



Urea Cycle

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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

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 \longrightarrow **Ammonia (NH₃)**

Remaining carbon skeleton \longrightarrow **Energy metabolism**

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**

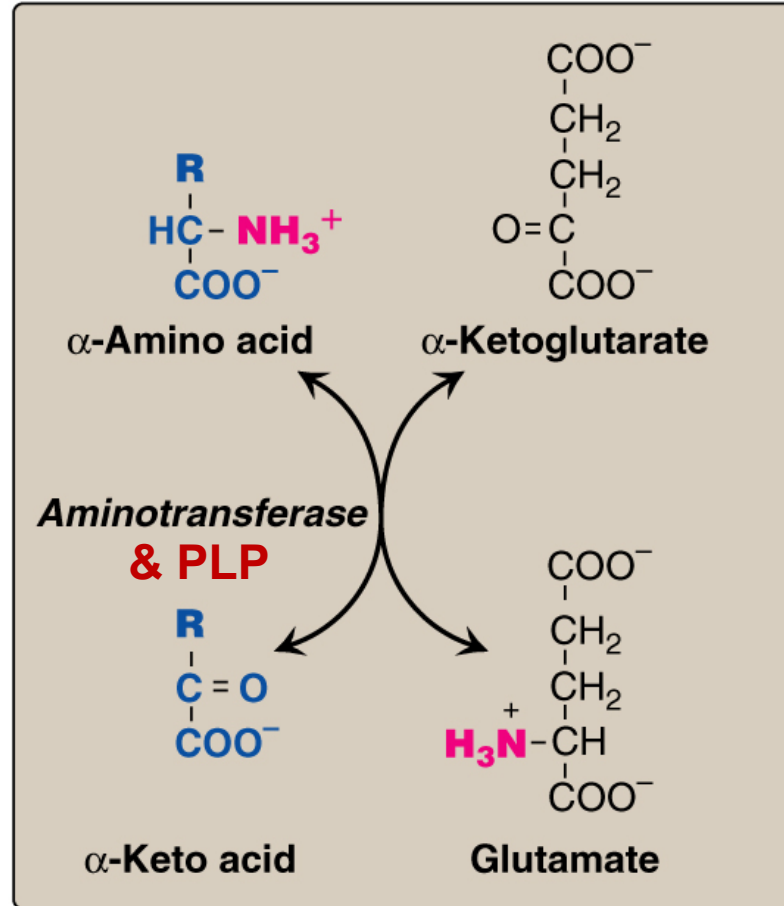
B: Blood transport of ammonia into liver:

- 1. in the form of glutamine (most tissue)**
- 2. in the form of alanine (muscle)**

A: Removal of α -amino group & formation of ammonia

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

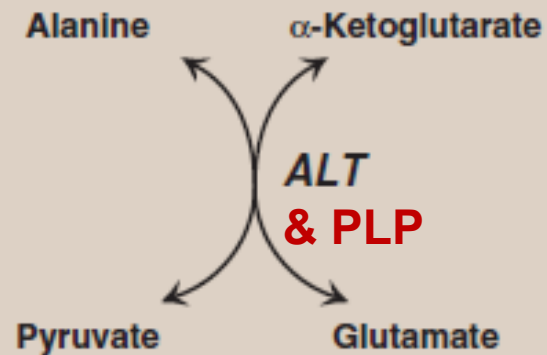
Transamination



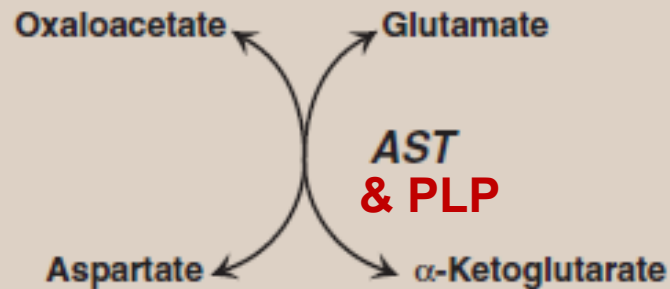
PLP: Pyridoxal phosphate, a co-enzyme that is derived from vitamin B6

Transamination by ALT & AST

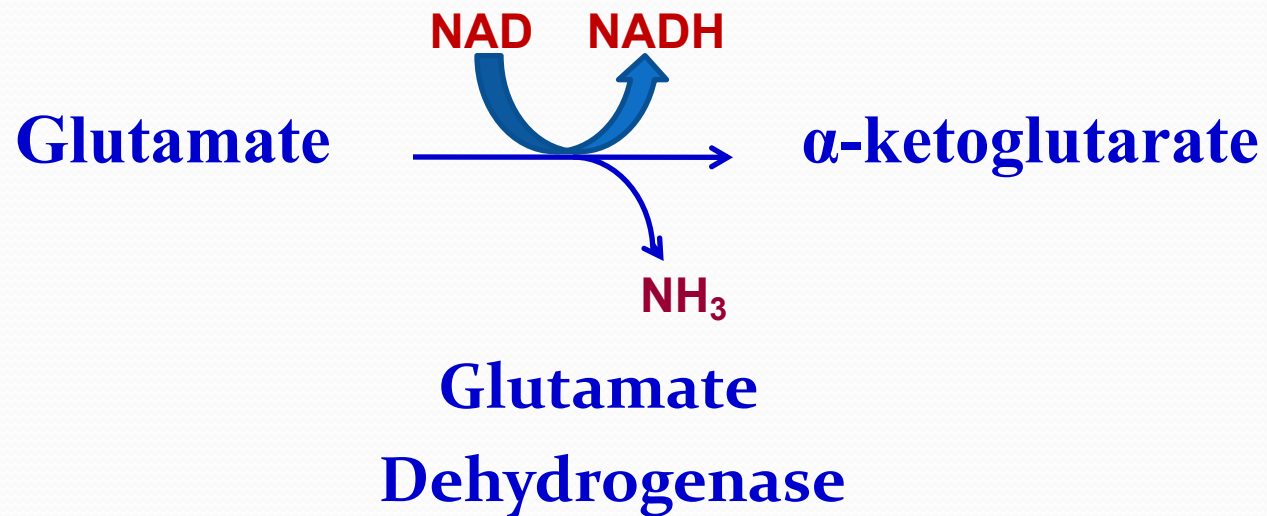
A Alanine aminotransferase



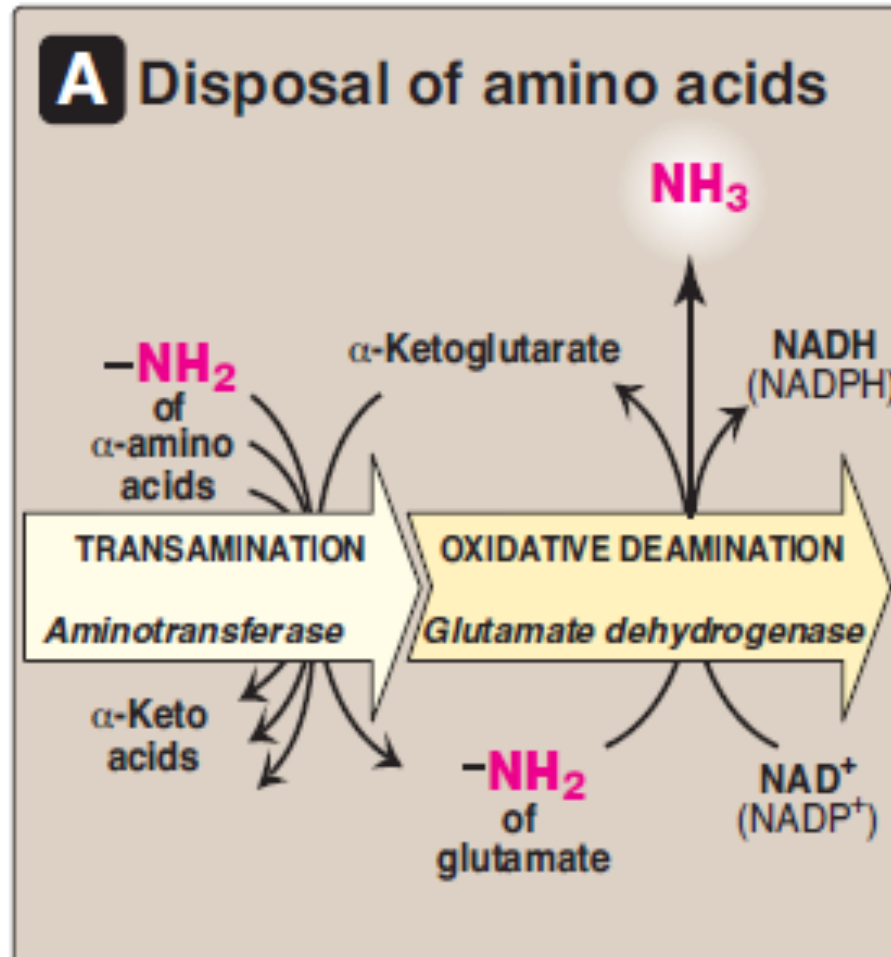
B Aspartate aminotransferase



Oxidative Deamination



Summary: Removal of α -amino group of amino acid & formation of ammonia



B: Transport of NH_3 from peripheral tissues into the liver

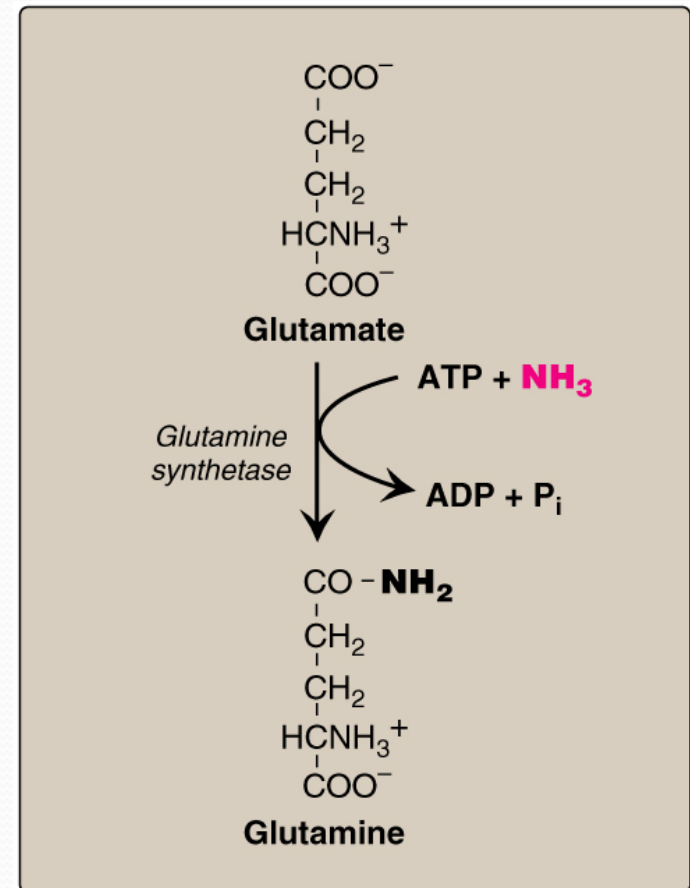
- **Ammonia is produced by all tissues and the main disposal is via formation of urea in liver**
- **Blood level of NH_3 must be kept very low, otherwise, hyperammonemia and CNS toxicity will occur (NH_3 is toxic to CNS)**
- **To solve this problem, NH_3 is transported from peripheral tissues to the liver via formation of:**
 - Glutamine (most tissues)**
 - Alanine (muscle)**

Transport of NH_3 from peripheral tissues into the liver

Cont'D

From most peripheral tissues:

NH_3 is transported into the liver through forming glutamine by glutamine synthetase



Transport of NH_3 from peripheral tissues into the liver

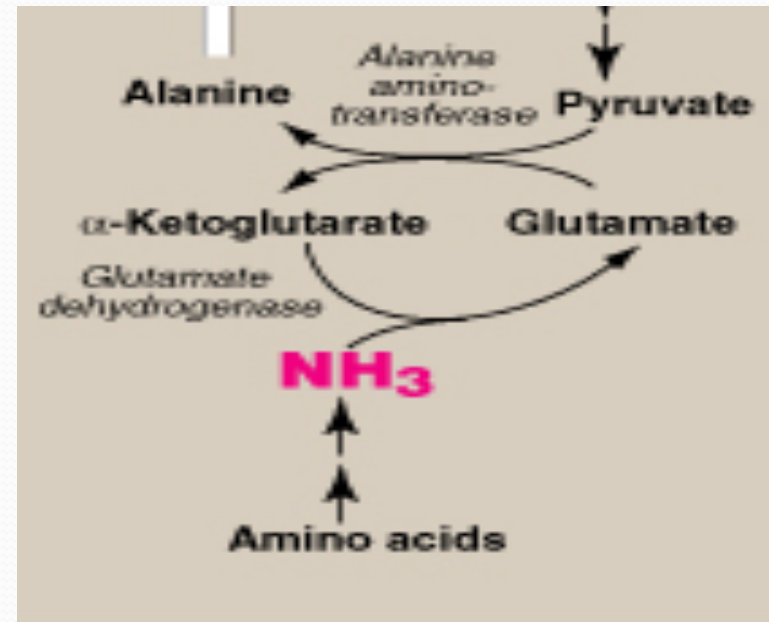
Cont'D

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**

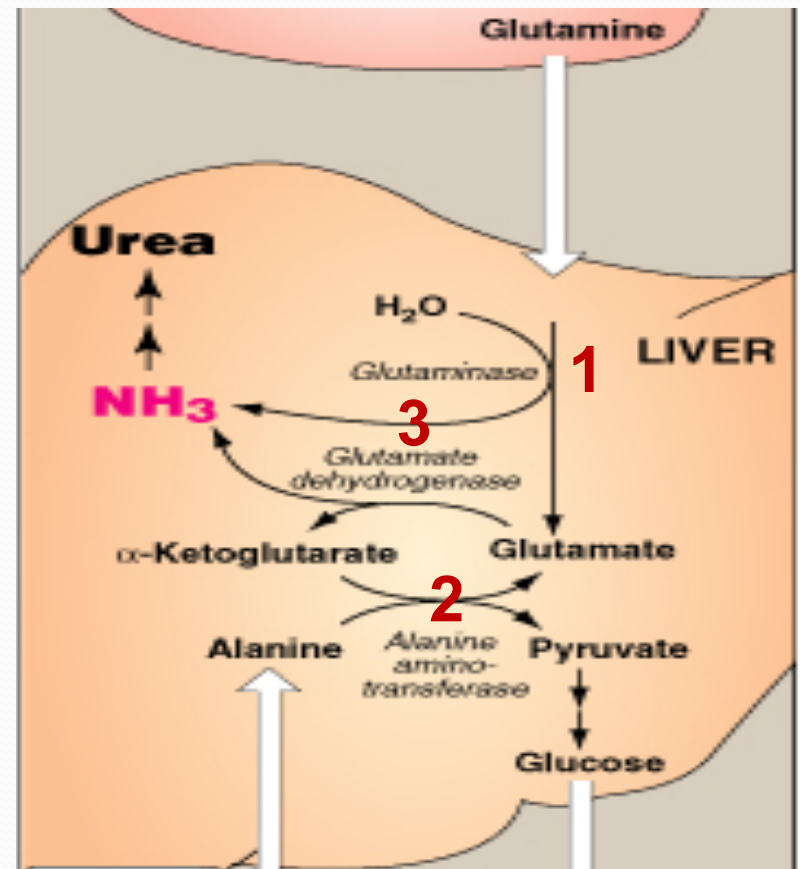
Therefore, NH_3 is transported from muscle into the liver through forming **alanine**



Release of ammonia from glutamine and alanine in the liver

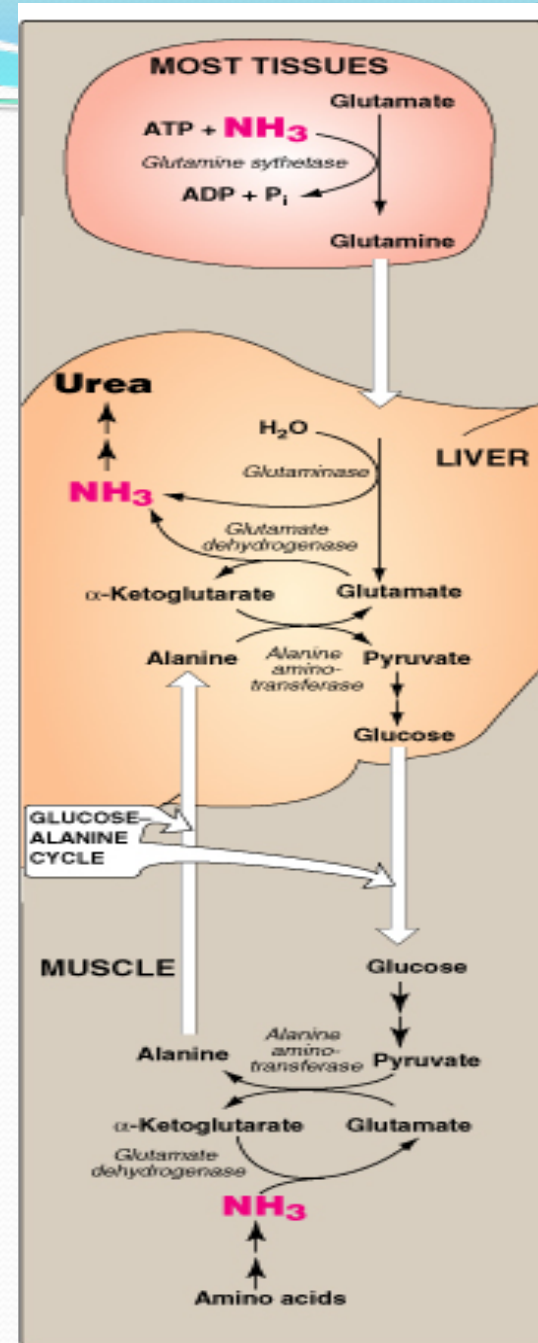
In the Liver:

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



Summary

Blood transport of NH_3 from peripheral tissues (in the form of glutamine and alanine) into the liver and the release of NH_3 back in the liver to start the urea cycle



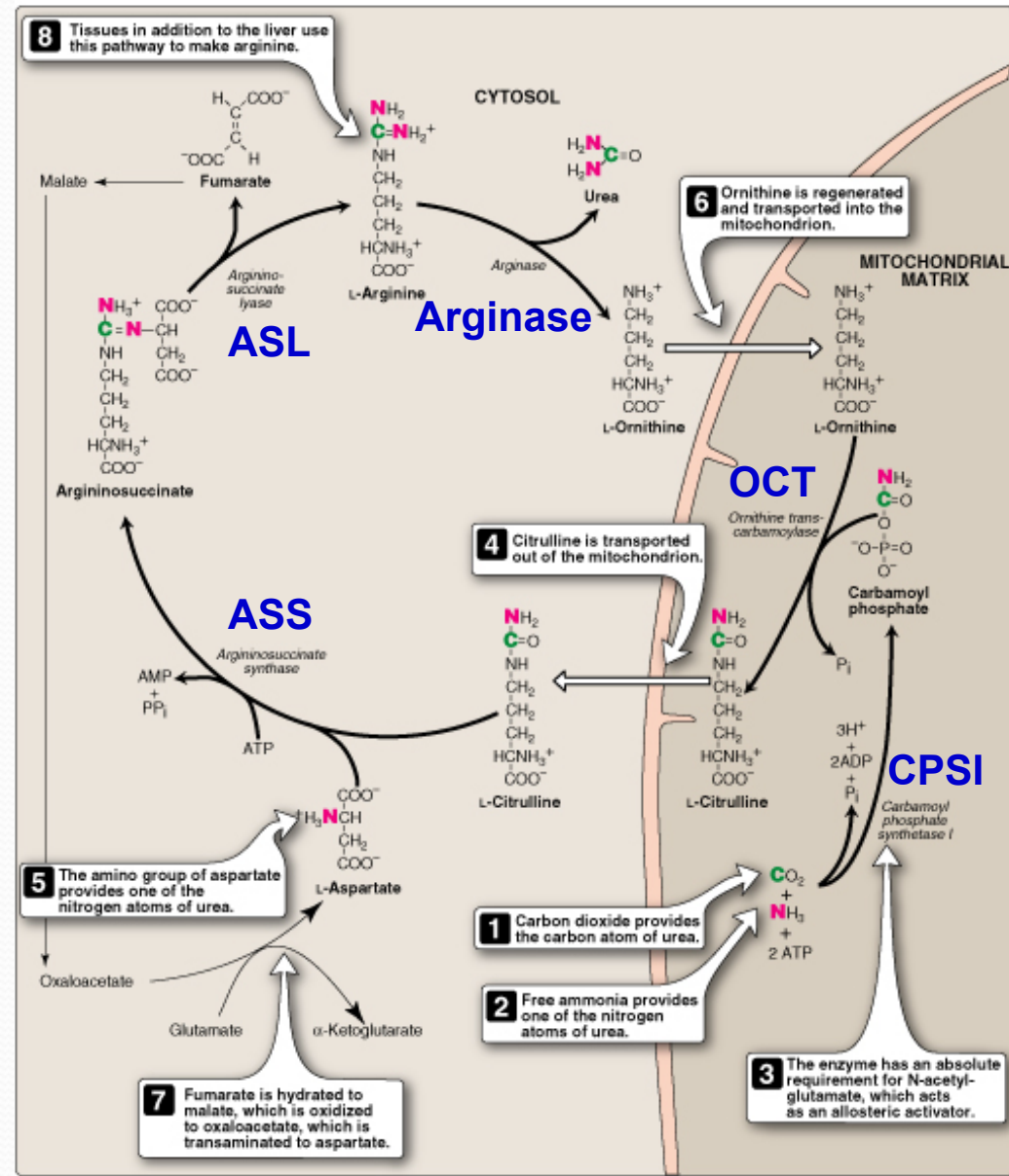
Urea Cycle

- 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 NH_3 and the other nitrogen from aspartate
- Urea is transported in the blood to the kidneys for excretion in urine

Urea Cycle

CONT'D

- The five enzymes of urea cycle:
- Carbamoyl phosphate synthetase I
 - Ornithine transcarbamoylase (OCT)
 - Argininosuccinate synthase
 - Argininosuccinate lyase
 - Arginase



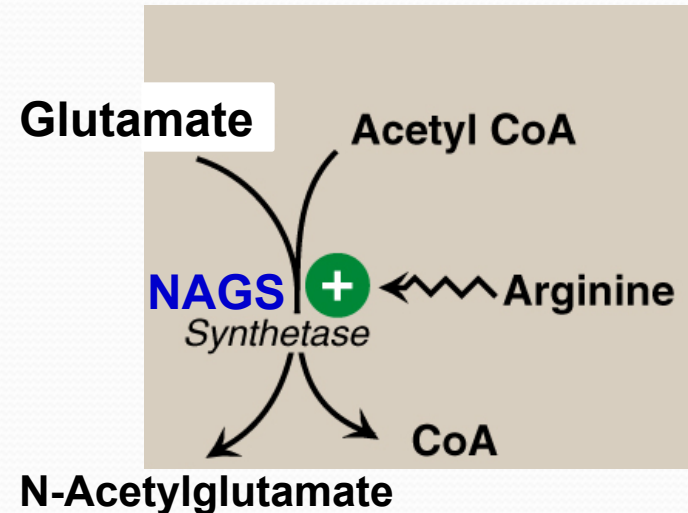
Urea Cycle: Regulation

Rate-limiting enzyme of urea cycle:
Carbamoyl phosphate synthetase I
(CPSI)

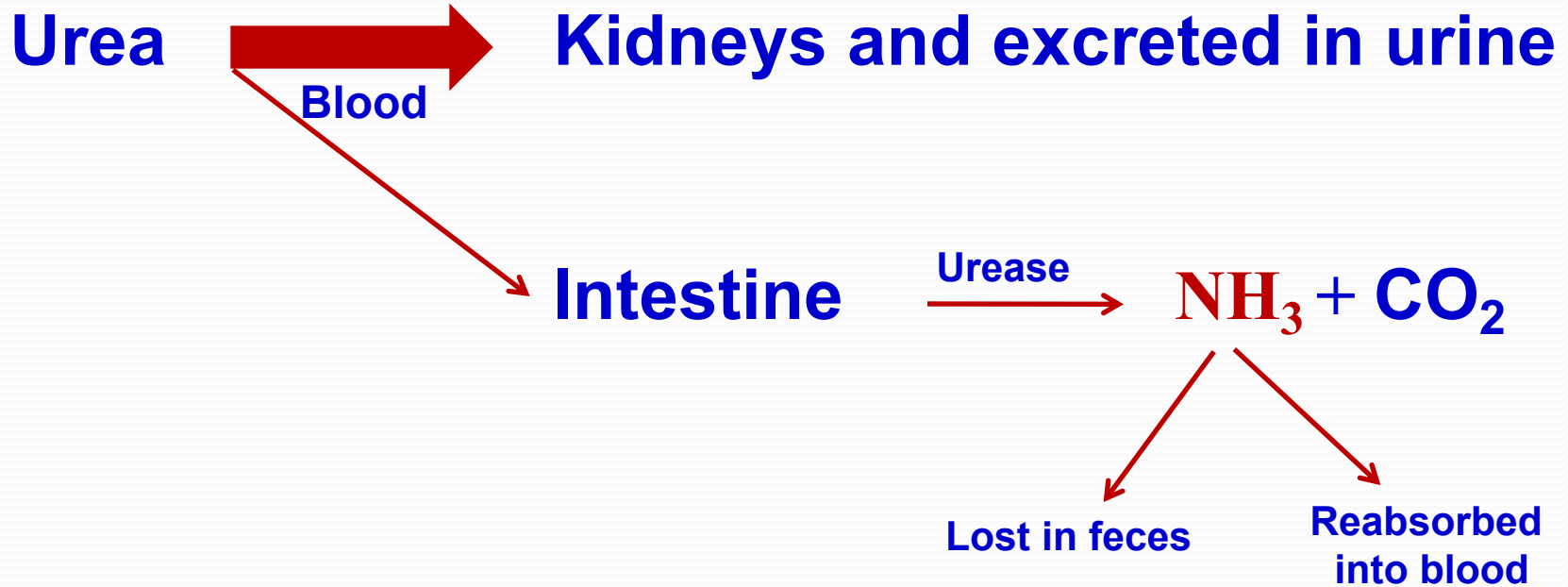
Allosteric activator of CPSI:
N-Acetylglutamate

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

NAGS deficiency is efficiently treated
with Carbaglu, a CPS1 activator



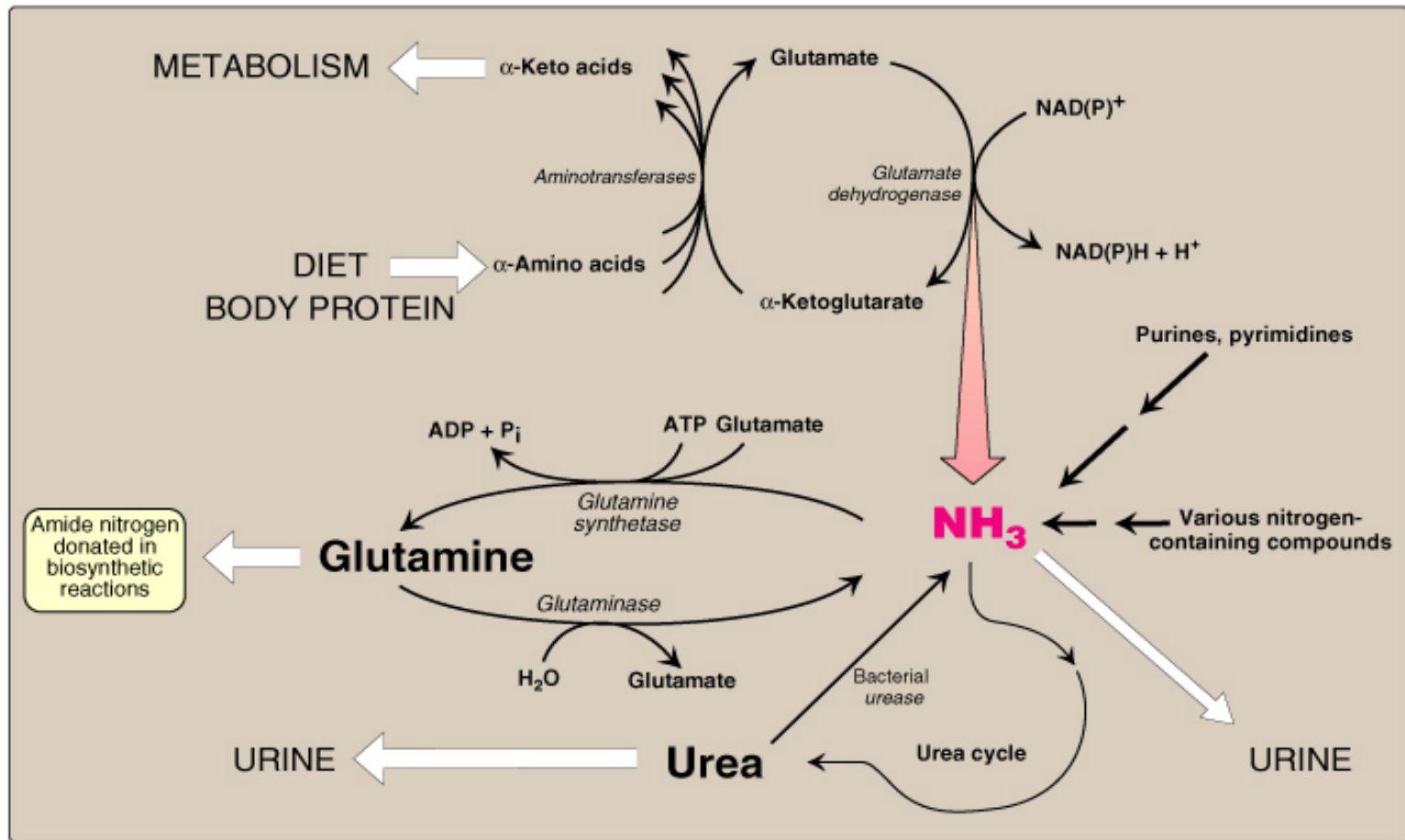
Fate of Urea



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



Sources and Fates of Ammonia



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

➤ 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

Inherited Hyperammonemia

- **Ornithine transcarbamoylase deficiency:**
 - X-linked recessive**
 - 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**

Management of Hyperammonemia

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

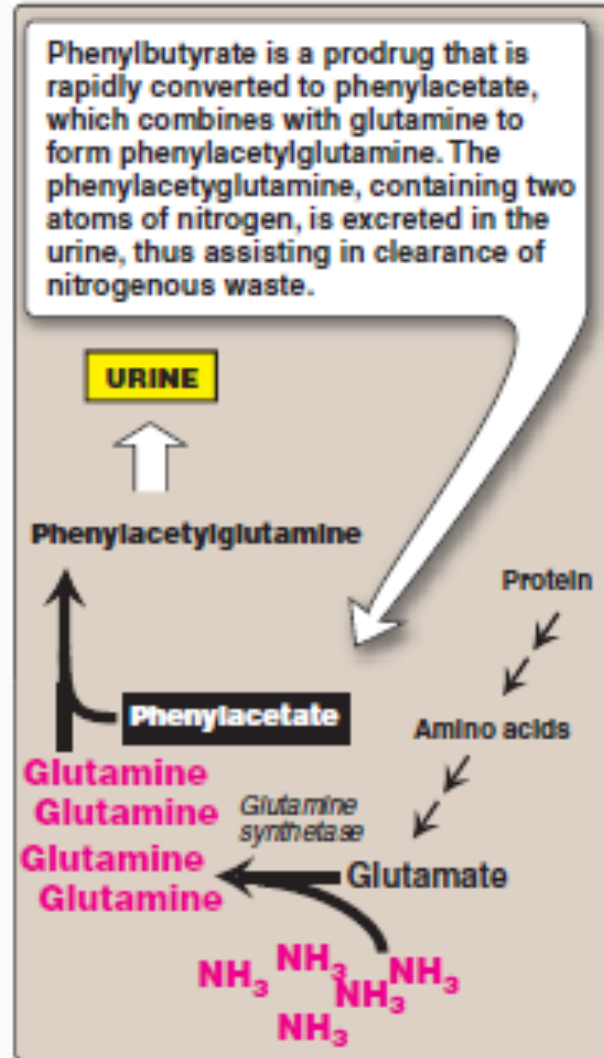
Drug Treatment of Hyperammonemia

- A. Drugs that scavenge ammonia by creating an alternate pathway to excrete N_2 - precursors:**
- 1. I.V. Sodium phenylacetate & sodium benzoate (Ammonul)**
 - 2. Oral sodium phenyl butyrate (Buphenyl)**
 - 3. I.V. Arginine: for all UCDs except UCD due to arginase deficiency (argininemia)**
- B. Activators to CPSI (Carglumic acid “Carbaglu”):
For hyperammonemia due to NAGS deficiency**

Sodium phenyl butyrate (Buphenyl)

Sodium phenyl butyrate (Buphenyl):
Prodrug that is converted to
phenylacetate.

Phenylacetate condenses with
glutamine forming phenylacetylglutamine
that is excreted in urine



References

- Lippincott's Illustrated Reviews in Biochemistry 6th Edition pages-253-258