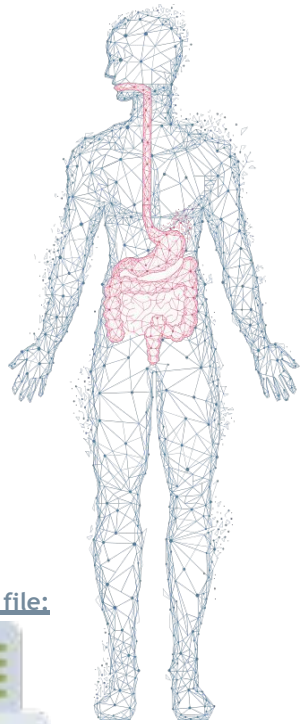
L10:

Urea Cycle

GNT Block



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- Extra notes

Editing file:

Objectives:

- Understand the reactions for removal of α- 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 urea as the major form for the disposal of amino groups derived from amino acids.
- Identify the causes (hereditary & acquired), clinical manifestations and management of hyperammonemia.

Lecture presented by :

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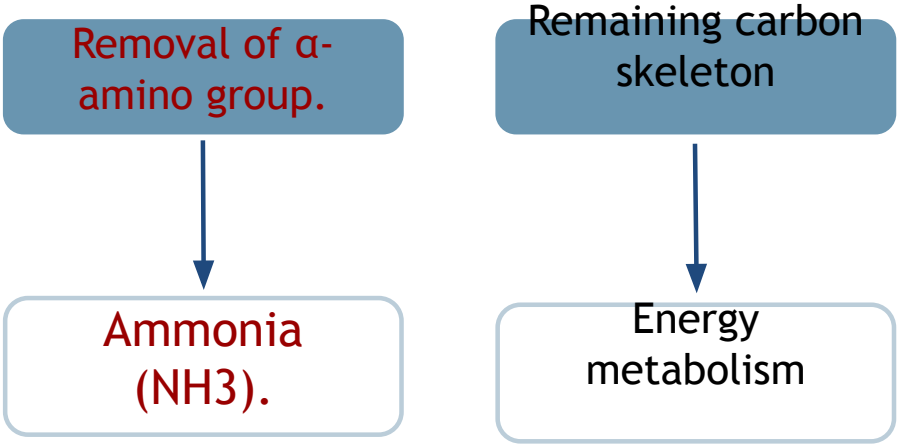
Background

- 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, Formation of Ammonia and Its transport to liver

A) Removal of α-amino group of amino acids and formation of ammonia:

1-Transamination to **Glutamate.**

2-Oxidative deamination of **Glutamate**

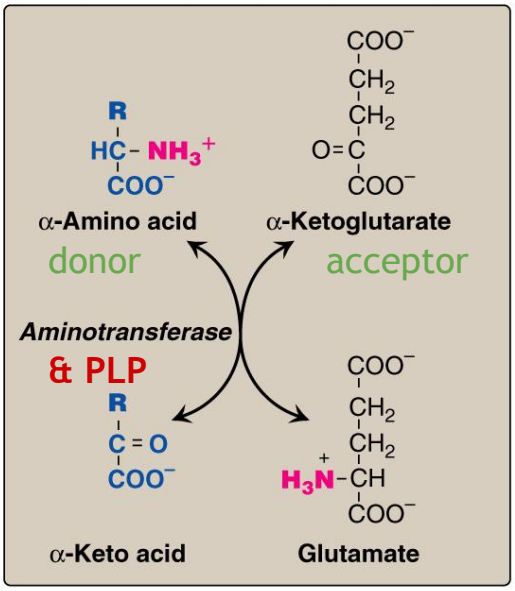
B) Blood Transport of Ammonia into liver:

1-In the form of **Glutamine** (most tissue).

2-In the form of **Alanine** (muscle).

Step1: Removal of α- amino Group

A — Transamination to Glutamate

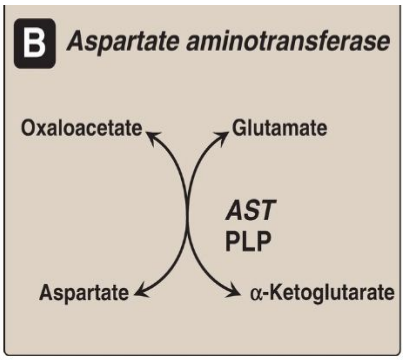


-Amino groups of amino acids are **funneled** "Transmitted" to glutamate by transamination reactions with α-ketoglutarate.
- (**why** to glutamate?) **Glutamate** is unique. it is the only amino acid that undergoes **rapid oxidative deamination**
-Several types of amino acids donate their NH3 group to α-ketoglutarate.
-The enzyme of this process will be named after the donor amino acid (AA) with the suffIx- Aminotransferase + PLP.
-The products will be Glutamate + α- keto acid "this product depend on the AA that entered the reaction.

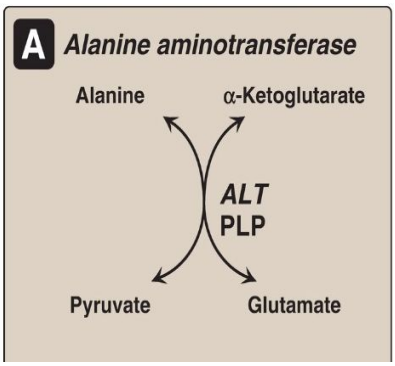
PLP: pyridoxal phosphate a coenzyme that is derived from vitamin B6.

Examples :

most famous



Transamination by AST

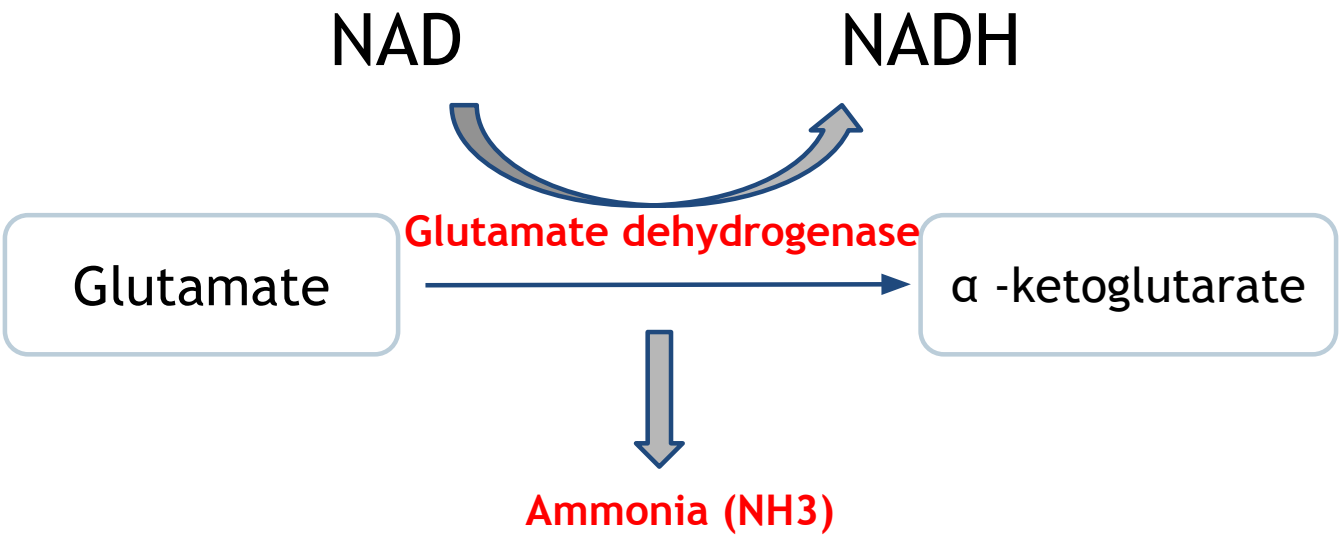


Transamination by ALT

The reaction is **bidirectional**

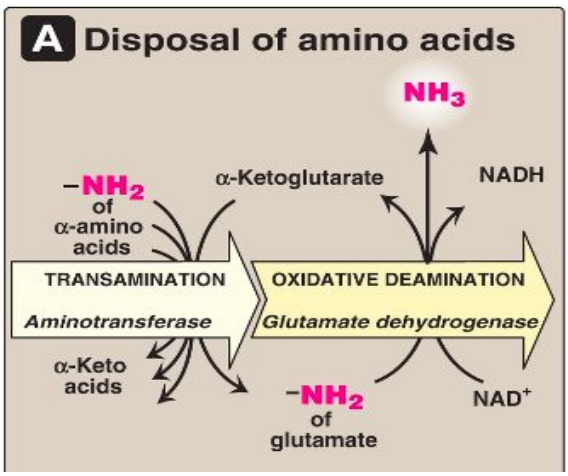
Step1: Removal of α- amino Group

B	Oxidative deamination to Glutamate :



Oxidative deamination of glutamate will release NH3 and regenerate α-ketoglutarate.

Summary:



Removal of α-amino group of amino acid & formation of ammonia.

Step2: Transport of NH3 From Peripheral Tissues Into the Liver

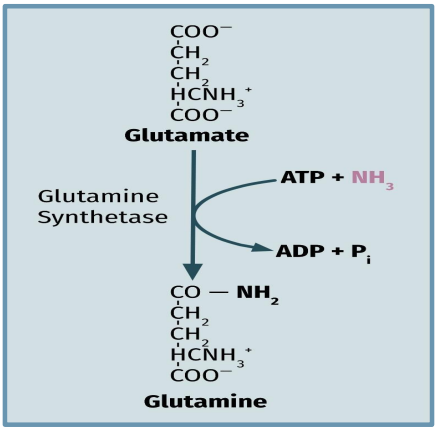
1) Ammonia is produced by all tissues and the main disposal is via formation of urea in liver

2) Blood level of NH3 must be kept **very low**, otherwise, hyperammonemia and CNS toxicity will occur (NH3 is toxic to CNS).

3) To solve this problem, NH3 is transported from peripheral tissues to the liver via formation of Glutamine (most tissues) & Alanine (muscle).

Peripheral tissues

NH3 is transported into the liver through forming **Glutamine** by **Glutamine synthetase**



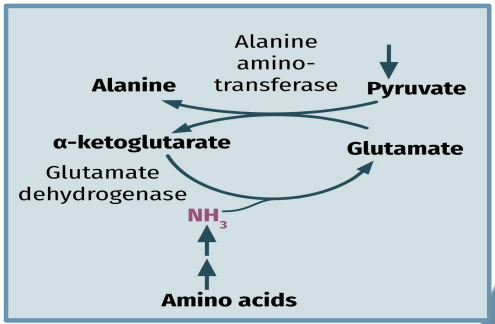
VS

Muscles

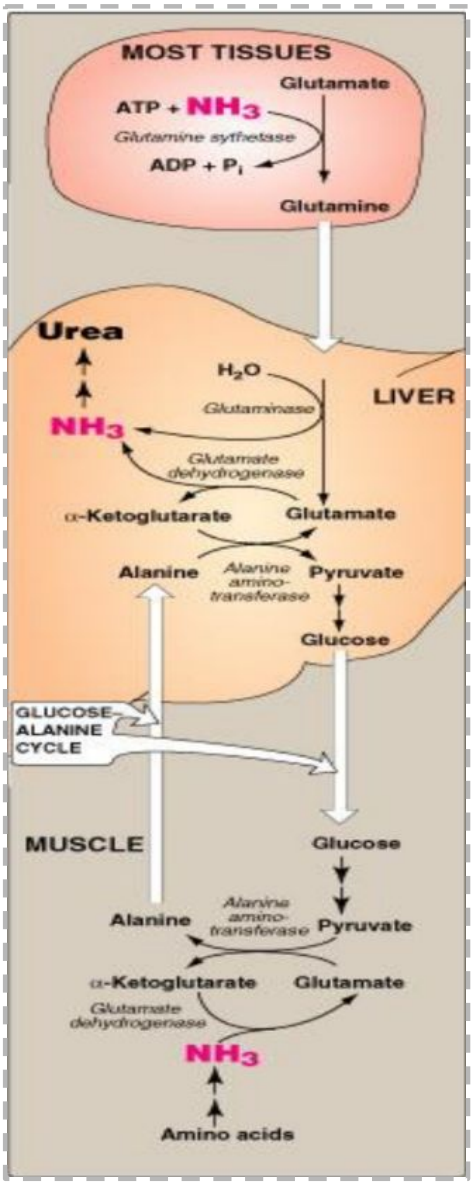
-First NH3 will be transferred into α-ketoglutarate to form glutamate

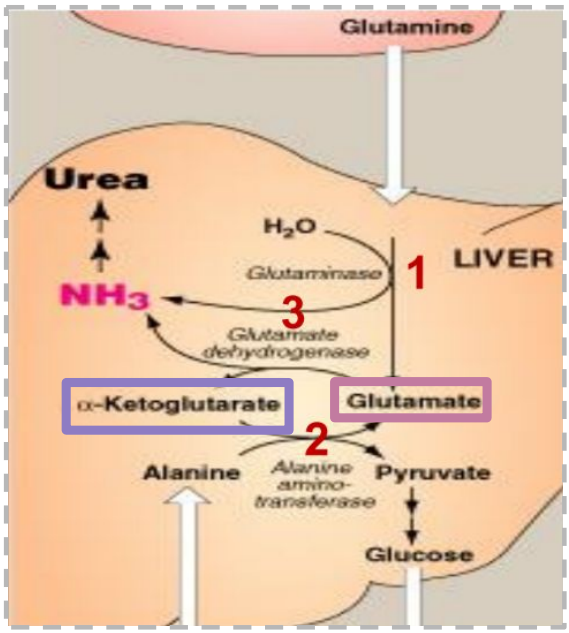
-Then, Glutamate will give its amino group to pyruvate to form alanine by **ALT.**

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



Step 3: Release of NH3 from Glutamine & Alanine in the Liver





In The Liver

-Both Glutamine & Alanine will form Glutamate.
-Glutamate will be converted to α-ketoglutarate and release **NH3 in liver**.

Important

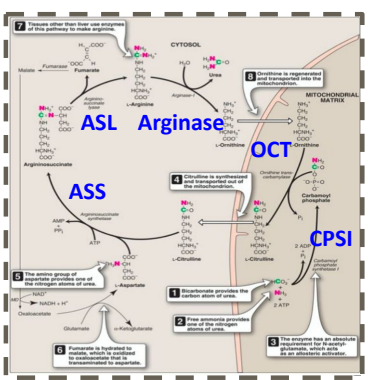
Glutamine	Converted into Glutamate by **Glutaminase**.
Alanine	Will give its amino group to α-ketoglutarate to form Glutamate by **ALT**
Glutamate	Is converted into α-ketoglutarate and releasing NH3 by **Glutamate Dehydrogenase**.

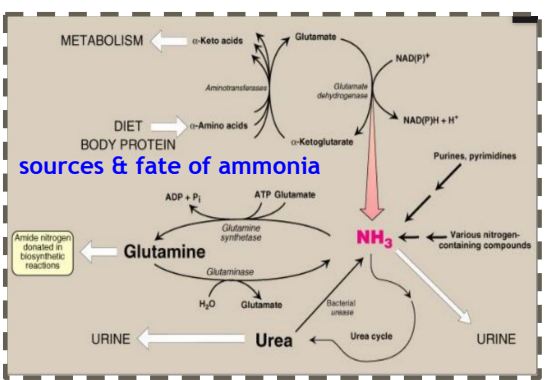
Step 4 : Urea cycle

Urea is the major form for disposal of amino groups derived from amino acids.
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

The Five enzymes of urea cycle "**Important**"

Enzyme	Reaction
1- Carbamoyl phosphate synthetase I (CPSI)	CO2 + NH3→Carbamoyl phosphate
2- Ornithine transcarbamoylase (OCT) Most mutated  Remember October	Carbamoyl phosphate +ornithine→Citrulline
3- Argininosuccinate synthase (ASS)	Citrulline + Aspartate→Argininosuccinate
4- Argininosuccinate lyase (ASL)	Argininosuccinate→ Fumarate + Arginine
5- Arginase Unique to liver only, regenerates Ornithine	Arginine → Ornithine + urea

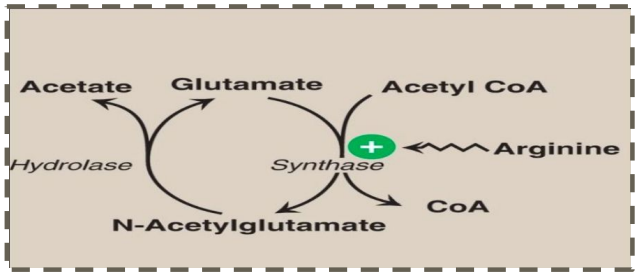




Normal blood level of ammonia: 5 - 50 µmol/L

Step 4 : Urea cycle

Regulation of Urea cycle

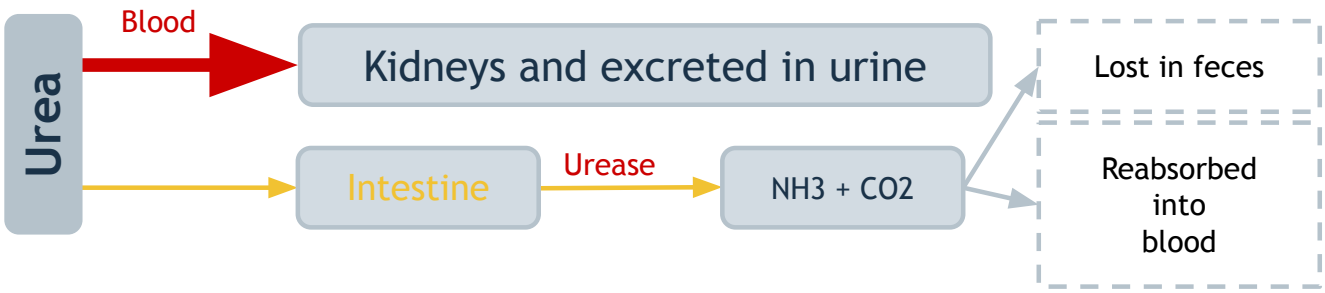


Important

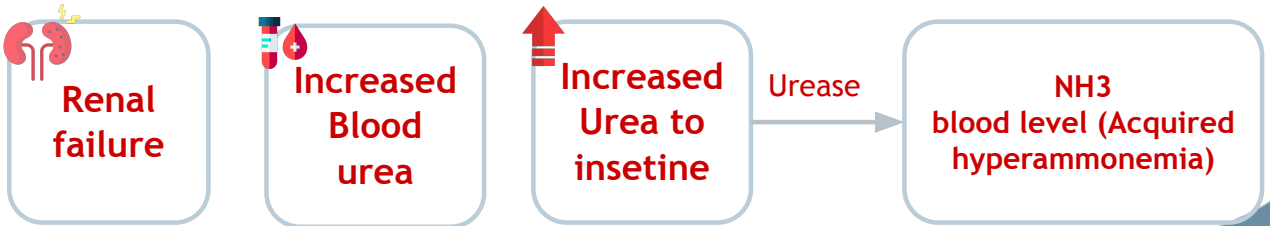
Rate-limiting enzyme of urea cycle	**Carbamoyl phosphate synthetase I** (CPSI)
Allosteric activator of (CPSI)	**N-Acetylglutamate** ↑ from protein intake & catabolism ⟶ ↑ CPSI activity
N-Acetylglutamate is synthesized by:	**N-Acetylglutamate synthetase (NAGS) in presence of arginine.** Remember Nuggets
NAGS deficiency is efficiently treated with:	**Carbaglu**, a CPS1 activator.

Fate of urea

the big arrow indicates the major pathway



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

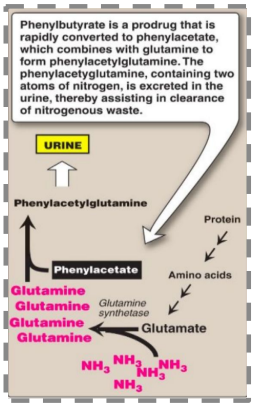


Hyperammonemia

<table>
<tr><td rowspan="3">Etiology</td><td rowspan="2">Acquired</td><td>1.Liver Disease</td><td>- Acute: Viral hepatitis or hepatotoxic.
- Chronic: Cirrhosis by hepatitis or alcoholism</td></tr>
<tr><td>2.Renal failure
*Important</td><td>Renal failure → ↑Blood urea → ↑Urea in the intestine → Activation of Bacterial Urease enzyme (break down urea into CO2 +NH3) → ↑NH3 (Hyperammonemia)</td></tr>
<tr><td>Inherited</td><td>Genetic deficiency
Genetic deficiencies of any of the 5 enzymes of urea cycle or the activator enzyme for CPSI:
CPSI, OTC, ASS, ASL, arginase or NAGS</td><td>Ornithine transcarbamoylase deficiency (OCT) :
X-linked recessive
most common congenital hyperammonemia, marked decrease of citrulline and arginine.

others : autosomal recessive</td></tr>
<tr><td>Clinical Presentation</td><td colspan="3">• Tremors
• Convulsions
• Coma and death
• Vomiting and cerebral edema
• Lethargy and somnolence</td></tr>
<tr><td>Management</td><td colspan="3">1. Protein restriction.
2. Volume repletion to maintain renal function
(Use 10% dextrose in water but limit the use of normal saline).
3. Ammonia removal by hemodialysis &/or drugs.
4. Avoid drugs that increase protein catabolism (eg, glucocorticoids) or inhibit urea synthesis (eg, valproic acid), or have direct hepatotoxicity.</td></tr>
</table>

Treatment of Hyperammonemia

Drugs that scavenge ammonia by creating an alternate pathway to excrete N2-precursors	1. I.V. Sodium phenylacetate & sodium benzoate (**Ammonul**)
	2. Oral sodium phenylbutyrate (Buphenyl). -Prodrug that is converted to phenylacetate -Phenylacetate condenses with Glutamine forming phenylacetylglutamine that is excreted in urine. it bypasses the liver by binding to glutamine turning it to phenylacetylglutamine to be excreted in urine, making it a great drug in case of liver cirrosis. **Important** 
	3. I.V. Arginine: for all UCDs (urea cycle enzyme deficiency) except UCD due to arginase deficiency which is the enzyme that act on arginine, so deficiency in this enzyme will lead to accumulation of arginine in blood (439) (argininemia).
Activators to CPSI (Carglumic acid "Carbaglu")	For hyperammonemia due to NAGS deficiency

Quiz

MCQs

Q1: one nitrogen of urea is from NH3 & the other is from ? from female Dr.
A- Arginine
B- glutamine
C- glycine
D- aspartate

Q2: which of the following is a Urea cycle enzyme?
A- Carbamoyl phosphate synthetase I (CPSI)
B- Ornithine transcarbamoylase (OCT)
C- Argininosuccinate synthase (ASS)
D- all the above

Q3: A unique amino acid that undergoes rapid oxidative deamination is_____
A- Alanine
B- α- ketoglutarate.
C- Aspartate
D- Glutamate

Q4: what enzyme genetic deficiency is X-linked? from female Dr
A- Carbamoyl phosphate synthetase I (CPSI)
B- Ornithine transcarbamoylase (OCT)
C- Argininosuccinate synthase (ASS)
D- Arginase

Q5: Glutamate is converted into α-ketoglutarate via:
A- Glutamate dehydrogenase.
B- Aminotransferase
C- Aspartate aminotransferase.
D- Glutamine synthetase.

Q6:which of the following considered an acquired cause of hyperammonemia?
A- liver disease
B- renal failure
C- genetic deficiency of OCT
D- A and B

Answers:Q1:D|Q2:D|Q3:D|Q4:B|Q5:A|Q6:D

SAQ

Q: how does sodium phenyl butyrate (Buphenyl) aid in excreting ammonia/nitrogen in patients with liver disease? from female Dr.

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