# Urea Cycle

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# Objectives:

- Understand the reactions for removal of a-amino group of amino acids and formation of ammonia
- Identify the importance of blood transport of ammonia to the liver in the form of glutamine/alanine
- Understand the importance of conversion of ammonia into urea by the liver through urea cycle
- Identify the causes (hereditary & acquired), clinical manifestations and management of hyperammonemia

# Background:

- Unlike glucose and fatty acids, amino acids are **not** stored by the body.
- Amino acids in excess of biosynthetic needs are degraded.
- Sources of amino acid in the body:
  1) Diet
  2) Protein turnover
  3) Biosynthesis such as nonessential amino acid

- Degradation of amino acids involves:
  1. Removal of α-amino group [1] → Ammonia ($NH_3$)
  2. Remaining carbon skeleton → Energy metabolism

If the body want to degrade the amino acid, it has to **remove** the **amino group** in the form of "**ammonia**", but because the ammonia is toxic we also have to get rid of it. To get rid of it: body must transport it first to the liver, then in the liver the ammonia will be **converted** to "**urea**" and then excreted.

1. Amino group, protects the amino acid from being metabolized. Remove it involves **two** reactions: **Trans**amination & **De**amination

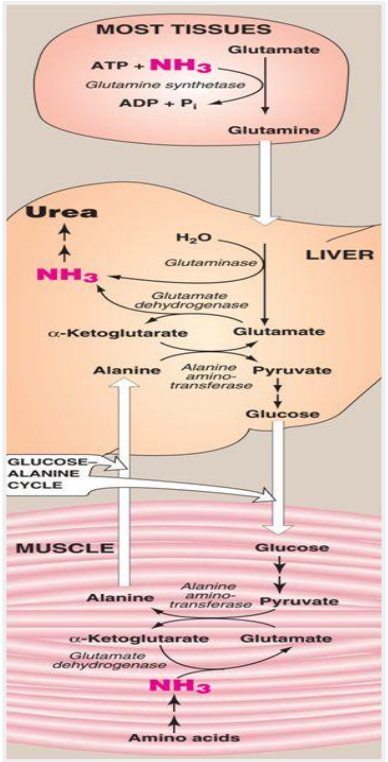
# Amino Acid Degradation (α-amino group)

## First:
**"Removal of α-amino group of amino acids & formation of ammonia"**

1. **Trans**amination to **Glutamate**.
   (Except in the Muscles → to Alanine)
2. **Oxidative de**amination of **Glutamate**

★ Amino groups of amino acids are funneled to "**Glutamate**" by: transamination reactions with α-ketoglutarate. Because Glutamate is unique & It is the **only** amino acid that undergoes rapid oxidative deamination.

★ **Oxidative de**amination of glutamate will release **$NH_3$** and **re-generate α-ketoglutarate** & **NADH**.




## Second:
**"Blood transport of ammonia into liver"**

1. In the form of **Glutamine**[1] (**most tissue**)
2. In the form of **Alanine** (**muscle**[2])

★ 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).

★ To solve this problem, $NH_3$ is transported from peripheral tissues to the liver via formation of:

- ➢ Glutamine (most tissues)
- ➢ Alanine (muscle)

1. Dibasic amino acid, the only transporter of glutamate molecules from other tissues to liver.
2. Because the final product of anaerobic metabolism is pyruvate which is a main component of alanine.

# The First Step:
## (Removal of α-amino group of amino acids & formation of ammonia)

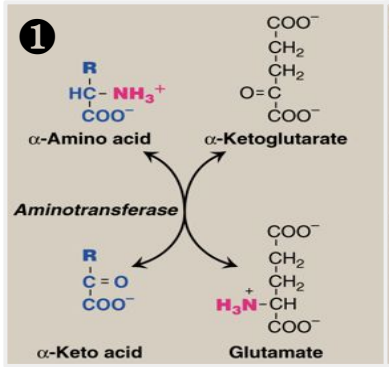
01 **Transamination:** The amino group is transferred from the **α-amino acid** to **α-Ketoglutarate** (acceptor of amino groups) by **Aminotransferase** with the help of **PLP**, forming **glutamate** & **α-keto acid** "Note that the reaction is bidirectional".

➔ Two common examples for this reaction is transamination of alanine and aspartate:

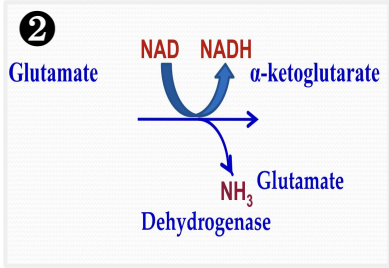
A. The amino group is transferred from the **alanine** to the **α-Ketoglutarate** (acceptor of amino groups) by **ALT** with the help of **PLP**, forming **glutamate** & **pyruvate**.

B. The amino group is transferred from the **aspartate** to **α-Ketoglutarate** (acceptor of amino groups) by **AST** with the help of **PLP**, forming **glutamate** & **oxaloacetate**. "Note that the reaction can go in the other direction where the amino group is transferred from glutamate to oxaloacetate forming aspartate which is needed for urea cycle".

02 **To remove the amino group from glutamate, it undergoes deamination.** **Deamination:** involves **reducing** NAD to **NADH** (gains H) and **oxidising** glutamate to **α-Ketoglutarate** by the enzyme **glutamate dehydrogenase**. The reaction is called **oxidation- reduction reaction**. This result in the **removal of ammonia**, and the **regeneration of α-Ketoglutarate**.




- PLP : Pyridoxal phosphate, a coenzyme that is derived from vitamin B6.
- Transamination by : ALT & AST.




- Oxidative deamination

Summary : Transamination is done in tissue, while Deamination in liver.

- It's important to know the names of these reactions, their substrates, enzymes and products.

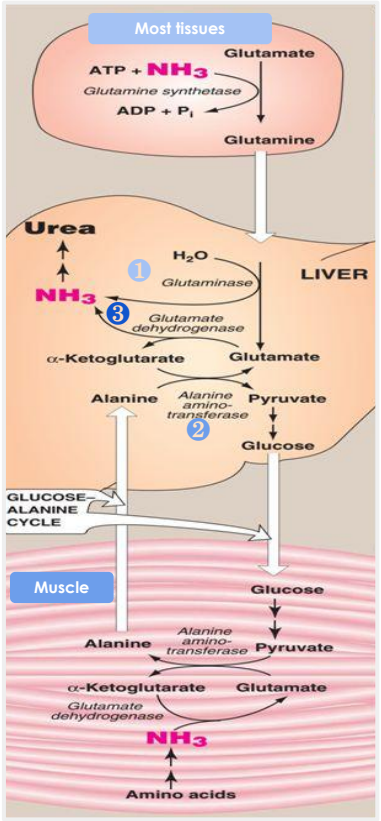
# The Second Step:
## (Blood transport of ammonia into liver)

### From most peripheral tissues:

- $NH_3$ is transported Into the liver through **forming glutamine** by **glutamine synthetase**[1].

### 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** .
- Therefore, $NH_3$ is transported from muscle into the liver through **forming alanine**.




## Release of ammonia from glutamine and alanine in the liver:

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

**2 Alanine** → will give its amino group to α-ketoglutarate to form **glutamate** by **ALT**.

**3 Glutamate** → is converted into **α-ketoglutarate** and **releasing $NH_3$** by **glutamate dehydrogenase**[2].

**In summary:**

- ★ Blood transport of $NH_3$ from peripheral tissues (in the form of glutamine and from the muscles in the form of alanine ) into the liver.
- ★ The release of $NH_3$ black in the liver to start the urea cycle.

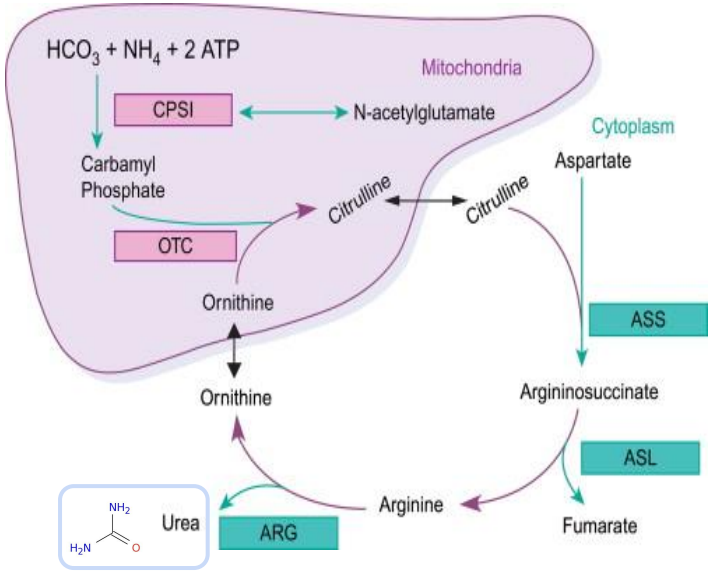
1. Turn glutamate into glutamine "glutamic acid" by adding ammonia Requires ATP "any synthetase requires ATP".
2. Deamination process.

# Urea Cycle

It's occurs in the **liver**

**Urea**

- ★ is transported in the blood to the kidney for excretion in urine.
- ★ is the major form for disposal of amino groups derived from amino acids.
- ★ One nitrogen of Urea is from NH3 (Ammonia) and the other nitrogen is from aspartate (2N from aspartate).




5 **enzymes of urea cycle:**

(M) mitochondria
(C) cytoplasm

- **Carbamoyl Phosphate Synthetase I (CPSI)**[1M]
- **Ornithine Transcarbamylase (OCT/OTC)**[2M]
- **Argininosuccinate Synthase (ASS)**[C]
- **Argininosuccinate Lyase (ASL)**[C]
- **Arginase (ARG)**[3C]

1. Rate limiting enzyme, needs N-acetyl glutamate to be activated. "activator" When I eat more protein, I will have More arginine and more glutamate, which will increases n acetyl glutamate, which in turn increases the production of urea.
2. Alternative name: Ornithine carbamoyltransferase that's why we call it "OCT"Could also be called (OTC) MOST COMMON.
3. Present only in the liver, this is why the urea cycle happens only in the liver.


# Urea Cycle

Female doctor note: "knowing the enzymes is extremely important but understanding the cycle is for yourself".

**437 notes:**

I. The ammonia in the presence of ATP & CO2 will create the Urea backbone with the use of Carbamoyl phosphate synthetase I Enzyme in the presence of N-Acetylglutamate as an activator will convert it to Carbamoyl Phosphate.

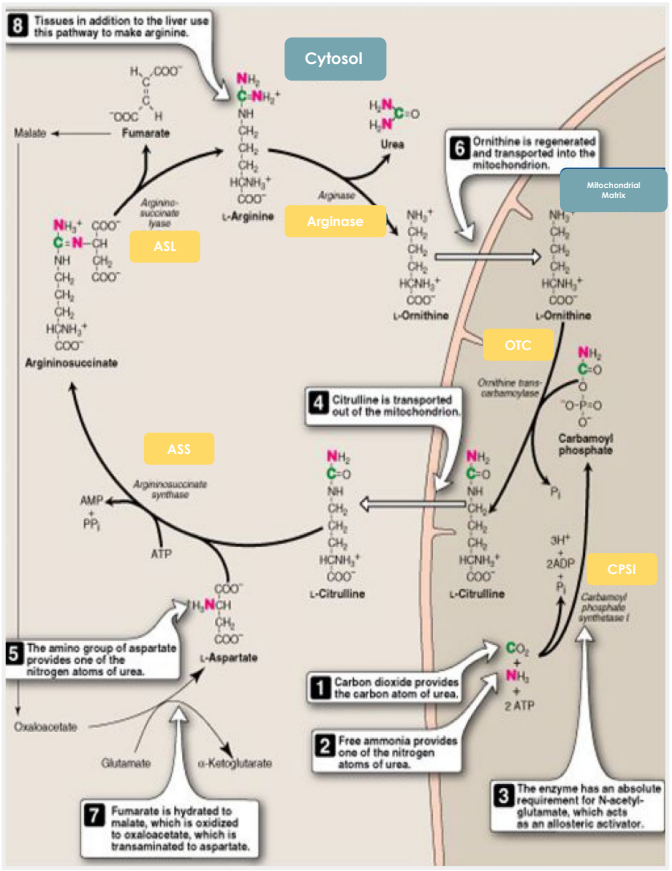
II. Carbamoyl Phosphate in the presence of Ornithine and OTC Enzyme (Ornithine transcarbamylase) will convert it to Citrulline.

III. Citrulline will leave the mitochondria to go to the cytosol where a nitrogen group will be added to it from aspartate by Argininosuccinate synthase which will convert it to Argininosuccinate.

IV. Argininosuccinate will be converted to arginine by Argininosuccinate lyase.

V. Arginine will be converted to Ornithine by Arginase. This is the MOST IMPORTANT step as it will lead to the release of urea & The cycle precursor ( The Ornithine ).

VI. Ornithine will leave the cytosol to go the mitochondria to start another Cycle.



# Urea Cycle: Regulation

**Rate-limiting enzyme of urea cycle:**

Carbamoyl phosphate synthetase I (CPSI)

**Allosteric activator of CPSI:**

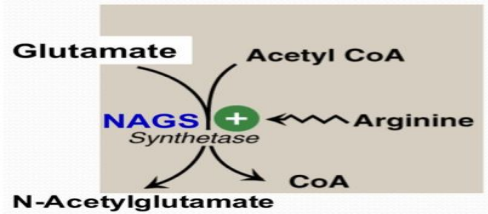
N-Acetylglutamate

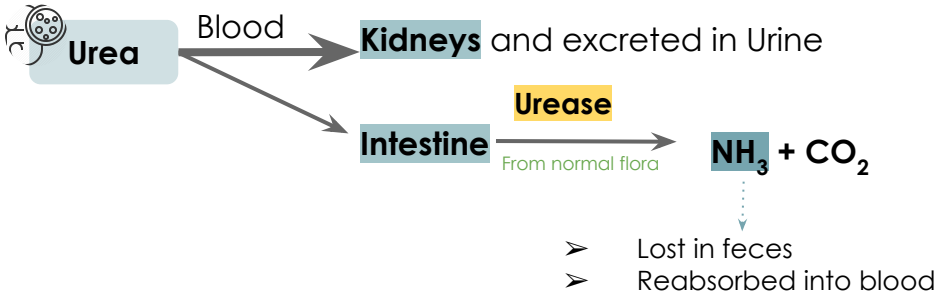
**N-Acetylglutamate is synthesized by:**

N-Acetylglutamate synthetase (NAGS) in presence of arginine

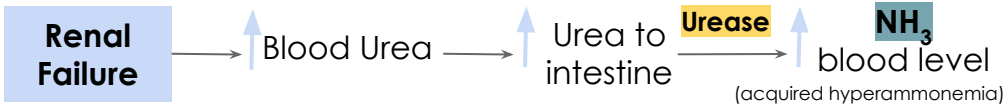
**NAGS deficiency is efficiently treated with**

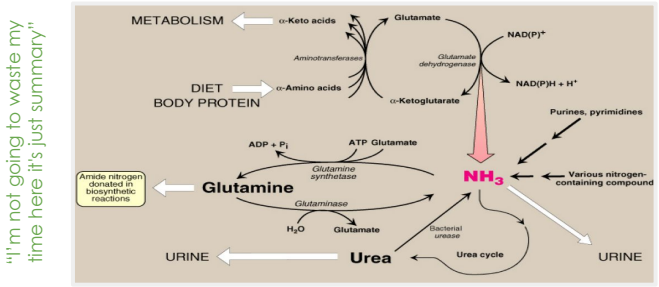
Carbaglue → a CPS1 activator




**The action of intestinal Urease to form NH3 is clinically significant in renal failure:**




"I'm not going to waste my time here it's just summary"

- Sources & Fate of ammonia
  Normal blood level of ammonia: **5-50µmol/L**

# Hyperammonemia

## Acquired hyperammonemia:

1. **Liver disease**
   - ➔ **Acute**: Viral hepatitis or hepatotoxic
   - ➔ **Chronic**: Cirrhosis by hepatitis or alcoholism
2. **Renal failure**

**Clinical Presentation**

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

"Not that important"

## Inherited hyperammonemia:

Genetic **deficiencies of any of the 5 enzymes** of urea cycle or the **activator enzyme for CPSI**:

➔ CPSI, OTC, ASS, ASL, arginase or NAGS

- ❖ **Ornithine transcarbamylase** deficiency:
  - X-linked recessive
  - Most common of congenital hyperammonemia
  - Marked decrease of citrulline and arginine
- ❖ **Others**: Autosomal recessive

# Hyperammonemia cont.

## Management:

- Protein restriction
- Volume repletion to maintain renal function
  - Use 10% dextrose in water but limit the use of normal saline
- Ammonia removal by hemodialysis & or drugs
- Avoid drugs that increase protein catabolism (eg, glucocorticoids) or inhibit urea synthesis (eg, valproic acid), or have direct hepatotoxicity

## Drugs of treatment:

**01**

Drugs that scavenge ammonia by creating an alternate pathway to excrete N 2- precursors:

- I.V. Sodium phenylacetate & sodium benzoate (Ammonul)
- Oral sodium phenylbutyrate (Buphenyl)
- I.V. Arginine: for all UCDs except UCD due to arginase deficiency (argininemia)

**Sodium phenylbutyrate (Buphenyl):**

- Prodrug that is converted to phenylacetate.
- Phenylacetate condenses with glutamine (in blood) forming phenylacetylglutamine that is excreted in urine.

**02**

Activators to CPSI (Carglumic acid 'Carbaglu'):

- For hyperammonemia due to NAGS deficiency

# Summary

## ❶ Removal of α-amino group, formation of ammonia

★ **Transamination**:
- By **ALT & AST**.
- Amino groups of amino acids are funneled to glutamate by transamination reactions with α-ketoglutarate.

★ **Oxidative deamination**:
- in liver By **Glutamate dehydrogenase**.
- The glutamate will release $NH_3$ & Regenerate α-ketoglutarate.

## ❷ Transport of $NH_3$ from peripheral tissues into the liver

★ **Glutamine** (from most tissues to liver). Glutamine formed by **glutamine synthetase.**

★ **Alanine** (from muscles to liver).

## ❸ Release of ammonia from glutamine and alanine in the liver

01. **Glutamine** is converted back into glutamate by **glutaminase**.
02. **Alanine** will give its amino group to α-ketoglutarate to form glutamate by **ALT**.
03. **Glutamate** is converted into α-ketoglutarate and releasing $NH_3$ by **glutamate dehydrogenase.**

## Urea Cycle

### Enzymes of urea

1. Carbamoyl Phosphate synthetase (**CPSI**)
2. Ornithine Transcarbamylase (**OTC**)
3. Argininosuccinate Synthase (**ASS**)
4. Argininosuccinate Lyase (**ASL**)
5. Arginase

### Regulation of urea cycle

★ **RATE-LIMITING ENZYME** of urea cycle: **(CPSI).**

★ **Allosteric activator of CPSI: (N-Acetylglutamate).**

★ **N-Acetylglutamate is synthesized by:** N-Acetylglutamate synthetase **(NAGS)** in presence of **arginine.**

★ **Treatment of NAGS deficiency: (Carbaglu, CPS1 activator).**

### Fate of urea

1. **To the kidneys** (**Mostly**) excreted in urine.
2. **To the intestine** by urease gives $NH_3$ (lost in feces or reabsorbed into blood + $CO_2$ ).

### Hyperammonemia

1. **Acquired (liver diseases – Renal failure).**
2. **Inherited (all the enzymes are autosomal recessive except OTC which is X-linked recessive).**

- **Treatment**: Oral sodium phenylbutyrate (Buphenyl) a Prodrug that is converted to phenylacetate.

# Quiz

## MCQs :

**Q1: Blood transport of ammonia into liver in form of:**

**a)** Glutamate (in most tissues) **b)** Glutamine (in most tissues)
**c)** Alanin (in muscle) **d)** Both b & c

**Q2: Glutamine is converted into glutamate by:**

**a)** Glutamine synthetase **b)** Glutaminase
**c)** Glutamate dehydrogenase **d)** ALT

**Q3: Which one of the following is the rate limiting enzyme of urea cycle?**

**a)** Arginase **b)** CPSI
**c)** OCT **d)** Argininosuccinate Lyase

**Q4: What is the allosteric activator enzyme of urea?**

**a)** NAGS **b)** Carbaglue **c)** N-Acetylglutamate **d)** CPS1

**Q5: Which one of the following enzymes is X linked recessive**

**a)** Arginase **b)** OCT
**c)** NAGS **d)** Argininosuccinate synthase

**Q6: Which drugs work as activator for CPSI, can be used in case of hyperammonemia due to NAGS deficiency?**

**a)** Carglumic acid **b)** Buphenyl **c)** Sodium phenylacetate **d)** I.V. Arginine

## SAQs :

**Q1: What are the products of oxidative deamination reaction of glutamate?**
**Q2: Explain the steps of releasing ammonia from glutamine and alanine in the liver.**
**Q3: 35 y.o patient was diagnosed with hyperammonemia, which drugs he must avoid it?**
**Q4: How can Sodium phenylbutyrate (Buphenyl) treat hyperammonemia?**

★ **MCQs Answer key:**

1) D 2) B 3) B 4)A 5) B 6) A

★ **SAQs Answer key:**

1) $NH_3$ "ammonia", a-ketoglutarate and NADH "NADPH".

2) Glutamine is converted into glutamate by **glutaminase**. Alanine will give its amino group to a-ketoglutarate to form glutamate by **ALT**. Glutamate is converted into a-ketoglutarate and releasing $NH_3$ by **glutamate dehydrogenase**.

3) Valproic acid and glucocorticoids.

4) It's a prodrug that converted to phenylacetate. Phenylacetate then condenses with glutamine (in blood) forming phenylacetylglutamine that is excreted in urine. (scavenge ammonia by creating an alternate pathway)

# Team members

**Girls Team:**

- Ajeed Al-Rashoud
- Alwateen Albalawi
- Amira AlDakhilallah
- Arwa Al Emam
- Deema Almaziad
- Ghaliah Alnufaei
- Haifa Alwaily
- Leena Alnassar
- Lama Aldakhil
- Lamiss Alzahrani
- **Nouf Alhumaidhi**
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- Sarah Alkhalife
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**Boys Team:**

- Abdulrahman Bedaiwi
- Alkassem Binobaid
- Khayyal Alderaan
- Mashal Abaalkhail
- Naif Alsolais
- Omar Alyabis
- Omar Saeed
- Omar Odeh
- Rayyan Almousa
- Yazen Bajeaifer

# Team Leaders

Lina Alosaimi

Mohannad Alqarni

★ Do something today that your future self will thank you for


We hear you