[lecture 7]

Urea Cycle

Biochemistry Team

Teams

The Objectives

- Identify the major form for the disposal of amino groups derived from amino acids.
- Understand the importance of conversion of ammonia into urea by the liver.
- Understand the reactions of urea cycle.
- Identify the causes and manifestations of hyperammonemia, both hereditary and acquired.

Red = Import-ant

Blue = explain

Green = addition notes

Done By : Haifa Aldabjan

Reviewed By: Abdulaziz Alanazi

Biochemistry Team

Mind Map

- Background
  - Transamination
  - Oxidative Deamination
- Transport of NH_3 into the liver
- Fate of glutamine and alanine in the liver
- Urea Cycle
- Fate of Urea

Background

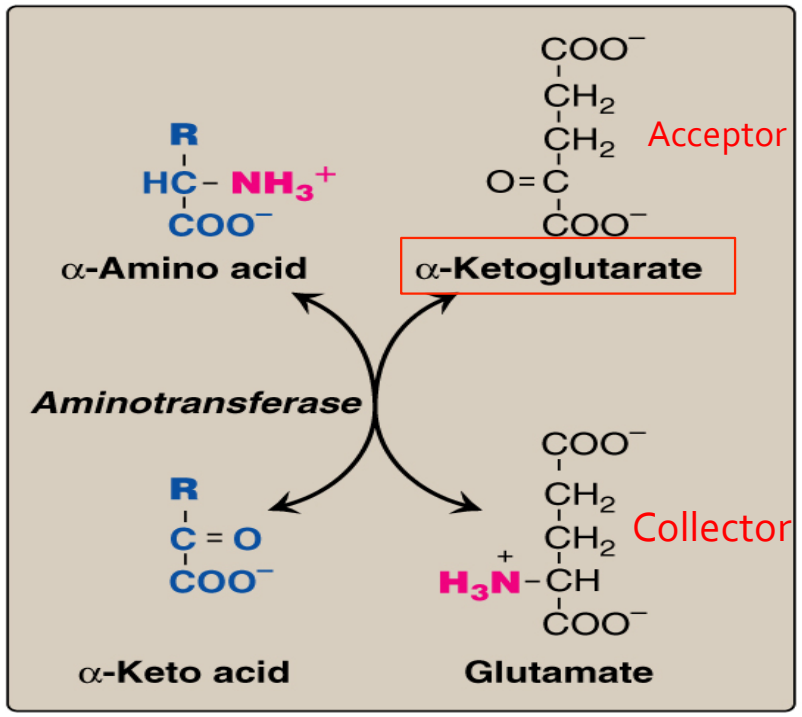
- Unlike glucose and fatty acids, amino acids are not stored by the body.
- Amino acids in excess of biosynthetic needs are degraded.
- Degradation of amino acids involves:
  - Removal of α-amino group ⟶ Ammonia (NH_3) which eventually will give urea
  - Remaining carbon skeleton ⟶ Energy metabolism

So, when we eat more protein, more urea will be execrated in urine

Removal of α-amino group

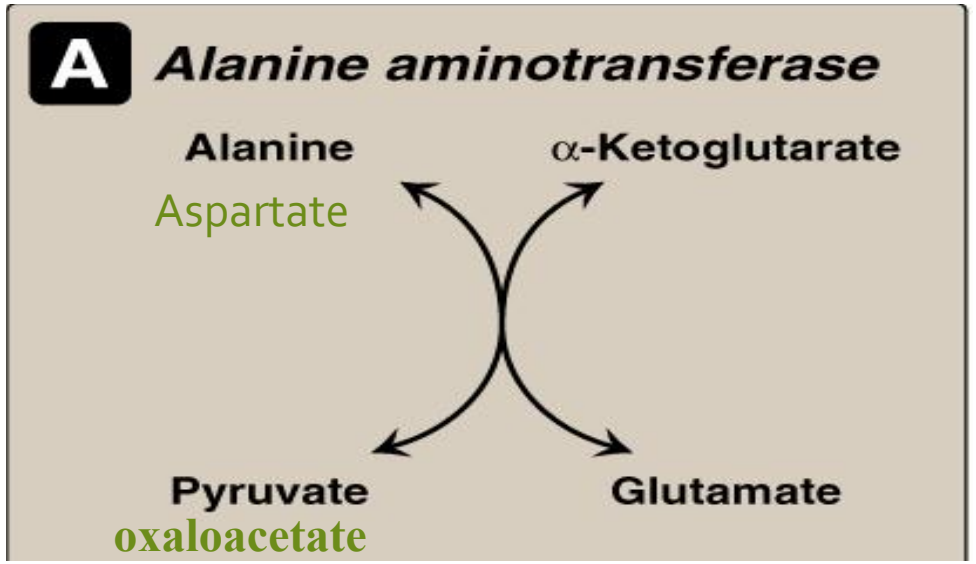
- Amino groups of amino acids are funneled to glutamate by transamination reactions with α-ketoglutarate
- Oxidative deamination of glutamate will release NH_3 and re-generate α-ketoglutarate
- Glutamate is unique. It is the only amino acid that undergoes rapid oxidative deamination

Transamination (funneling of amino acid)



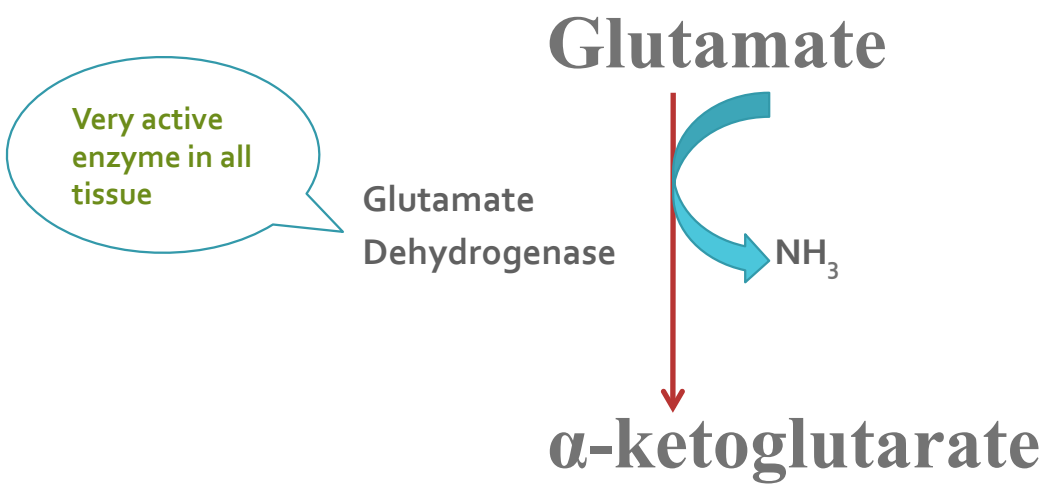
First step of catabolism of amino acid is removing the amino group by aminotransferase from one carbon skeleton to another which is α-ketoglutarate to give Glutamate

This reaction reversible



Alanine will be converted into pyruvate after donating the amino group to α-ketoglutarate to give Glutamate

Oxidative Deamination



Oxidative deamination of glutamate will release NH_3 (Ammonia) and re-generate α-ketoglutarate by glutamate dehydrogenase

Glutamate is unique. the only amino acid under go Oxidative Deamination very rapid.

Transport of NH_3 from peripheral tissues into the liver

- Ammonia is produced by all tissues and the main disposal is via formation of urea in liver
- Blood level of NH_3 must be kept very low, otherwise, hyperammonemia and CNS toxicity will occur (NH_3 is toxic to CNS)

Because NH_3 not charged. So, it diffuse freely and produce toxicity

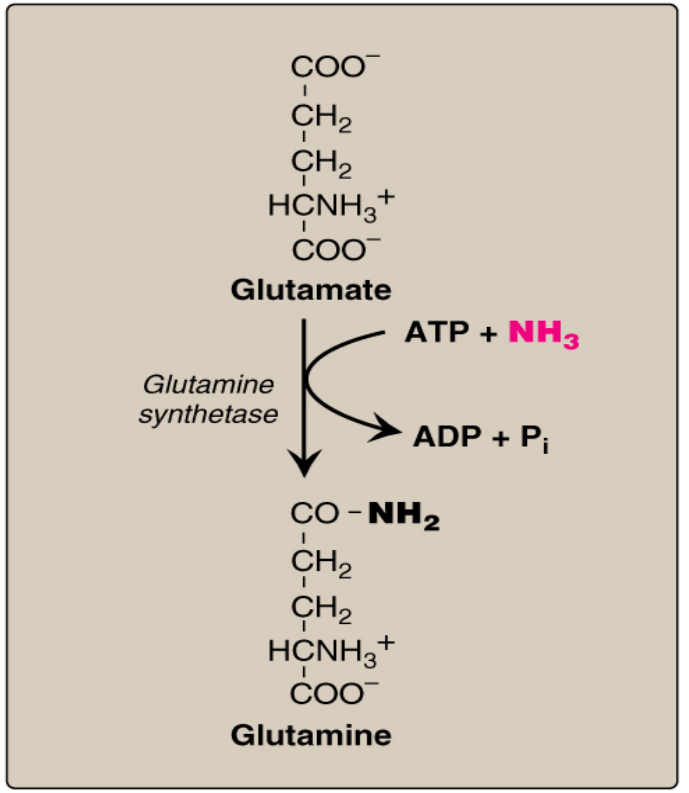
- To solve this problem, NH_3 is transported from peripheral tissues to liver via formation of: **go to liver to form urea which is less toxic and execrated in urine**

Glutamine (most tissues)

Alanine (muscle)

1-From most peripheral tissues:

NH_3 is transported Into the liver through forming glutamine by glutamine synthetase. **(need energy)**



Glutamine like car will transport the NH_3 from peripheral tissues to liver. Drop the ammonia then go back as glutamate

Transport of NH_3 from peripheral tissues into the liver

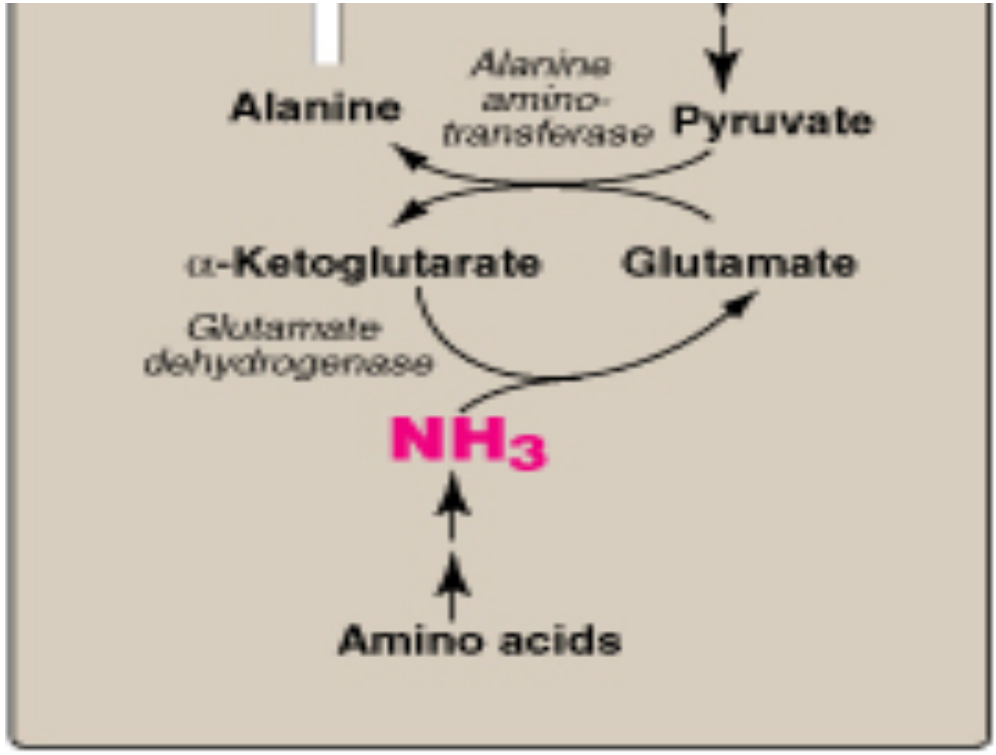
2-From the muscle:

First, NH_3 will be transferred into α-ketoglutarate to form glutamate.

Then, glutamate will give its amino group to pyruvate to form alanine by ALT (alanine aminotransferase)

Glutamate always work as acceptor but here will work as donor. Will donate the amino group to pyruvate.

Therefore, NH_3 is transported from muscle into the liver through forming alanine



Fate of glutamine and alanine in the liver

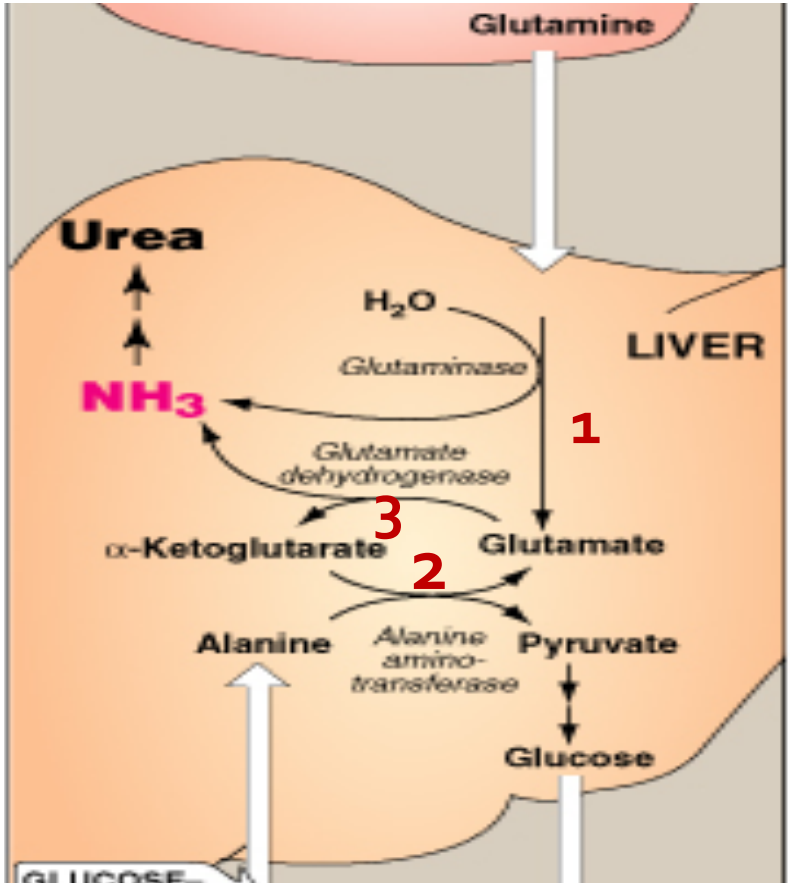
In the Liver:

1. *Glutamine* is converted into glutamate by **glutaminase.**

2. *Alanine* will give its amino group to α-ketoglutarate to form glutamate by **ALT** (alanine aminotransferase)

3. *Glutamate* is converted into α-ketoglutarate and releasing $\underline{NH_3}$ by **glutamate dehydrogenase.**

NH_3 is transported by glutamine and alanine into liver where both will release NH_3 inside the liver to start urea cycle



Urea Cycle

- Urea is the major form for disposal of NH_3
- Urea cycle occurs **in the liver**
- One nitrogen of urea is from NH_3 and the other nitrogen from aspartate
- Urea is transported in the blood to the kidneys for excretion in urine

The five enzymes of urea cycle:

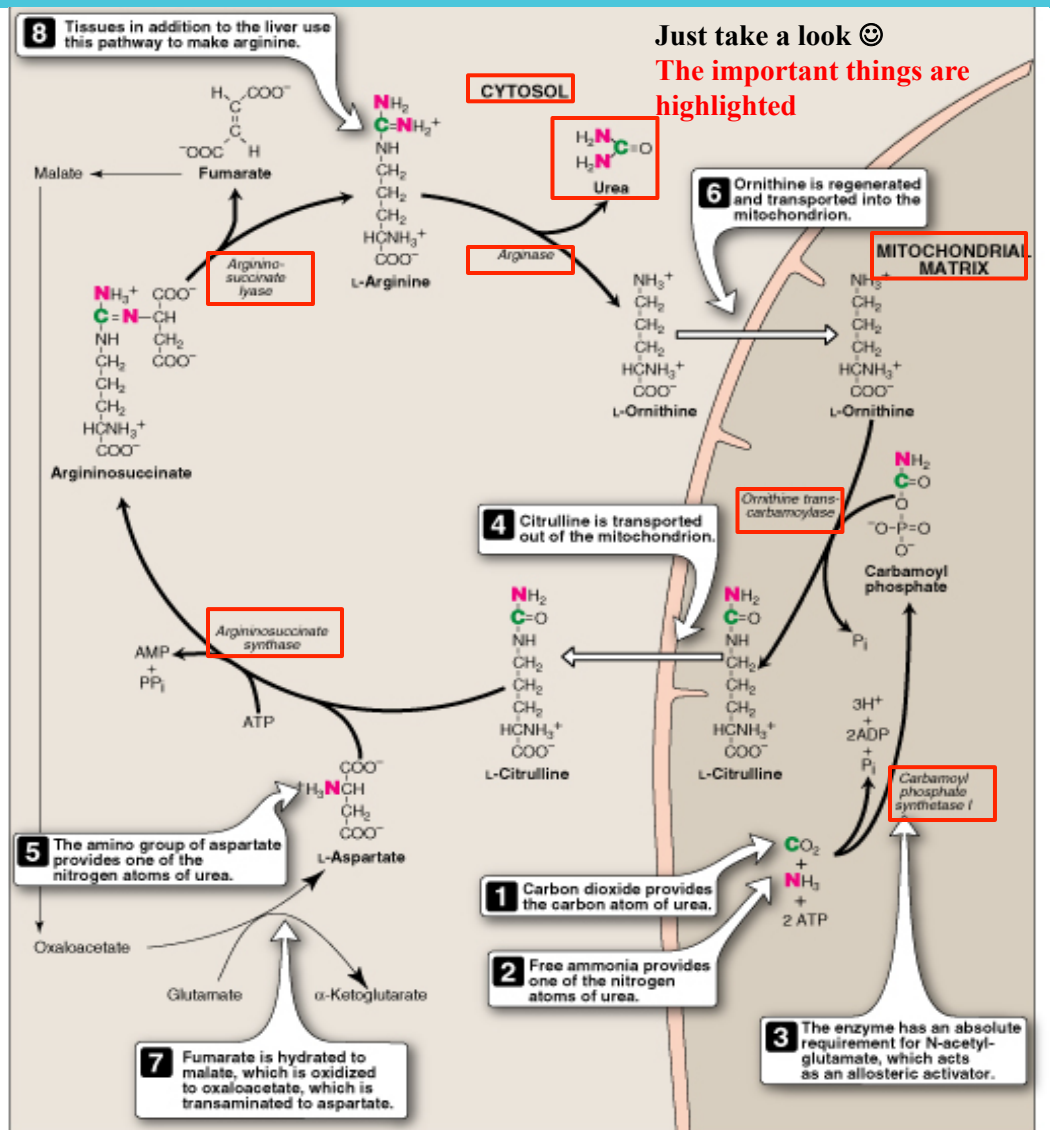
- Carbamoyl phosphate synthetase I
- **Ornithine transcarbamoylase (OCT)***

} In mitochondria

- Argininosuccinate synthase
- Argininosuccinate lyase
- Arginase **(just in liver)**

} In cytosol

*** the most common enzyme deficient and cause hyperammonemia in infants.**



Fate of Urea

Urea → Blood → Kidneys and excreted in urine

Blood → Intestine → (Urease*) $NH_3 + CO_2$

* by normal flora of intestine

$NH_3 + CO_2$ → Lost in feces

$NH_3 + CO_2$ → Reabsorbed into blood

- The action of intestinal urease to form NH_3 is clinically significant in renal failure:

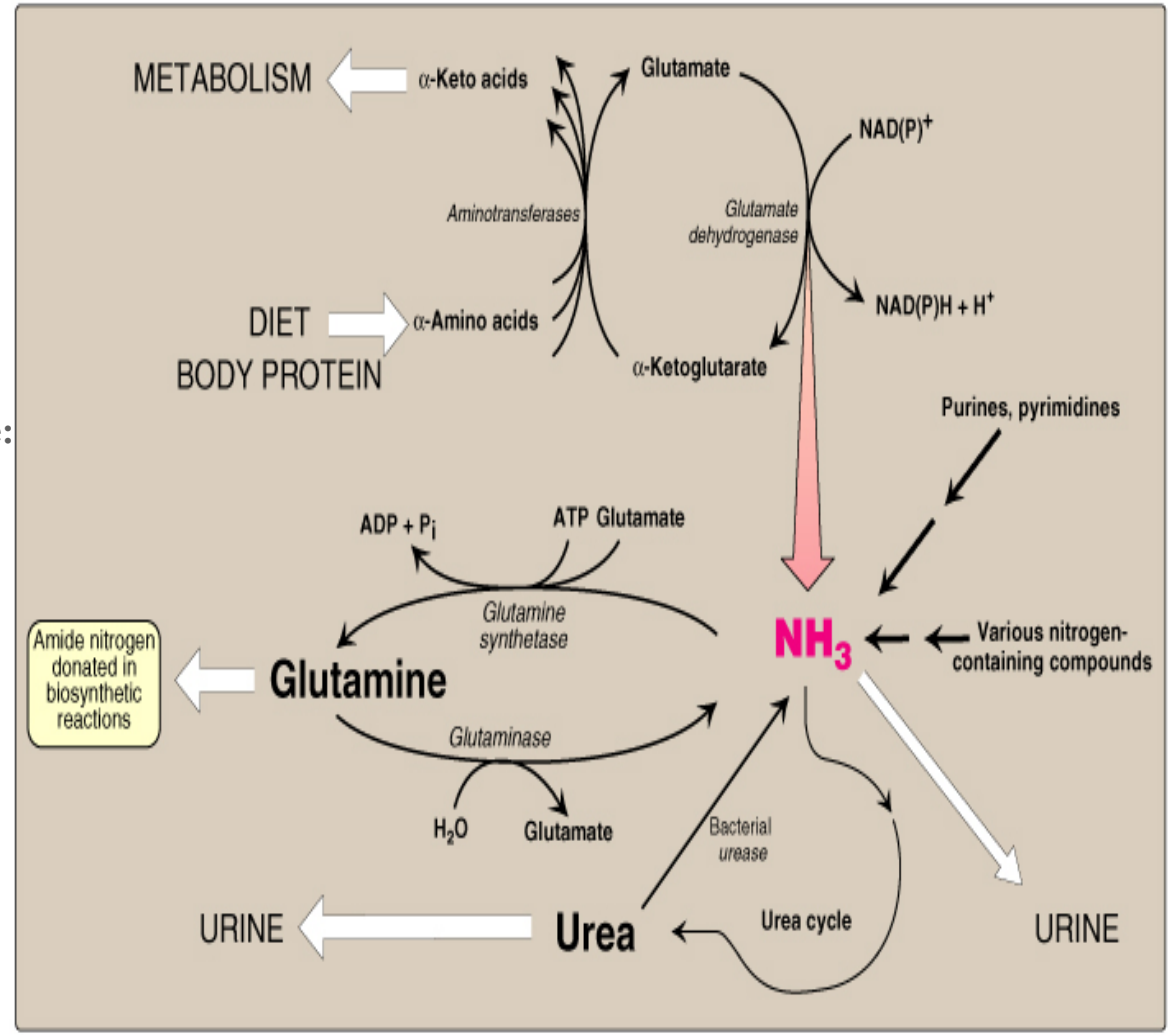
Renal failure ↑ → Blood urea ↑ → Urea to intestine → (Urease) ↑ NH_3 blood level

(Acquired hyperammonemia)

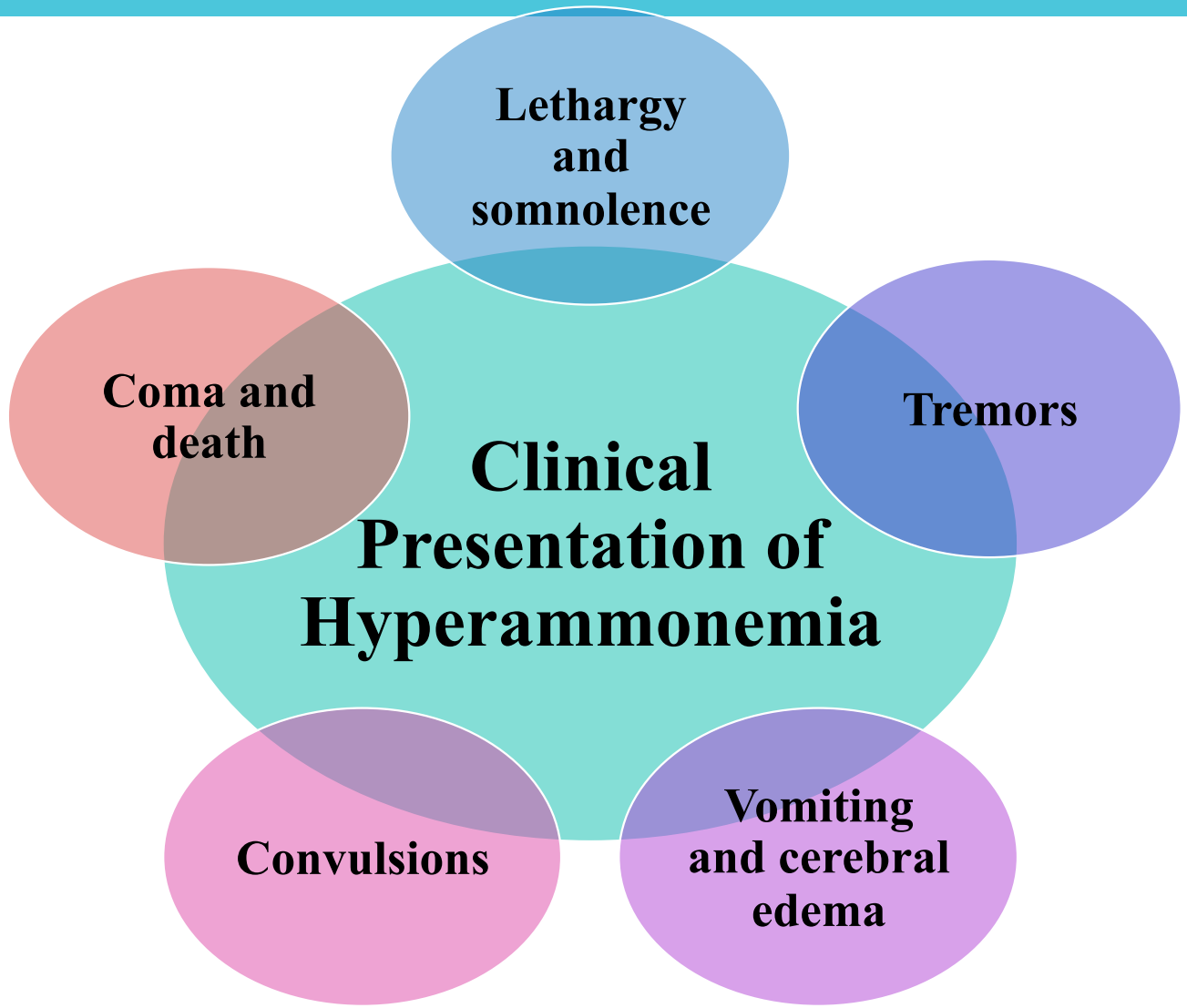
Sources of Ammonia

- Amino acids
- Glutamine
- Bacterial urease in intestine
- Amines e.g., catecholamines
- Purines & pyrimidines

Normal blood level of ammonia: 5 – 50 µmol/L

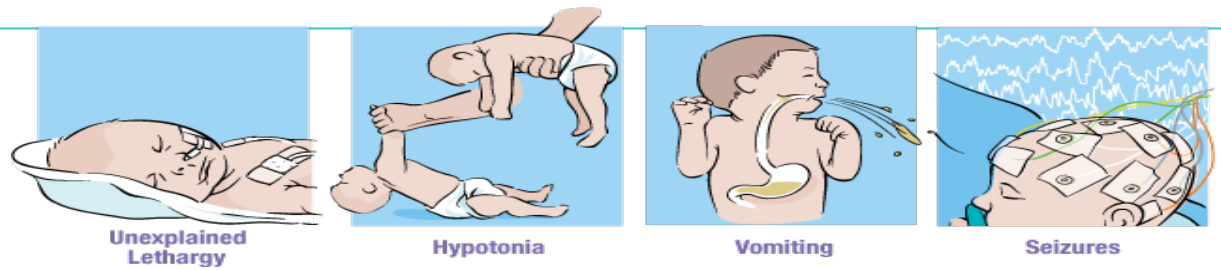


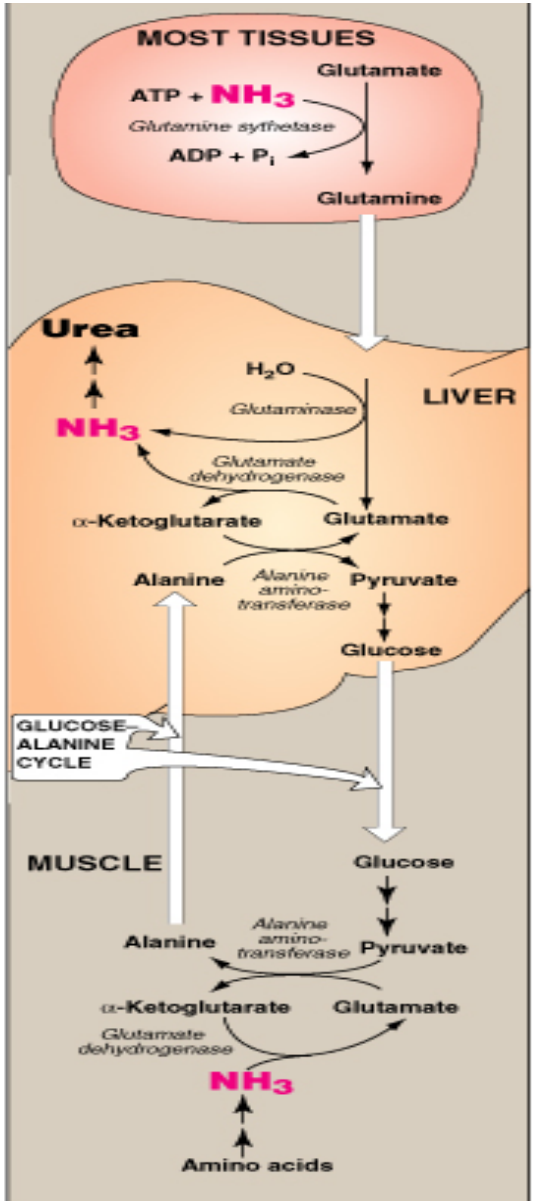
- **Hyperammonemia**
  - **Acquired hyperammonemia**
    - **Liver diseases**
      - **Acute**
        Viral hepatitis or hepatotoxic
        Destruction of hepatocytes
      - **Chronic**
        Cirrhosis by hepatitis or alcoholism
        Perihepatic shunt: the portal blood will go to systemic circulation Without passing through the liver
    - **Renal failure**
  - **Inherited hyperammonemia**
    - **Genetic deficiencies of any of the 5 enzymes of urea cycle**
      - **Ornithine transcarbamoylase deficiency**
        X-linked recessive
        Most common of congenital hyperammonemia
        Marked decrease of citrulline and arginine
      - **Others: Autosomal recessive**


Lethargy and somnolence
Coma and death
Tremors
Clinical Presentation of Hyperammonemia
Convulsions
Vomiting and cerebral edema

Summary

- Amino acids are not stored by the body So, we must **degraded**
- First we remove the amino group from amino acid by **Transamination**
- Then **Oxidative deamination of glutamate to form ammonia**
- Ammonia will be transported to liver by **Glutamine** from most tissues and **Alanine** from muscle.
- Both will release NH_3 inside the liver to start **urea** cycle.
- Urea is transported in blood to the kidneys for excretion in **urine.**
- **Hyperammonemia** excess of ammonia in the blood. It can be **acquired** or **inherited**
- Clinical Presentation of Hyperammonemia





Test your knowledge ..!

1) NH_3 is transported from muscles to liver by ?

A) Glutamine
B) Alanine
C) Glutamate
D) a & b

2) Glutamine is converted into glutamate by ?

A) Alanine aminotransferase (ALT)
B) glutamate dehydrogenase
C) Arginase
D) Glutaminase

3) One of this enzymes <u>are not</u> included in urea cycle ?

A) Ornithine transcarbamoylase (OCT)
B) glutaminase
C) Argininosuccinate synthase
D) Carbamoyl phosphate synthetase I

4) The most common enzyme deficient and cause congenital hyperammonemia is ?

A) Argininosuccinate lyase
B) Carbamoyl phosphate synthetase I
C) Ornithine transcarbamoylase
D) Argininosuccinate synthase

Answers
1) B
2) D
3) B
4) C

Biochemistry
Team

If you find any mistake, please contact us:)
Biochemistryteam@gmail.com

Biochemistry team leaders:
Basil ALSuwaine & Manar ALEid

Thank you