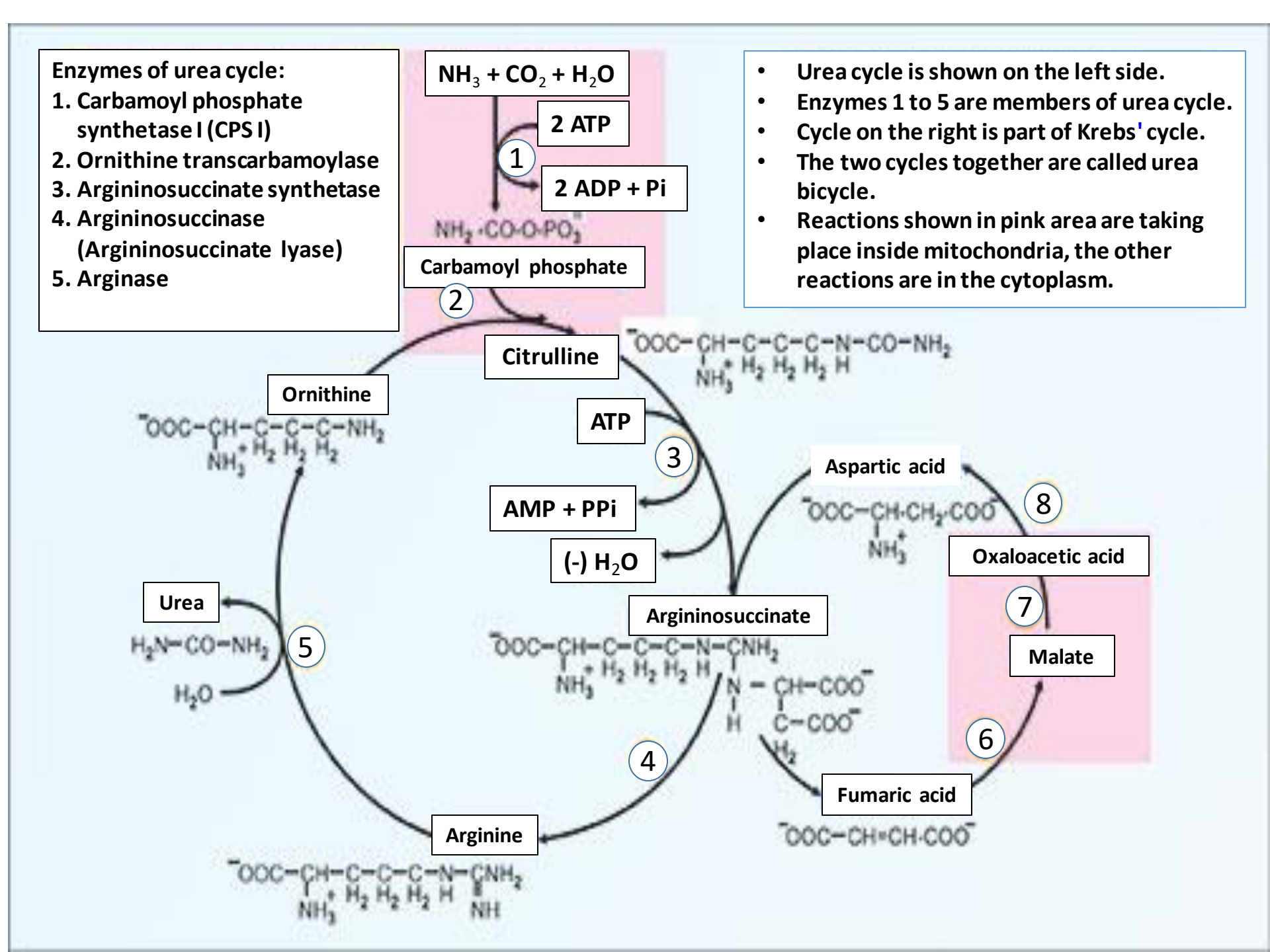
## Steps of Urea cycle:

### I. Mitochondrial reactions:

a. Carbamoyl phosphate synthetase I (CPS I)
b. Ornithine transcarbamoylase

### II. Cytosolic reactions:

a. Argininosuccinate synthetase
b. Argininosuccinase (Argininosuccinate lyase)
c. Arginase


Enzymes of urea cycle:
1. Carbamoyl phosphate synthetase I (CPS I)
2. Ornithine transcarbamoylase
3. Argininosuccinate synthetase
4. Argininosuccinase (Argininosuccinate lyase)
5. Arginase
NH3 + CO2 + H2O
2 ATP
1
2 ADP + Pi
NH2·CO·O·PO3
Carbamoyl phosphate
2
Citrulline
Ornithine
ATP
3
AMP + PPi
(-) H2O
Aspartic acid
8
Oxaloacetic acid
7
Malate
6
Fumaric acid
Urea
5
Argininosuccinate
4
Arginine
Urea cycle is shown on the left side.
Enzymes 1 to 5 are members of urea cycle.
Cycle on the right is part of Krebs' cycle.
The two cycles together are called urea bicycle.
Reactions shown in pink area are taking place inside mitochondria, the other reactions are in the cytoplasm.

# Urea cycle

## Steps of Urea cycle:

### I. Mitochondrial reactions:

### a. Carbamoyl phosphate synthetase I:

- The key enzyme of urea cycle.
- Synthesizes carbamoyl phosphate from ammonia, $CO_2$ and ATP (to provide the phosphate group).
- The second ATP molecule is required to supply energy for the reaction; N-acetylglutamate is an activator for the enzyme.

# Urea cycle

## Steps:

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#### b. Ornithine Transcarbamoylase:

- It condenses carbamoyl phosphate group with ornithine to form citrulline, which is transferred to cytosol.

# Urea cycle

## Steps:

### I. Cytoplasmic reactions:

a) First, citrulline unites with aspartate in presence of **argininosuccinate synthetase** enzyme to form argininosuccinate. Two high energy phosphate bonds are hydrolyzed to provide energy for the reaction.

b) Arginiosuccinate is converted to arginine and fumarate by **argininosuccinase** enzyme.

c) Arginine by **arginase** enzyme is hydrolyzed to urea and ornithine that repeat the cycle.

**N.B.** The two molecules of ammonia present in urea, one is derived from carbamoyl phosphate and the other from aspartate.

# Urea cycle

## Regulation:

1. Effect of feeding and fasting: the enzymes of urea cycle are increased by high protein diet and decreased by low protein diet.
2. N-acetylglutamate acts as activator for carbamoyl phosphate synthetase I (CPSI).

# Urea cycle

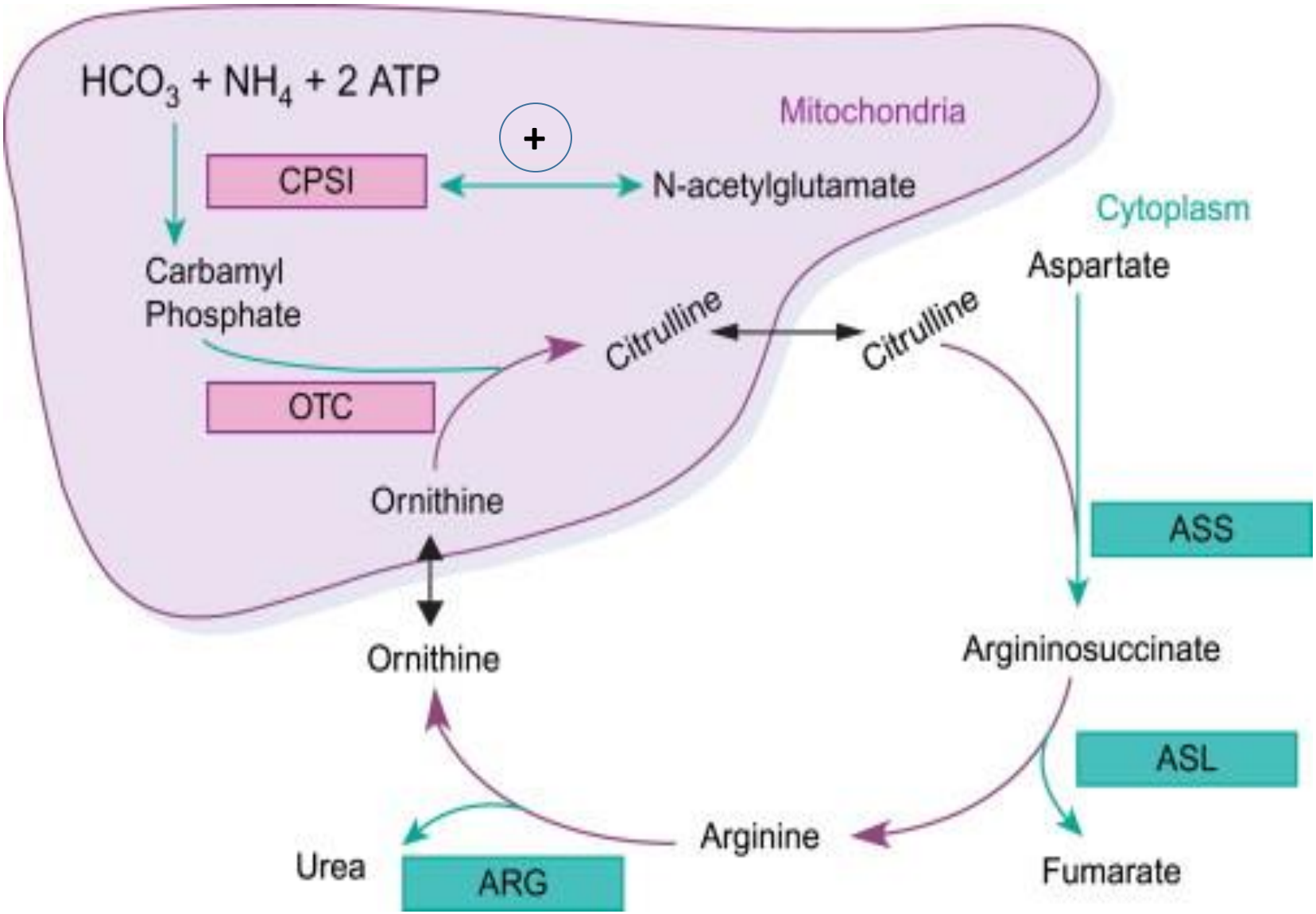
## Diagnostic importance of plasma urea determination:

1. Plasma urea is one of the kidney function tests.
2. Plasma urea is increased in kidney diseases like renal failure (**uremia**).
3. In liver failure: liver cells cannot convert ammonia to urea so there will be **hyperammonemia** (ammonia intoxication) and urea is decreased.

## Relationship between urea cycle and tricarboxylic acid cycle (Krebs' cycle):

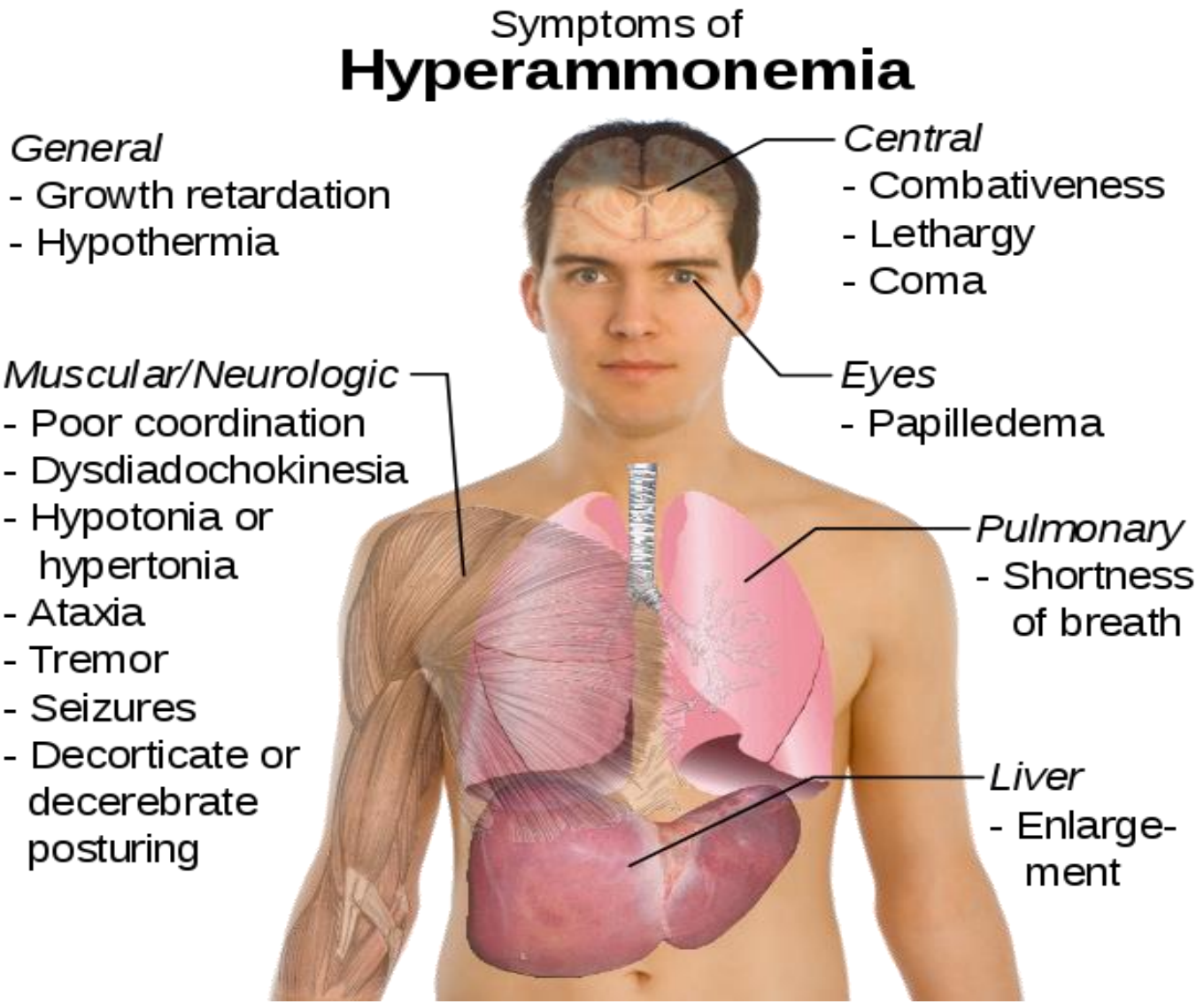
- Fumarate produced in urea cycle can be oxidized in Krebs' cycle to oxaloacetate which by transamination give aspartate needed for urea synthesis

# Urea cycle


$HCO_3$ + $NH_4$ + 2 ATP
Mitochondria
+
CPSI
N-acetylglutamate
Cytoplasm
Carbamyl Phosphate
Aspartate
Citrulline
Citrulline
OTC
Ornithine
ASS
Ornithine
Argininosuccinate
ASL
Arginine
Urea
ARG
Fumarate

# Hyperammonemia

**Normal ammonia level in blood is 0.05-0.1 mg/dl.**



# Hyperammonemia

## Types and causes of hyperammonemia:

### A. Acquired hyperammonemia :

1. **Liver failure** due to impaired urea synthesis.
2. **Renal failure** due to impaired excretion of urea & ammonia
3. **Shunt operation** between portal and systemic circulation
4. **Collaterals** between portal and systemic circulation due to liver cirrhosis by bilhariazsis and hepatitis

# Hyperammonemia

## Types and causes of hyperammonemia:

### B. Genetic defect in urea cycle enzymes:

1. Carbamoyl phosphate synthetase I: leads to Type I Hyperammonemia.
2. Ornithine transcarbamoylase: leads to Type II Hyperammonemia.
3. Argininosuccinate synthetase: leads to Citrullinemia.
4. Argininosuccinase (argininosuccinate lyase): leads to argininosuccinic aciduria.
5. Arginase: leads to Hyperargininemia

# Hyperammonemia

- **Type I and II** hyperammonemia are more severe than the other types.
- The **high serum ammonia produces brain damage** as ammonia will combine with α-ketoglutaric acid forming glutamate and glutamine, and this will decrease the energy production by Krebs' cycle in brain leading to brain damage. It is manifested by irritability, tremors, vomiting, blurring of vision, inverted sleep rhythm, coma and if not treated early in life it will leads to mental retardation. Also ammonia causes alkalosis.

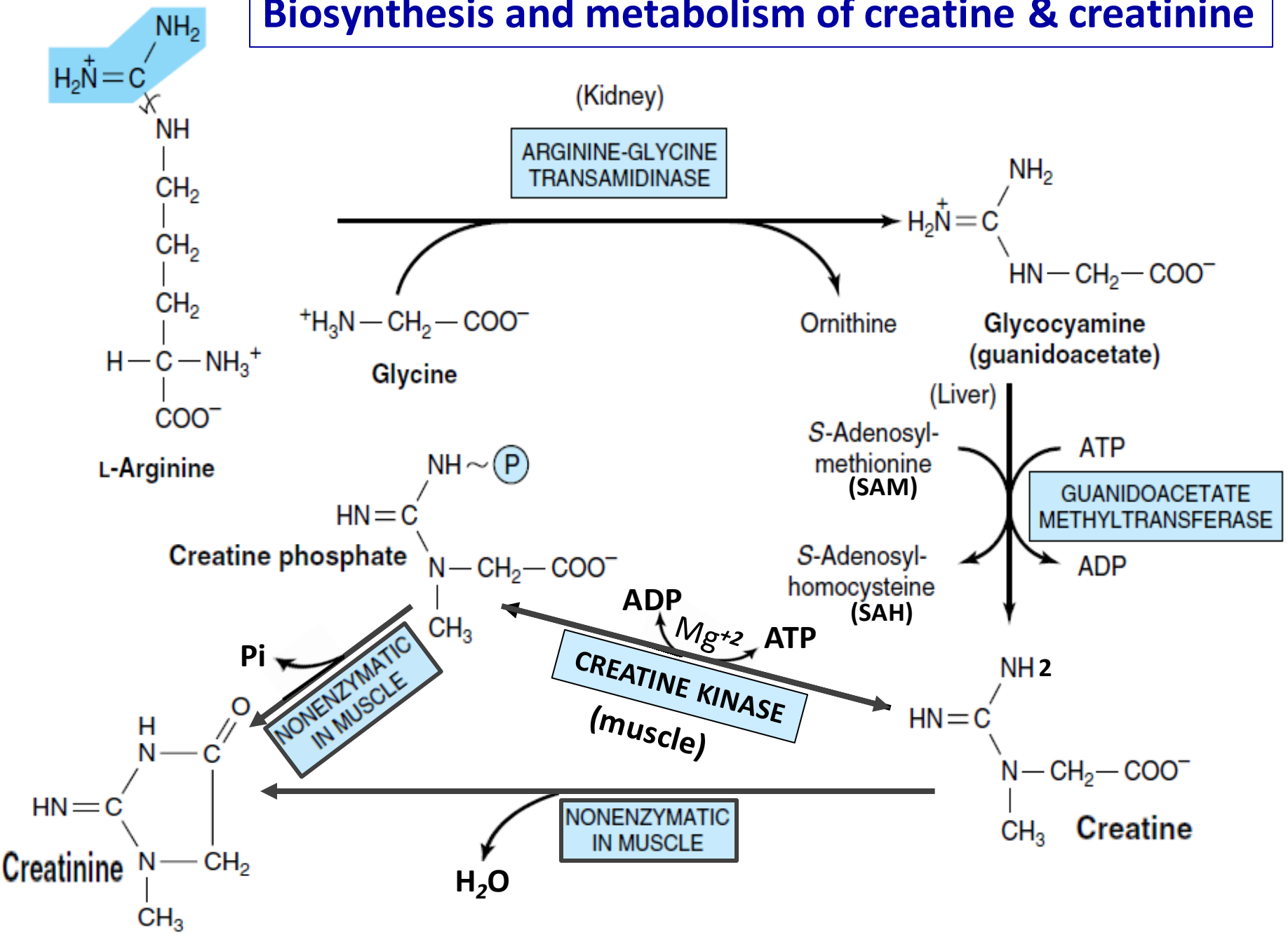
**Treatment:** by diet low in protein.

# Creatine and Creatinine Metabolism

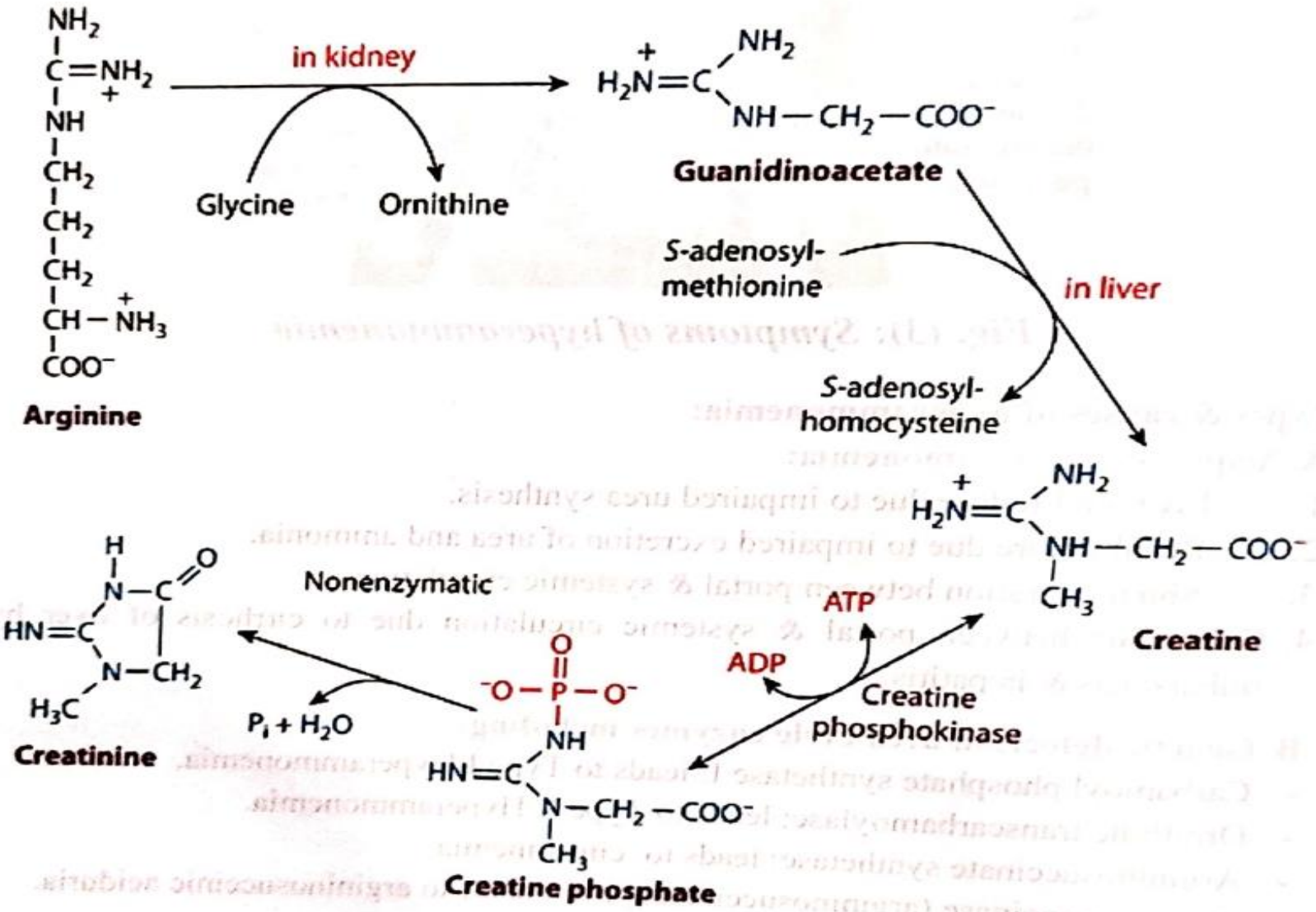
**Biosynthesis:**

- **1st step** is synthesis of **guanidoacetic acid** in kidneys from arginine and glycine by arginine glycine trans**amidin**ase (arginine glycine **amidin**otransferase).
- **2nd step** is methylation of guanidoacteic acid to form **creatine** in the liver by methyl transferase (guanidoacetate methyl transferase).
- **3rd step** is phosphorylation of creatine in the muscle to **creatine phosphate** (CP) by creatine kinase (CK) or creatine phosphokinase (CPK) which is used as storage of energy in muscle to be used during contraction.
- Creatinine is formed by **dephosphorylation** of creatine phosphate or by non enzymatic reaction from creatine in muscle.

# Biosynthesis and metabolism of creatine & creatinine



# Biosynthesis and metabolism of creatine & creatinine



# Creatine and Creatinine Metabolism

## Blood creatine and creatinine:

The normal plasma or serum levels are as follows:

**Creatine:** 0.2-0.9 mg/dl.

**Creatinine:** 0.5- 1.2 mg/dl.

- Plasma creatinine level increases in cases of kidney diseases and it is good index for renal functions as its level is not affected by diet.

## Excretion of creatine and creatinine:

- About 2% of body creatine is converted to creatinine
- About 1-2 g/day creatinine is excreted in urine daily and it is related to the muscle mass.
- Creatine is not excreted in significant amount in urine of normal adults, it is almost completely reabsorbed by renal tubules at normal plasma levels.

# Creatine and Creatinine Metabolism

**Creatinuria:** It is increase excretion of creatine in urine under normal physiological or pathological states.

**Causes of physiological creatinuria:**

1. In young children (decreased muscle mass).
2. In females during pregnancy & early postpartum period.

**Causes of pathological creatinuria:** **muscle wasting** condition

1. **Starvation.**
2. **Diabetes mellitus.**
3. **Fevers.**
4. **Hyperthyroidism.**
5. **Hypogonadism.**
6. **Vit E deficiency.**
7. **Degenerative muscle diseases (myopathies).**