- Urea Cycle -

Biochemistry team

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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:

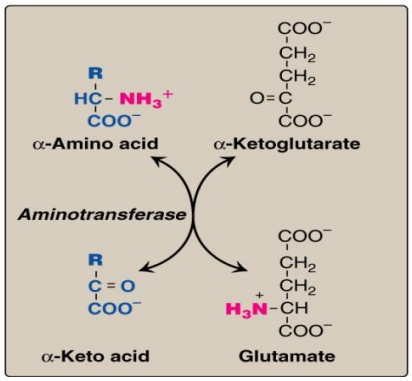
  Removal of α-amino group ----→ Ammonia (NH_3)

  Remaining carbon skeleton ----→ Energy metabolism

Carbon skeleton undergoes either gluconeogenesis or ketogenesis (forming keton bodies)

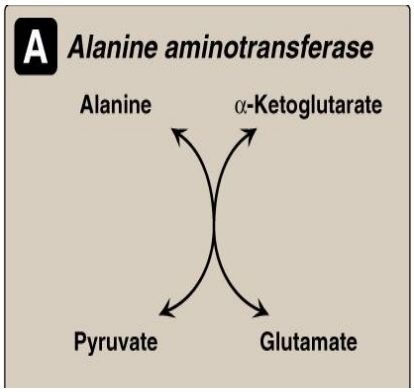
Removal of α-amino group:-

- Amino groups of amino acids are funneled (directed) to glutamate by transamination reactions with α-ketoglutarate (alpha ketoacids)
- Oxidative deamination of glutamate will release NH3 and re-generate α-ketoglutarate
- Glutamate is unique. It is the only amino acid that undergoes rapid oxidative deamination (in the liver)

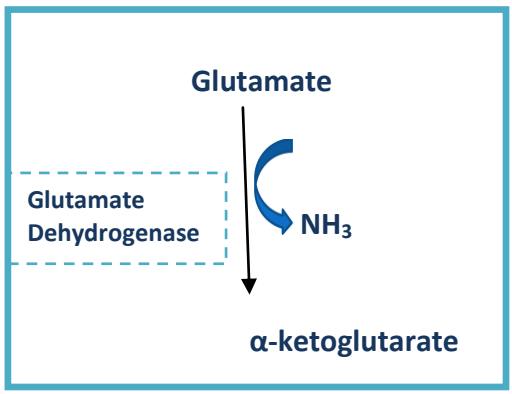


Transamination

Explanation:
Amino acids give their amino group to glutamate and are converted to a ketoacids. (Ketoacid is amino acid without amino group)



Transamination by ALT
-Alanine is amino acid.
-Pyruvate is α-ketoacid.



Oxidative Deamination

Transport of NH3 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 NH3 must be kept very low, otherwise, hyperammonemia and CNS toxicity will occur
- To solve this problem, NH3 is transported from peripheral tissues to liver via formation of: Glutamine (most tissues), Alanine (muscle)

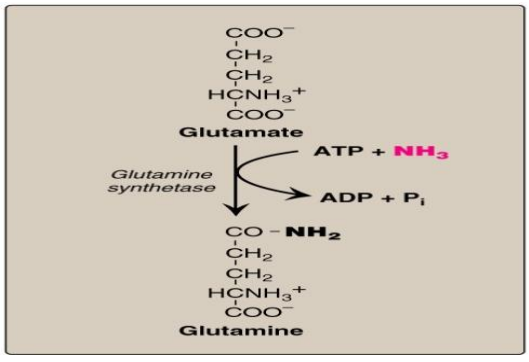
❖ From most peripheral tissues:

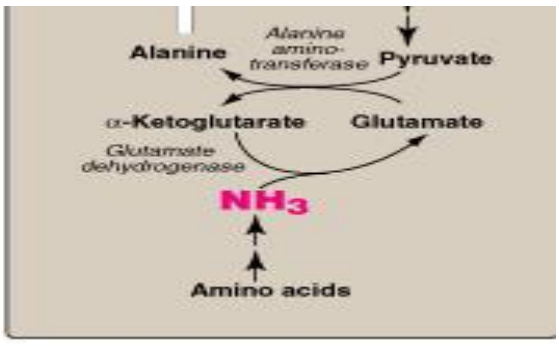
- NH3 is transported Into the liver through forming glutamine by glutamine synthetase

❖ From the muscle:

- First, NH3 will be transferred into α-ketoglutarate to form glutamate
- Then, glutamate will give its amino group to pyruvate to form alanine by ALT (Alanine transaminase)

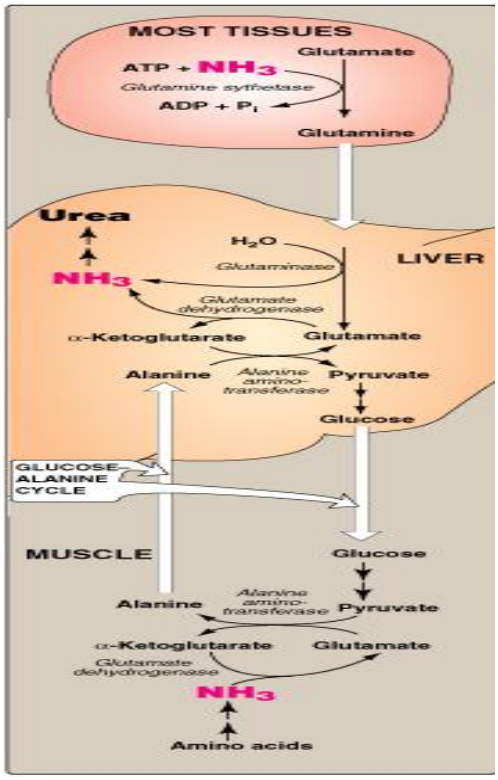
  Therefore, NH3 is transported from muscle into the liver through forming alanine





Fate of glutamine and alanine in the liver

-Glutamine is converted into glutamate by glutaminase.
- Glutamate is converted into α-ketoglutarate and releasing NH_3 by glutamate dehydrogenase.
- Alanine will give its amino group to α-ketoglutarate to form glutamate by ALT (alanine aminotransferase) .
- Glutamate is converted back into α-ketoglutarate and releasing NH_3.
- 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

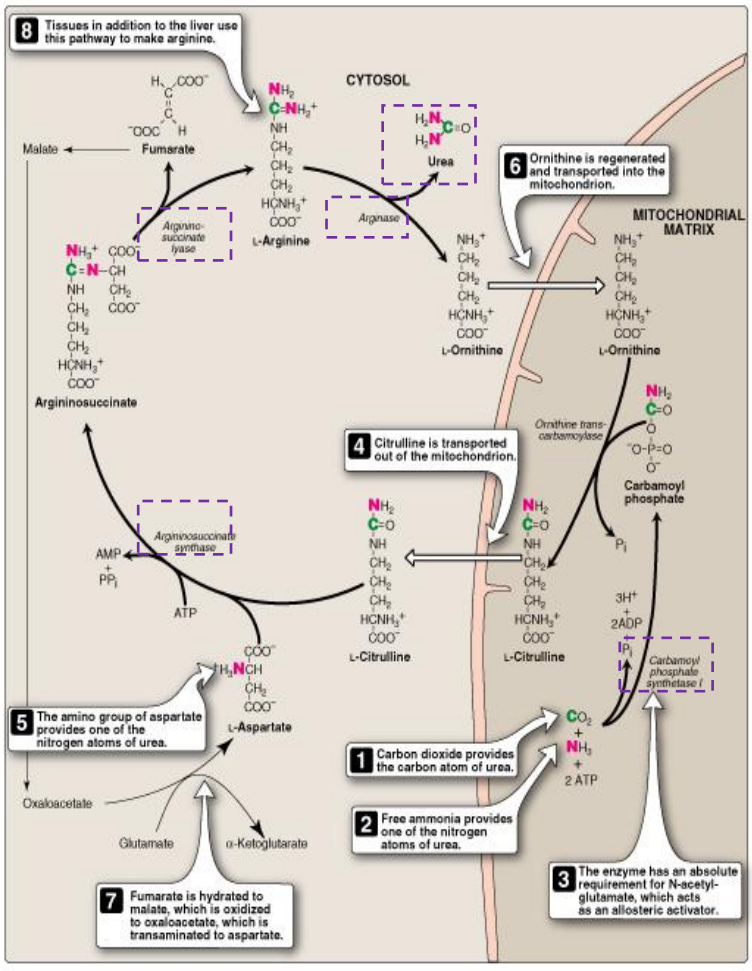
Don't memorize the cycle only the enzymes.

- 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(amino acid)
- 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)
- Argininosuccinate synthase
- Argininosuccinate lyase
- Arginase (is only present in the liver)

Ammonia provides one nitrogen atom of urea and carbon dioxide with **Carbamoyl phosphate synthetase I** → this will produce ***carbamoyl phosphate*** → ***carbamoyl phosphate*** with ***ornithine*** → will produce ***Citruline*** by **Ornithine transcarbamoylase (OCT)** in the mitocondria → ***Citruline*** goes out of the mitocondria with ***Aspartate*** (which gives one nitrogen atom of urea) by **Argininosuccinate synthase** → ***Argininosuccinate*** is produced → ***Argininosuccinate*** convert to ***Arginine*** by **Argininosuccinate lyase** → ***Arginine*** convert to **Urea** by **Arginase** .



Deficiencies of any of the 5 enzymes of urea cycle will cause hyperammonemia
How to know which enzyme is deficient? By measuring the products accumulated
The severity increases when the primary enzymes are deficient (e.g. Carbamoyl phosphate synthetase I)

Ammonia is toxic especially to CNS. (Because it can cross blood brain barrier) ,Urea cycle detoxify and excrete ammonia . Urea cycle occur in the hepatocyte in both mitochondria and cytosol. ,the first to reaction occur in the mitochondria, whereas the remaining cycle enzymes are located in the cytosol.Ornithine and citrulline are amino acids that they are not present in protein structure.
Succinate and furamate are isomers.

Fate of Urea

Urea → (Blood) → Kidneys and excreted in urine (water soluble).

Urea → Intestine → (Urease) → $NH_3 + CO_2$

- Lost in feces
- Reabsorbed into blood

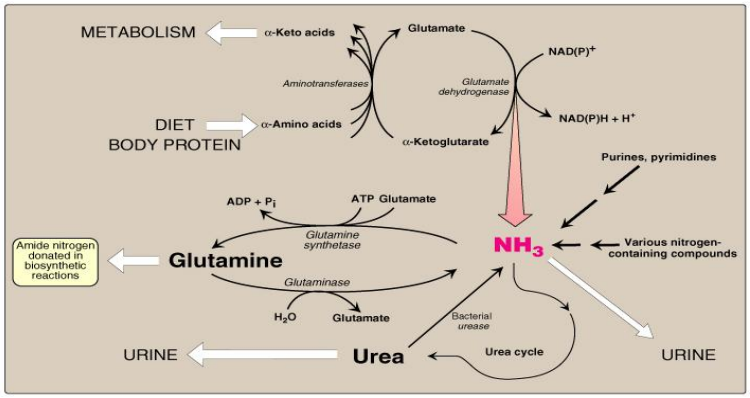
The action of intestinal urease to form NH_3 is clinically significant in renal failure:

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

(Acquired hyperammonemia)

Sources of Ammonia

- Amino acids
- Glutamine
  - (by renal glutaminase, NH3 excreted in urine as NH4)
- Bacterial urease in intestine
- Amines e.g., catecholamines
- Purines & pyrimidines



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

Hyperammonemia

- Acquired hyperammonemia:
  1. Liver diseases:
  Acute: Viral hepatitis or hepatotoxic
  Chronic: Cirrhosis by hepatitis or alcoholism
  2. Renal failure

(Hyperammonemia is higher in liver disease than in renal failure)

- Inherited hyperammonemia:
  Genetic deficiencies of any of the 5 enzymes of urea cycle

Inherited hyperammonemia:

- Ornithine transcarbamoylase deficency:
  X-linked recessive(mainly in males)
  Most common of congenital hyperammonemia
  Marked decrease of citrulline and arginine
- Others: Autosomal recessive

Clinical Presentation of Hyperammonemia

- Lethargy and somnolence
- Tremors
- Vomiting and cerebral edema
- Convulsions
- Coma and death

Summary

1. Transamination: all amino acids give their amino group to glutamate.
2. Oxidative Deamination: Glutamate releases their amino group by glutamate dehydrogenase.
3. Amino group will be transported to liver by glutamine from most tissues and alanine from muscles.
4. in liver:
a. Glutamine will release NH_3 by glutaminase and will become glutamate.
b. Glutamate will release another NH_3 by glutamate dehydrogenase and will become alpha ketoglutarate.
c. Alanine will give its amino group to alpha ketoglutarate which forms glutamate (by ALT) then glutamate will release NH_3 and become alpha ketoglutarate.
5. Ammonia becomes Urea in the urea cycle by 5 enzymes:
- Carbamoyl phosphate synthetase I
- Ornithine transcarbamoylase (OCT)
- Argininosuccinate synthase
- Argininosuccinate lyase
- Arginase

Review Questions

1. What is the major source of disposal of ammonia?

A-Urea
B- Alanine
C- Pyrimidines
D- Glutamine

2. Which of the following is a safe way for transporting ammonia from tissues?

A-Urea
B- Purines
C- Pyrimidines
D- Glutamine

3. Deficiency in which ONE of the following causes decreased cirtrulline and Arginine?

A. Ornithine transcarbamoylase
B. Argininosuccinate synthase
C. Argininosuccinate lyase
D. Arginase

4. Which of the following is a the way for transporting ammonia from tissues?

A. Alanine
B. Glutamate
C. alpha ketoglutarate
D. Glutamine

Answers: A-D-A-D