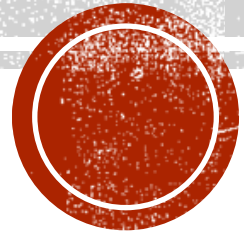
Ammonia & Urea cycle



Students Learning Outcomes

At the end of this lecture students should be able to:

1. Explain the production, sources and transport of ammonia
2. Identify the source of the two nitrogen atoms and the steps of the urea cycle and its site in the tissue.
3. Explain the reaction catalyzed by the enzyme carbamoyl phosphate synthetase and its regulation
4. Enumerate different disorders of the urea cycle and their consequences.

Content

I. Ammonia

1. Source
2. Fate
3. Transport

II. Urea cycle

1. Importance
2. Site
3. Steps
4. Link with Krebes cycle
5. Regulation
6. Disorders
7. Blood urea

Ammonia

1. Source
2. Fate
3. Transport

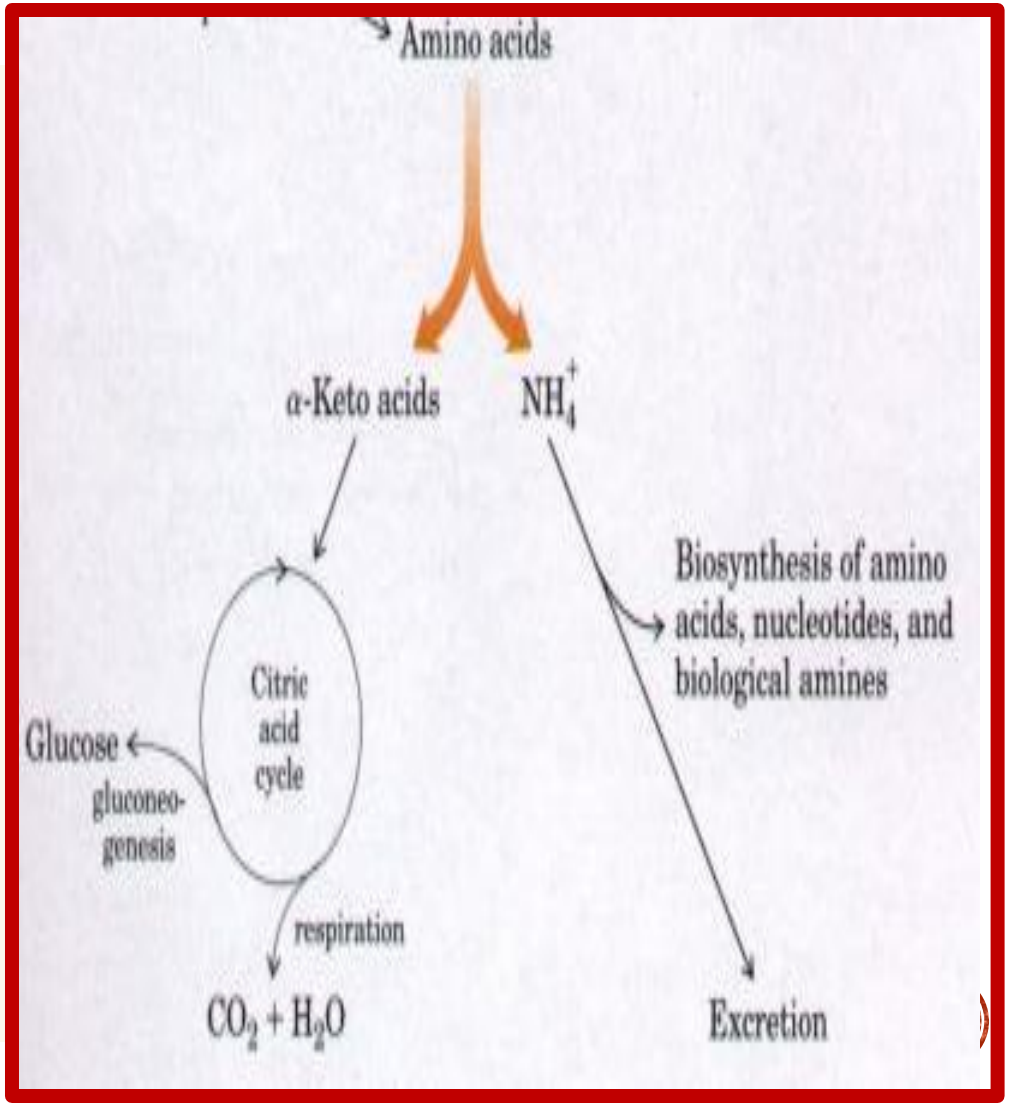
Background

✓ **Catabolism** of amino acids involves:

a) Removal of amino group→ **Ammonia** (NH3)

b) Removal of carbon skeleton→ Fate of **C skeleton**

1. Resynthesis of Amino Acids (Glucogenic & Ketogenic Pathway)
2. Krebs cycle → Energy production.



Ammonia

- Ammonia is **toxic** to the central nervous system and its accumulation in the body is fatal.
- Once formed in the body, ammonia must be removed from blood.
- The **liver** is the organ that **converts it to urea**, which is: Less toxic, Water soluble, Easily excreted in urine.

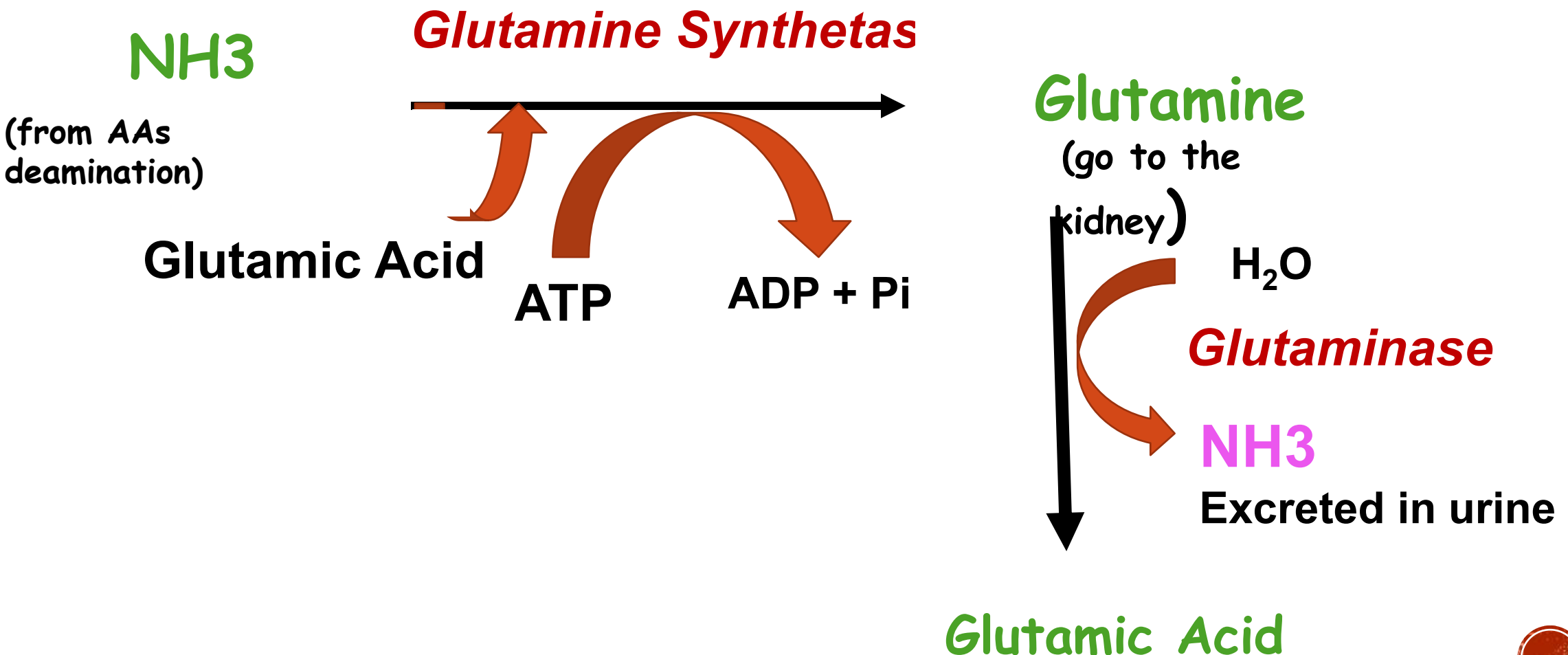
Sources of Ammonia

- **Major source: Deamination** (Transdeamination) of Amino Acids
- **Minor sources: 1. Bacterial action** on dietary proteins in GIT.
  2. Catabolism of purine and pyrimidine bases.
  3. Glutamine in the kidney by glutaminase enzyme

Fate of ammonia:

1. **Purine and pyrimidine bases:** used for biosynthesis of:
   - Nucleic acids: RNA, DNA.
   - Coenzymes (NAD, FAD).
   - Biologically active nucleotides (ATP, GTP)
2. **Amino sugars** e.g. glucosamine which are important for mucopolysaccharides formation.
3. **Biosynthesis of Non-essential amino acids.**
4. Biosynthesis of glutamine by glutamine synthetase enzyme.
5- Small amounts of ammonia are excreted in urine in the form of **amonim ions .**
6- **Urea biosynthesis.**

NH3 In Extra-renal Tissues



Urea Cycle

1. Importance
2. Site
3. Steps
4. Link with Krebes cycle
5. Regulation
6. Disorders
7. Blood urea

Urea cycle

Importance of urea cycle

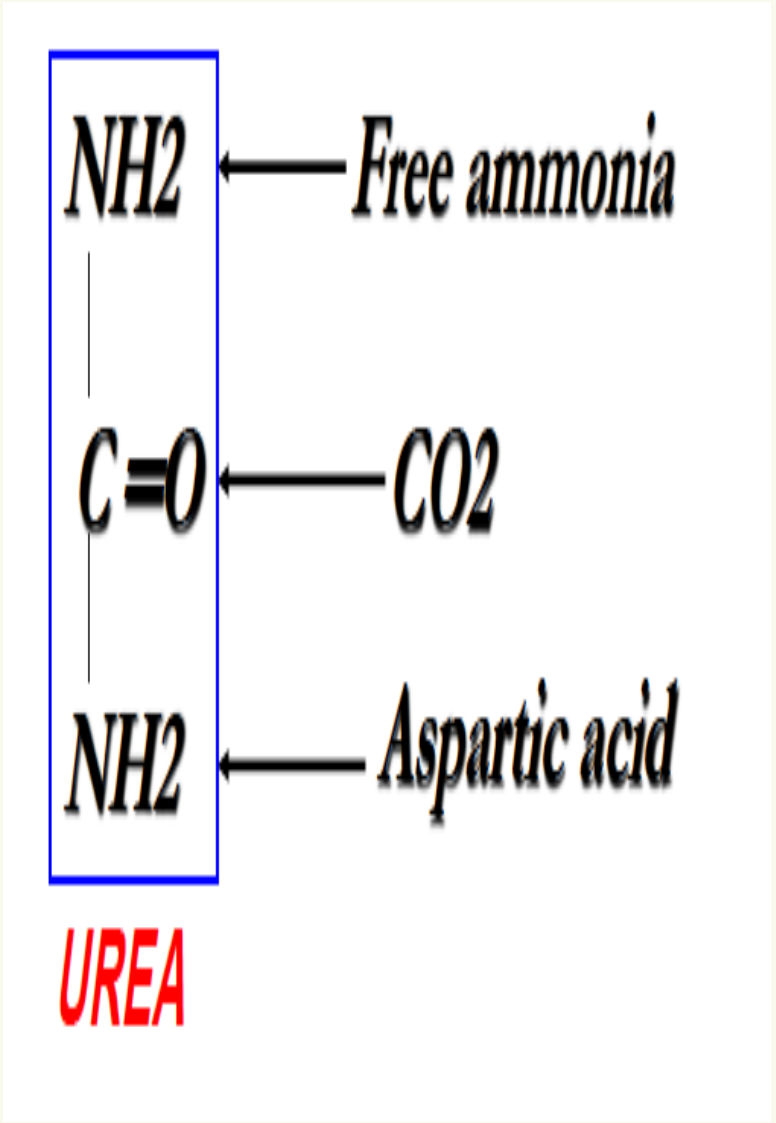
- ✓ The **principal pathway** of disposal of NH3 resulting from the deamination of AAs.
- ✓ It allows the body to get rid of about **80—90% of the amino groups** of AAs in a neutral non-toxic form (urea).
- ✓ Urea is the **main end product** of protein catabolism in human.

Site of urea synthesis

- ✓ **Tissue location:** only in the liver.
- ✓ **Subcellular location:**
  - **first 2 reactions** : Mitochondria
  - **subsequent 3 reactions:** Cytosol

Urea is synthesized from

1. **Ammonia** (from catabolism of AA)
2. **Carbon dioxide** (from Krebs)
3. **Amino group of aspartic acid.**



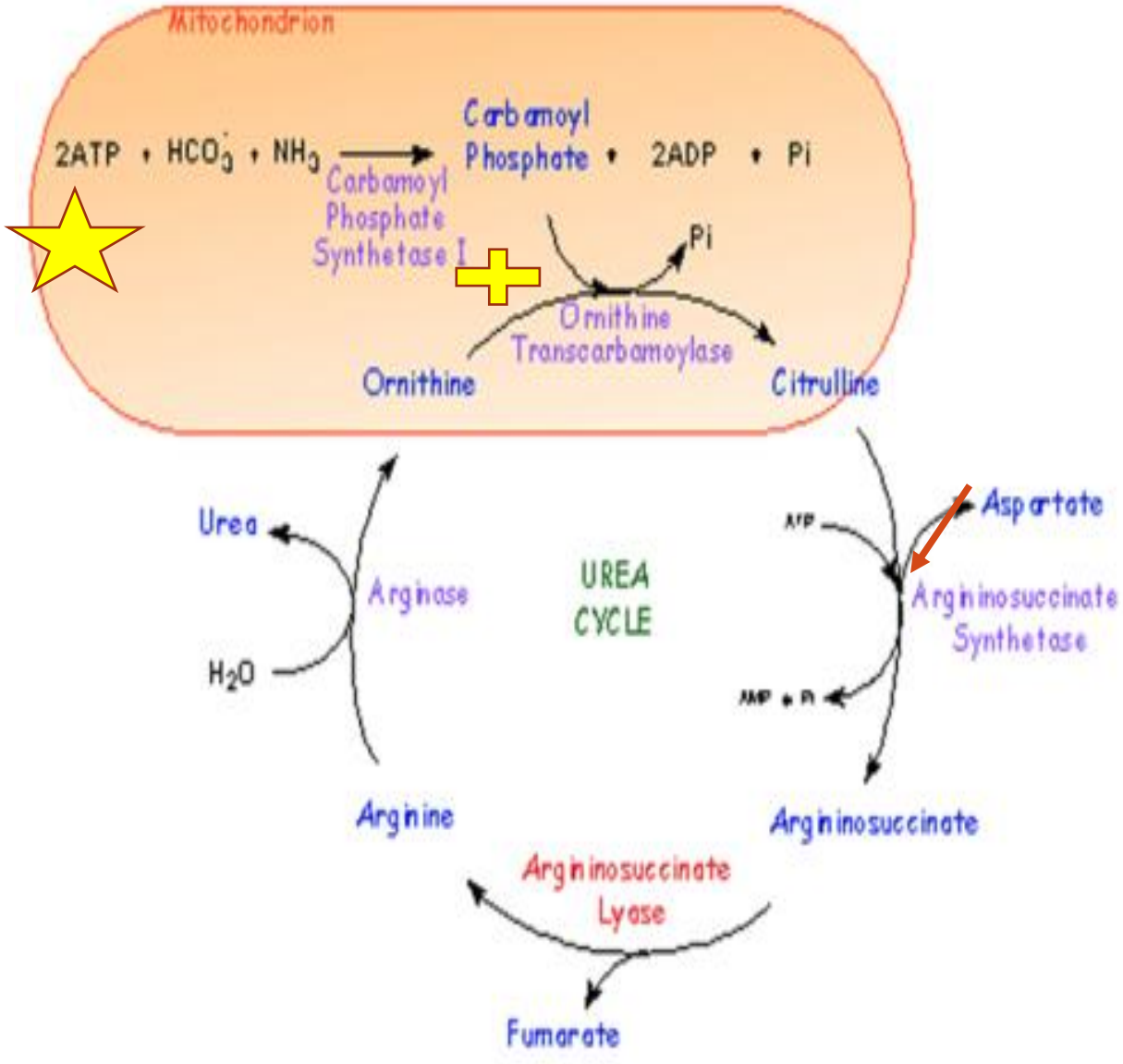
Steps of urea cycle

✓ **5 enzymes in urea cycle**

1. **Carbamoyl phosphate synthetase I**
2. Ornithine transcarbamylase
3. Arginosuccinate synthetase
4. Arginosuccinate lyase
5. Arginase

✓ **The rate limiting enzyme of urea formation**

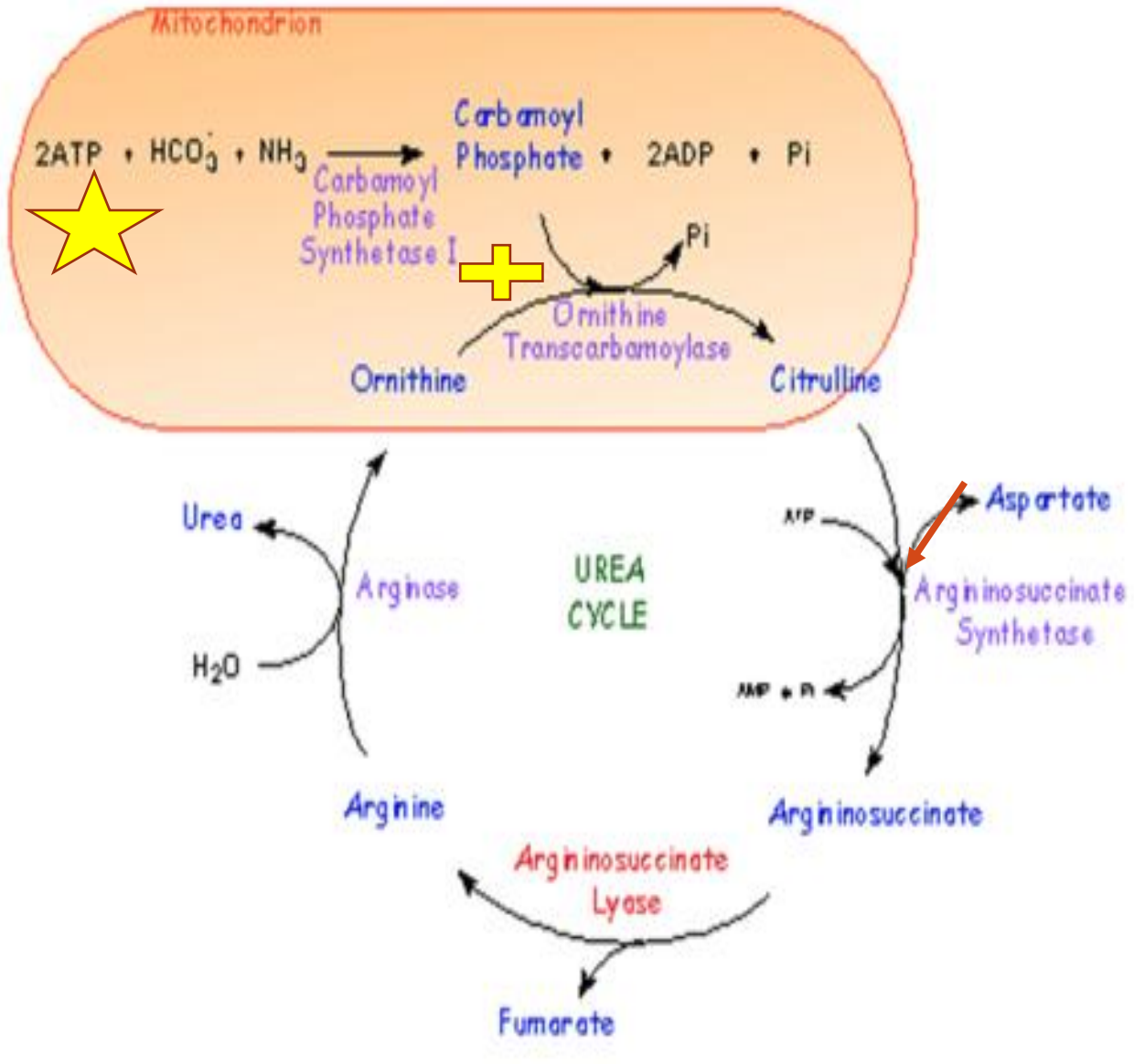
Carbamoyl phosphate synthetase I ***(CPS I)***



The 1st reaction of urea cycle

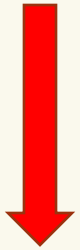
Characters of carbamoyl phosphate synthetase I:

- ✓ Present in **mitochondria of the liver**.
- ✓ Needs presence of **2 ATP**.
- ✓ Needs **N-acetyl glutamate** as activator.
- ✓ **Irreversible** reaction.
- ✓ Takes NH_3 from **deamination of AAs**



Overall reaction of urea cycle

$NH_3 + CO_2 +$ 1 Aspartate + 3 ATP + $1\ H_2O$



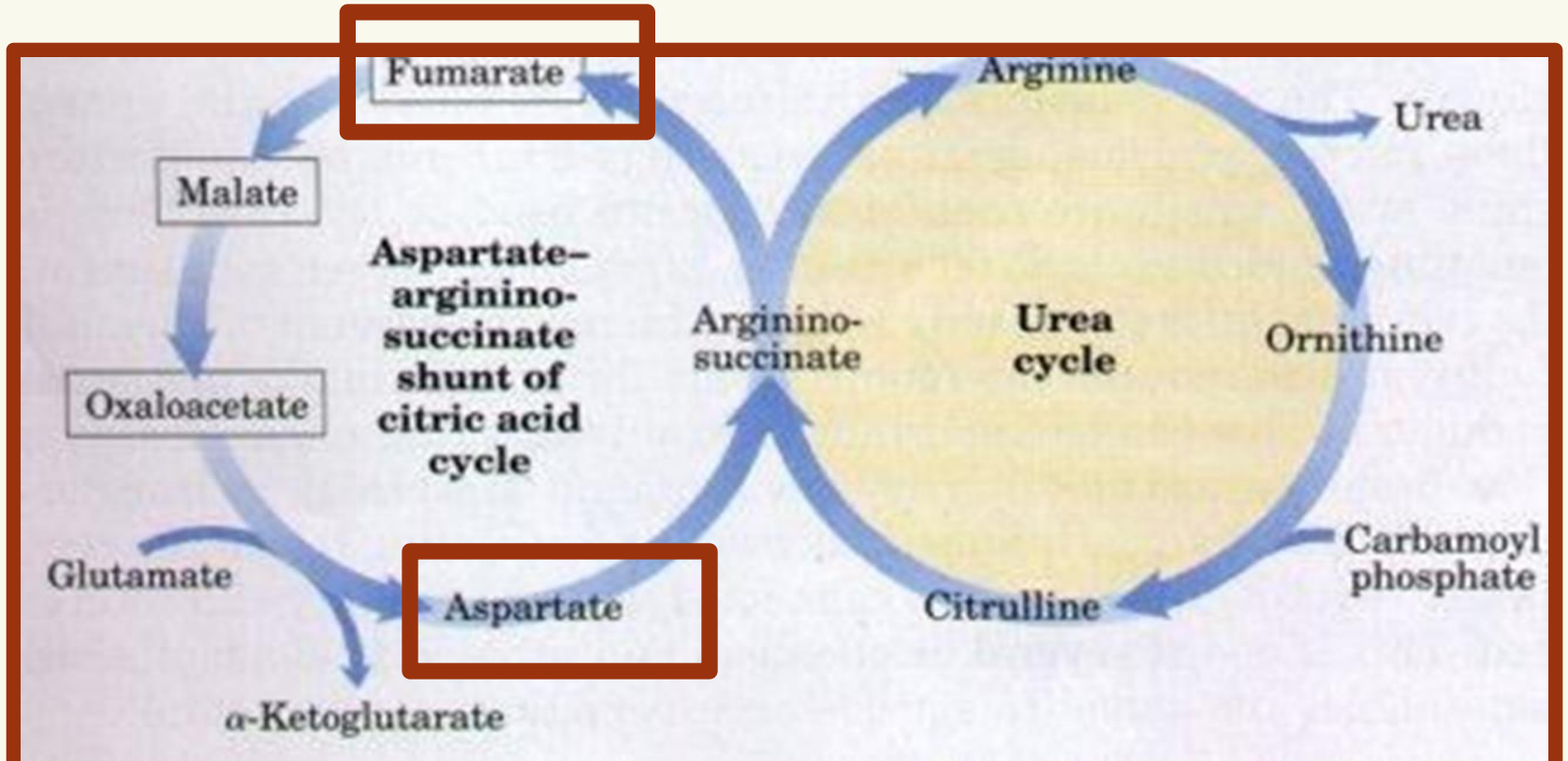
1 Urea+ 1 Fumarate +2 ADP + 2 Pi + 1AMP+1PPi

❖**Urea synthesis is an energy demanding process:**

A net of 3 ATP = (4 high energy phosphate bond) is used to synthesis 1 Urea

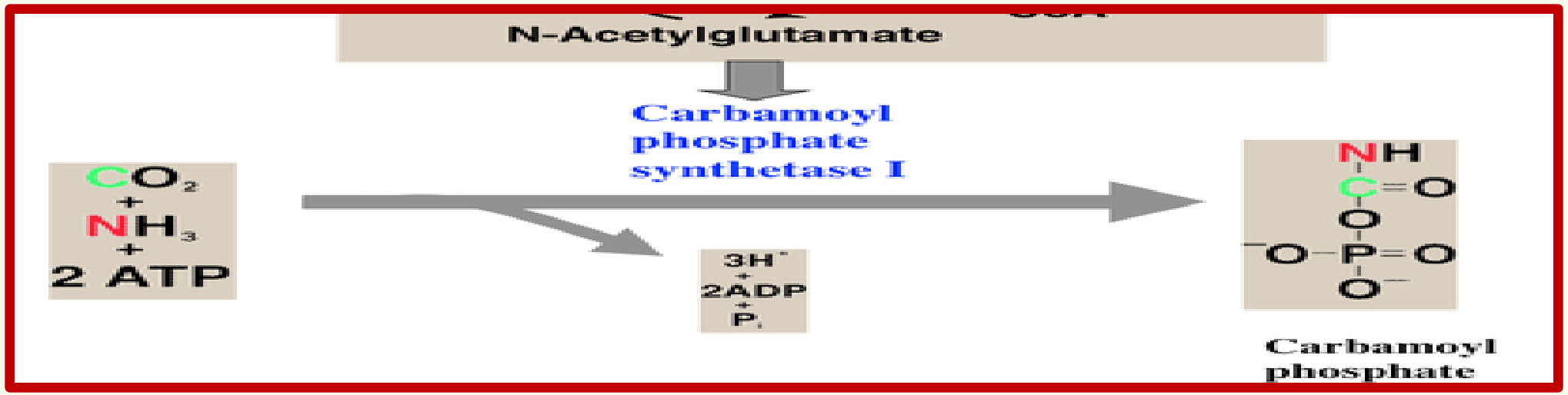
Link of Urea cycle to Krebs cycle

1. CO_2 used in urea cycle is produced by Krebs's cycle.
2. **ATP** needed by urea cycle is produced by Krebs's cycle.
3. **Aspartate** needed by urea cycle produced by Krebs cycle
4. **Fumaric acid** produced by urea cycle is oxidized via Krebs's cycle.



Regulation of Urea Synthesis

1. **Carbamoyl phosphate synthetase I** is activated by **N-acetylglutamate**



2. **Other urea cycle enzymes: activity** is based on the **concentrations of their substrates**: So, the levels of the enzymes of urea cycle **fluctuate** with changes in the feeding state of the individual.

Disorders of urea cycle

- ✓ It causes **hyperammonemia**→ may causes **ammonia intoxication**: Tremors, slurring of speech, loss of concentration and blurring of vision.
- ✓ At high concentrations ammonia can cause **coma and death.**
- ✓ **Classification of Hyperammonemia may be** :

A) inherited

- Due to deficiencies of any enzyme of the 5 enzymes of urea cycle.
- Overall incidence of 1 in 30,000 live births.
- NH_3 is not converted to urea → NH_3 intoxication
- Deficiency of the 1st 2 enzymes of urea cycle. → more severe disease.
  a. deficiency of carbamoyl phosphate synthetase-I→ hyperammonemia type I
  b. deficiency of ornithine transcarbamoylase→ hyperammonemia type II

B) Acquired

- **Liver disease : eg: Liver cirrhosis, Liver cell failiure**
- No ammonia detoxification→ hyperammonemia

Blood urea level

- ✓ **The main Non protein nitrogenous** compound (NPN).
- ✓ **Synthesized** by the liver and **excreted** by the kidney.
- ✓ **Blood urea level**: 20-40 mg/dL.
- ✓ **Urinary urea level**: 20-40 gm/day.
- ✓ **Factors affecting the level of blood urea**

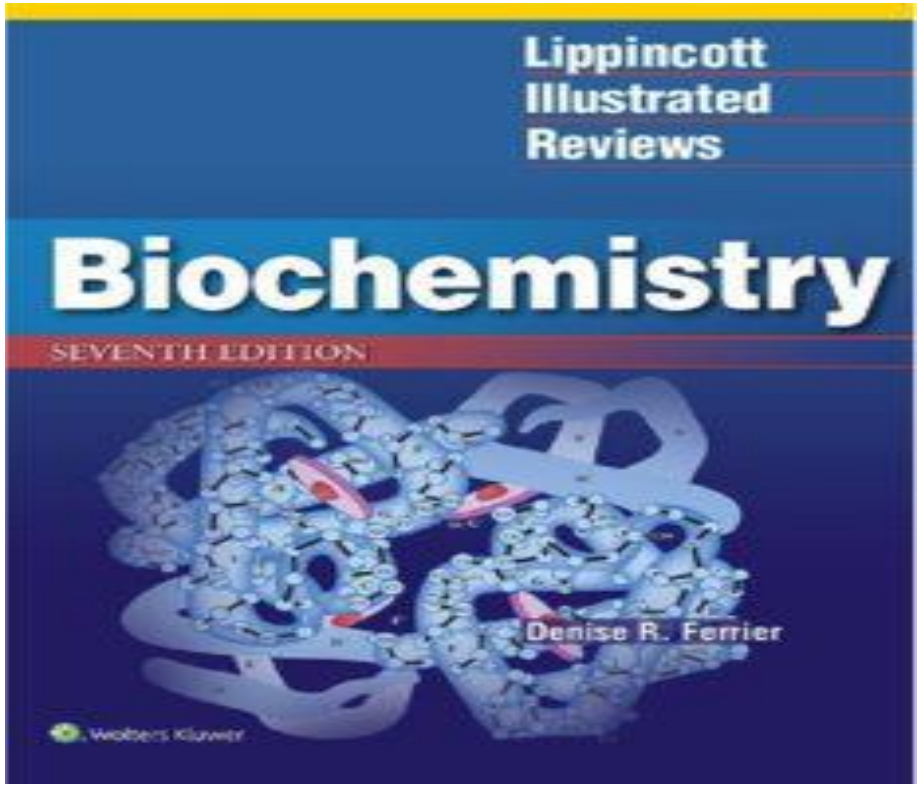
1. Protein diet:↑Protein diet→ digestion of protein→ AAs→ its catabolism → NH3→ converted by liver to Urea→ ↑urea formation.

2. Liver: diseased liver →↓urea formation→ ↓Blood urea →↑ Blood NH_3.

3. Kidney: It is the organ which excrete urea. So, in renal failure→↑ Blood urea due to ↓ excretion.


Life
isn't about
finding yourself.
...
Life
is about
creating yourself.

References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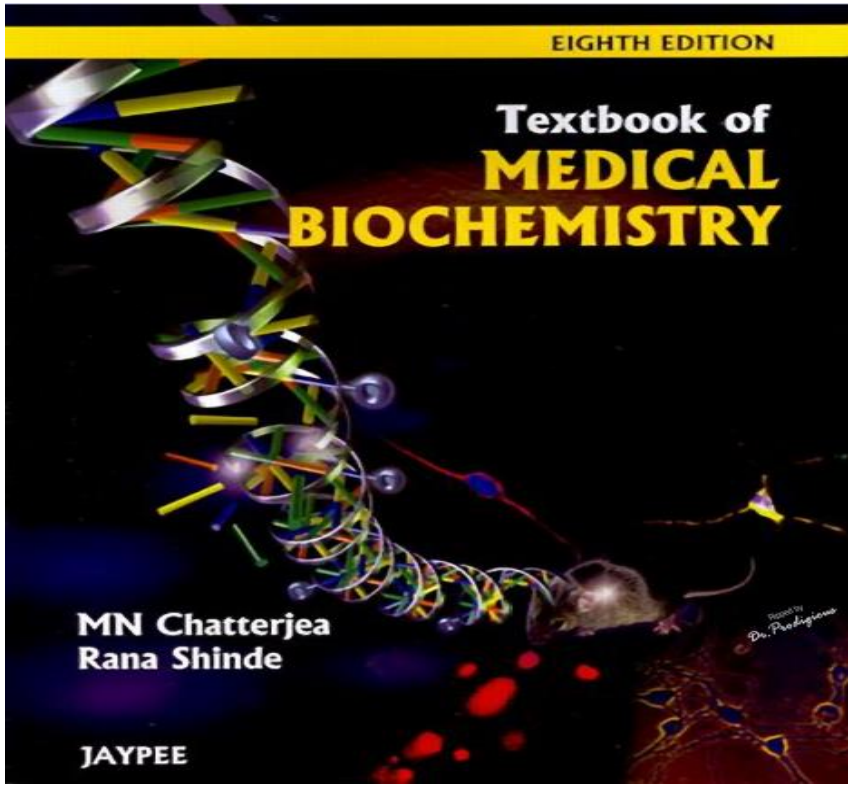
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