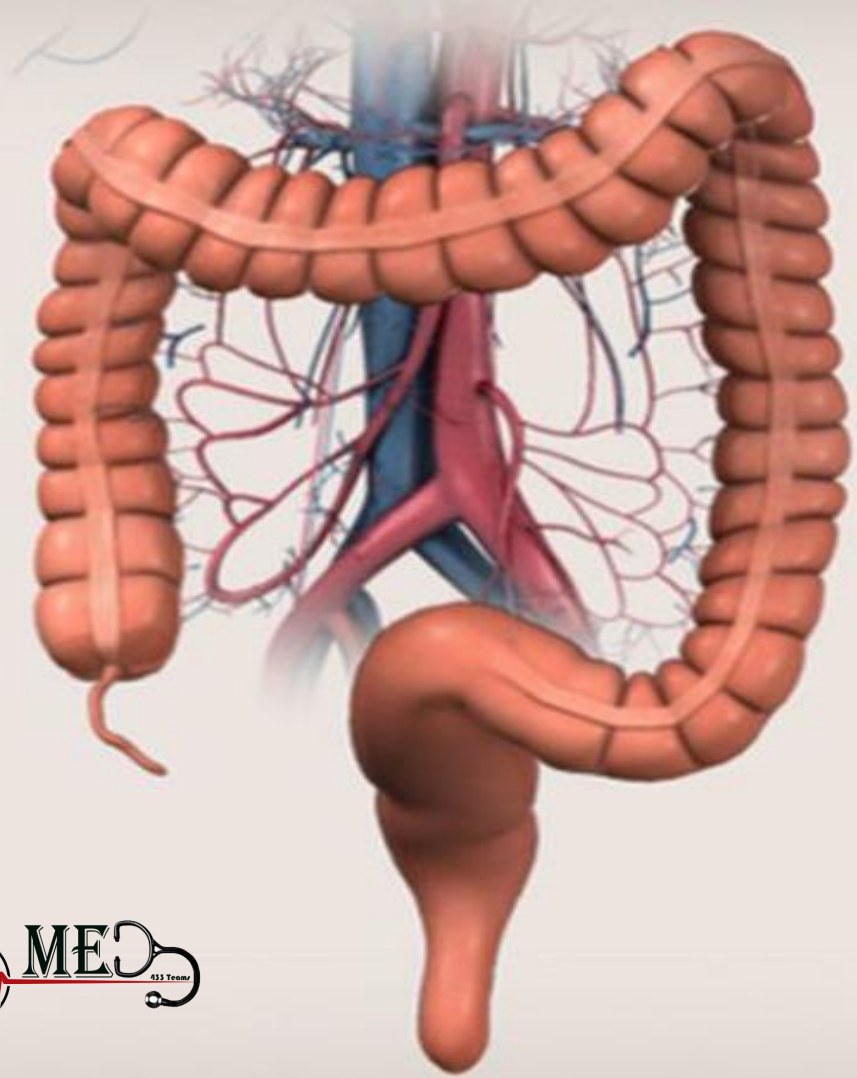

Urea Cycle

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

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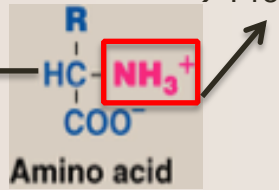
BACKGROUND

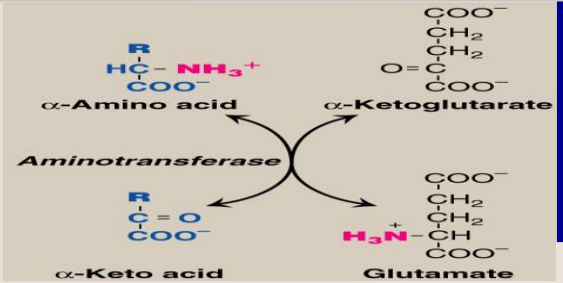
Amino acids degradation Involve:

1) Removal of carbon skeleton.
→ Produce α-keto acid
(used for energy metabolism)

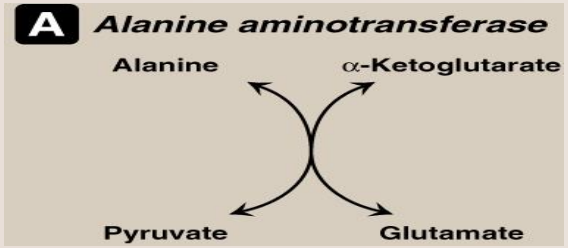
2) Removal of α-amino group
→ Produce Ammonia (NH_3)



Unlike glucose (stored as glycogen) and fatty acids (stored as TAGs)
Amino acids are not stored by the body so, amino acid excess of biosynthetic needs are degraded.



Amino groups of amino acids are funneled to Glutamate by Transamination Reactions with α-ketoglutarate . (The enzyme aminotransferase uses α-ketoglutarate as the Amino group acceptor)
In picture 2, Example of Transamination reaction by ALT in amino acid catabolism
WHY GLUTAMATE ?
It's unique because it's the only amino acid that undergoes rapid oxidative deamination



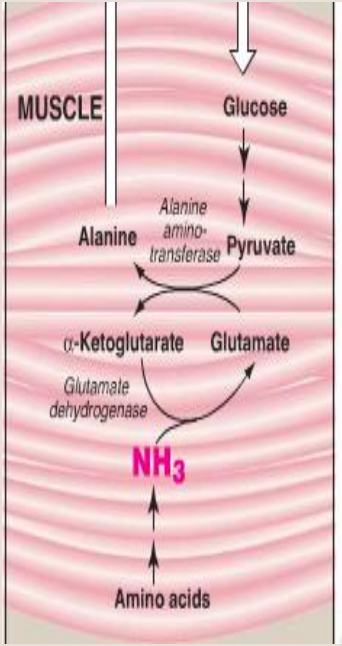
Oxidative deamination[1] of glutamate will release NH3 and re-generate α-ketoglutarate

Glutamate dehydrogenase
Glutamate → NH3 → α-ketoglutarate

1. Oxidative: loss of H, Deamination: removal of amino group in NH3 form.

Transport of NH3 from Peripheral Tissue into the Liver

- **Ammonia (NH3) is produced by all tissues and its main disposal is via formation of urea in Liver**
- Blood level of NH3 must be kept very low, otherwise, hyperammonemia and CNS toxicity will occur **(NH3 is very toxic to CNS)**



To solve this problem, NH3 is transported from

Muscles

1) NH3 is transferred to α-Ketoglutarate to form **Glutamate**
2) Glutamate will give its Amino Group to Pyruvate[1] to form **Alanine** by ALT

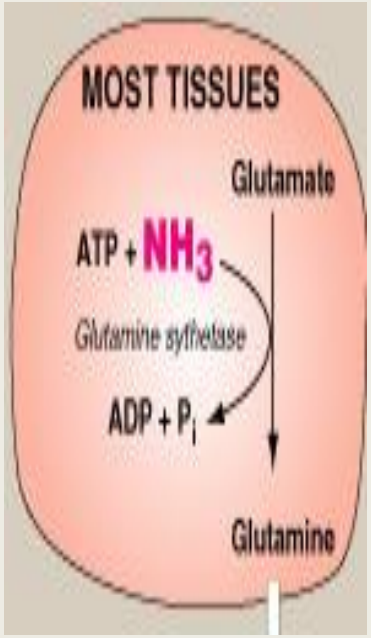
NH3 leaves Muscles in the form of ALANINE

Most peripheral tissues

1) NH3 is transferred to α-Ketoglutarate to form **Glutamate**
2) Glutamate is converted to Glutamine **by Glutamine Synthetase**

.

NH3 leaves peripheral tissue in the form of GLUTAMINE*



LIVER

*Glutamine carries more Ammonia and is not toxic

IN LIVER

ALANINE (from muscles)

will give its amino group to α-ketoglutarate to form GLUTAMATE by ALT.

GLUTAMINE (from most tissues)

Converted to GLUTAMATE by Glutaminase

Glutamate

Glutamate dehydrogenase

NH3

α-Ketoglutarate

NH3 has been transported from different organs to the Liver
where it is released again to start the UREA cycle

UREA CYCLE

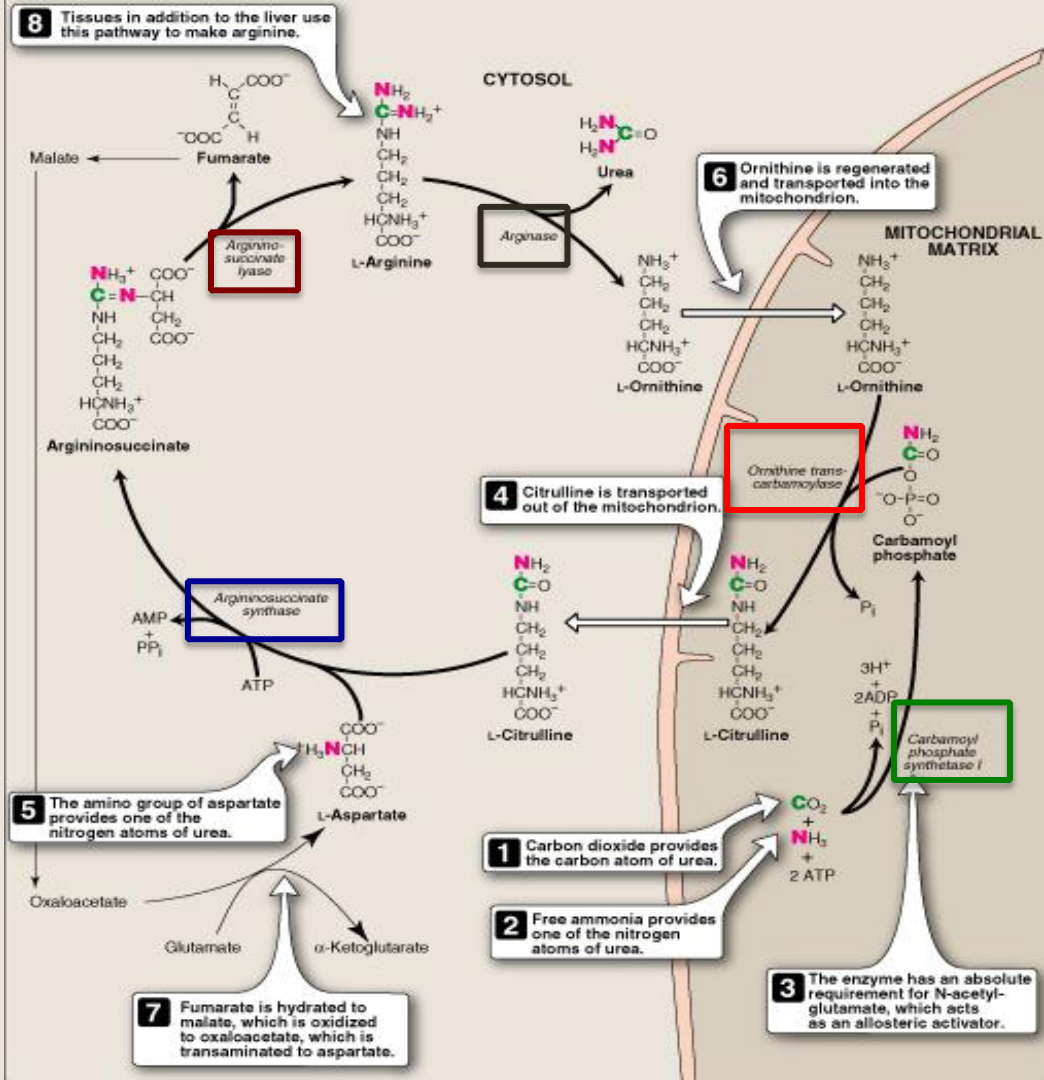
- **Urea is the major form for disposal of NH3**
- Urea cycle occurs in the **Liver**
- One nitrogen of urea is from NH3 and the other nitrogen from Aspartate
- Urea is transported in the Blood to the Kidneys for excretion in urine
- **Normal blood level of Ammonia: 5 – 50 µmol/L**

It occurs in the **mitochondria and the cytosol of hepatocytes.**

The reaction is catalyzed by FIVE enzymes (in sequence) :

1. Carbamoyl Phosphate Synthetase I
2. Ornithine Transcarbamoylase(OCT)
3. Argininosuccinate Synthase
4. Argininosuccinate Lyase
5. Arginase

Free Ammonia provides one (N) atom of Urea, CO2 provides the (C) atom.



Fate of UREA

Remaining

Major amount

INTESTINE

Catalyzed by **UREASE**[1]

into:

$NH3+CO_2$

NH3 fate:

1. Lost in feces
2. Reabsorbed into blood

BLOOD

Kidneys → Excretion in urine[2].

Sources of Ammonia	
	❑ Amino Acids **(Quantitively the most important source)**
	❑ Glutamine
	❑ Bacterial Urease in Intestine
	❑ Amines e.g., Catecholamines.
	❑ Catabolism of Purines & Pyrimidines

1. The action of intestinal urease to form NH3 is clinically significant in renal failure.
2. Most of ammonia is excreted in urine as NH4, which provides an important mechanism to maintain acid-base balance

Hyperammonemia

Inherited

Genetic deficiencies of any of the 5 enzymes of urea cycle

Ornithine transcarbamoylase deficiency:

- X-linked recessive
- Most common form of congenital Hyperammonemia
- Marked decrease of Citrulline and Arginine

Others :

Autosomal dominant

Acquired

Liver disease:

- ❑ **Acute:**
  - ✓ Viral hepatitis
  - ✓ Hepatotoxins E.g. Alcohol
- ❑ **Chronic**
  - ✓ Cirrhosis due to Hepatitis or Alcoholism

Renal failure:

↑ Blood urea

⇩

Delivery of urea to intestine

⇩

UREASE

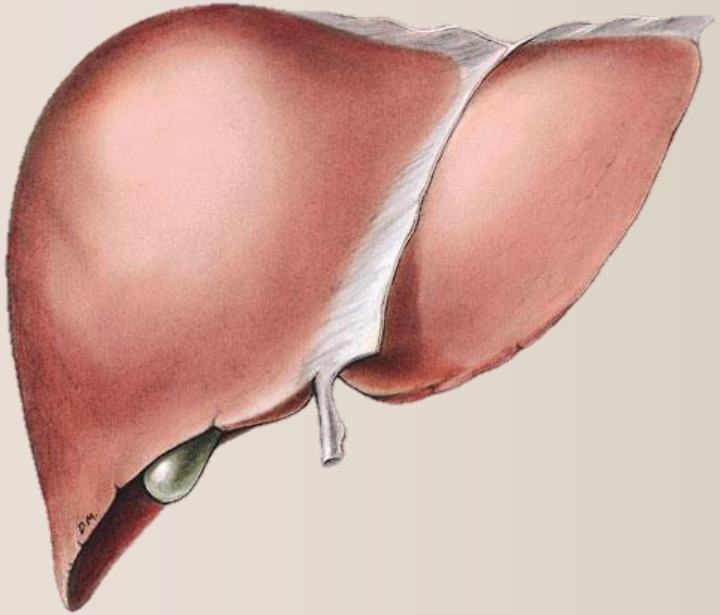
→↑ NH3 blood levels

Clinical presentation of Hyperammonemia	1. Lethargy and Somnolence 2. Tremors 3. Vomiting 4. Cerebral Edema 5. Convulsion 6. Coma and Death

1. 2-day-neonate presented with lethargy. 2 days later, he developed a seizure. CBC shows significant increase in Ammonia and decreased Cirtrulline and Arginine . Which ONE of the following Deficiency is the cause ?
    A. Ornithine transcarbamoylase
    B. Argininosuccinate synthas
    C. Argininosuccinate lyase
    D. Arginase
2. From most Peripheral tissues, NH3 is transported to the Liver through forming ……. by ……. :
    A. Alanine, Alanine Amino Transferase
    B. Glutamine, Glutamine Dehydrogenase
    C. Alanine, Alanine Synthase
    D. Glutamine, Glutamine Synthase
3. Where does the Urea Cycle Occur?
    A. Blood
    B. Kidney
    C. Liver
    D. Tissues
4. What is the major form for the disposal of NH3?
    A. Ammonia
    B. Urea
    C. Nitrogen
    D. Aspertate
5. Amino Group of Amino Acids are funneled to Glutamine by:
    A. Transamination
    B. Oxidative Deamination
    C. Decarboxylation
    D. Hydrolysis
6. NH3 is transported from Muscles to Liver via Formation of:
    A. Glutamine
    B. Alanine
    C. Nitrogen
    D. Pyruvate
7. In Muscles, Glutamate will give its Amino Group to ……..to form…….:
    A. Alanine, Pyruvate
    B. Pyruvate, Alanine
    C. Glutamine, Pyruvate
    D. Pyruvate, Glutamine
8. In the Liver, Alanine will give its Amino Group to ……. to form ……. :
    A. Alpha-Ketoglutarate, Glutamate
    B. Glutamate, Alpha-Ketoglutarate
    C. Alpha-Ketoglutarate, Pyruvate
    D. Glutamate, Pyruvate
9. The action of intestinal urease to form NH3 is clinically significant in:
    A. Liver Failure
    B. Renal Failure
    C. Hepatic Toxicity
    D. Renal Injury

Answers:

1-A 2-D 3-C 4-B 5-A 6-B 7-B 8-A 9.B



Thank You!

Done by:
Mohammed AlNafisah
Basmah AlDeghaither