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 ⟶ Ammonia (NH_3)

Remaining carbon skeleton ⟶ 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**

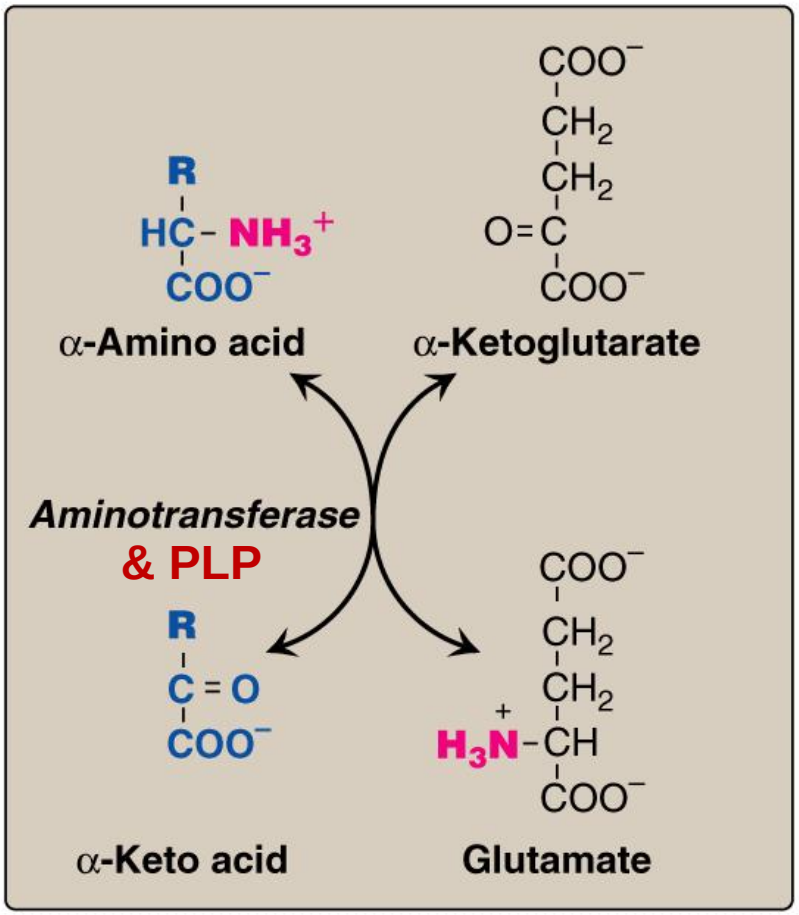
B: Blood transport of ammonia into liver:

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

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

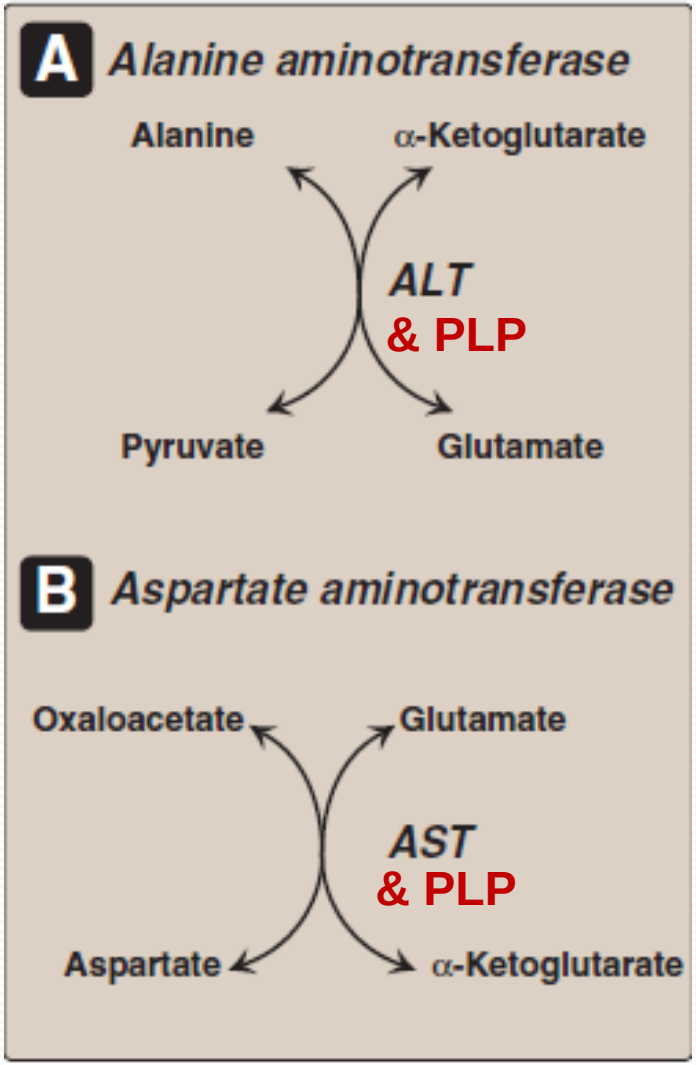
- **Amino groups of amino acids are funneled to glutamate (Why?) by transamination reactions with α-ketoglutarate**
- **Glutamate is unique. It is the only amino acid that undergoes rapid oxidative deamination**
- **Oxidative deamination of glutamate will release NH_3 and re-generate α-ketoglutarate**

Transamination

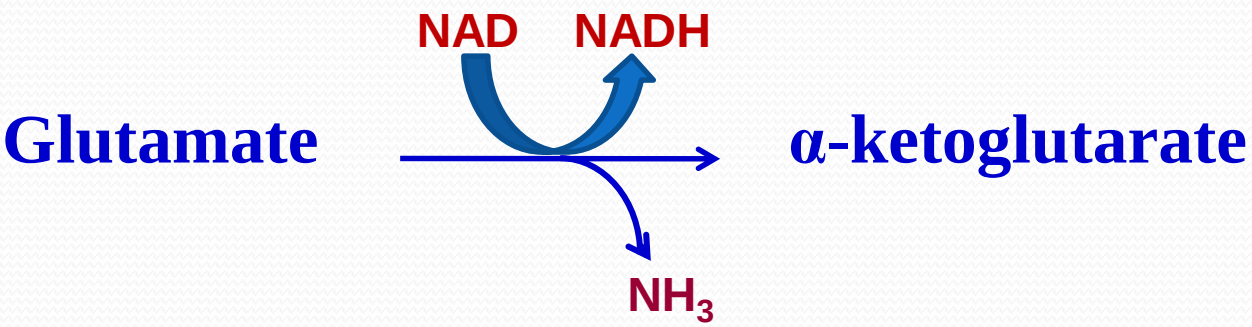


PLP: Pyridoxal phosphate, a co-enzyme that is derived from vitamin B6

Transamination by ALT & AST

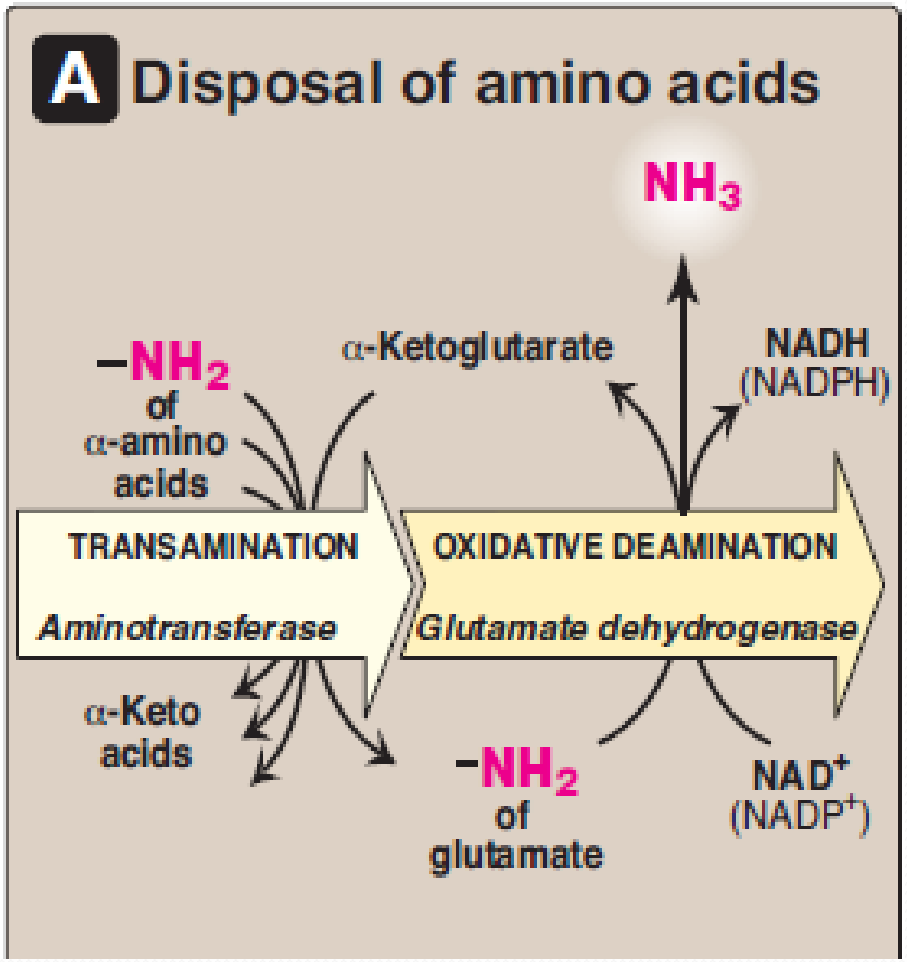


Oxidative Deamination



Glutamate Dehydrogenase

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)

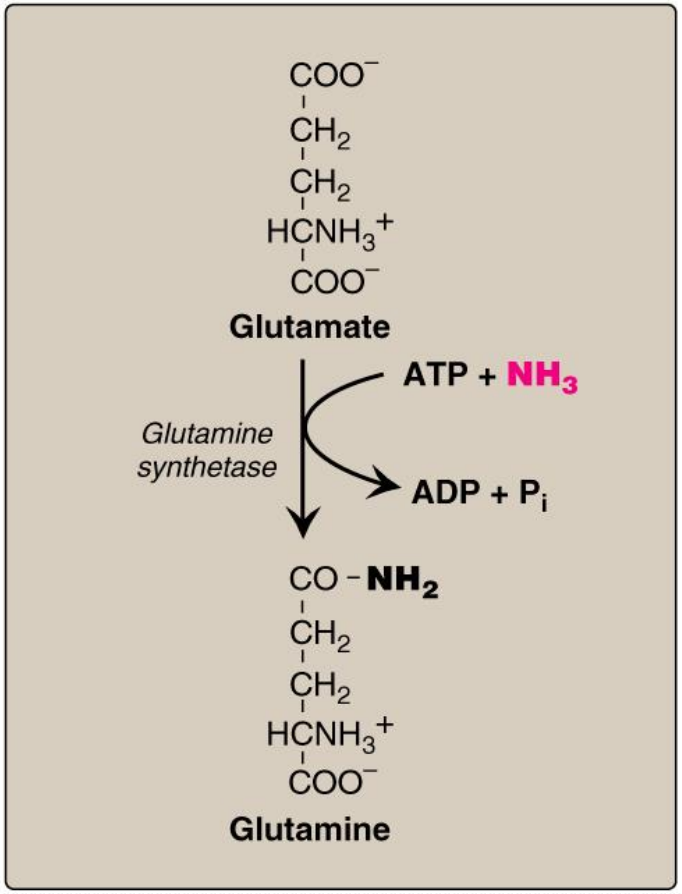
Alanine (muscle)

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



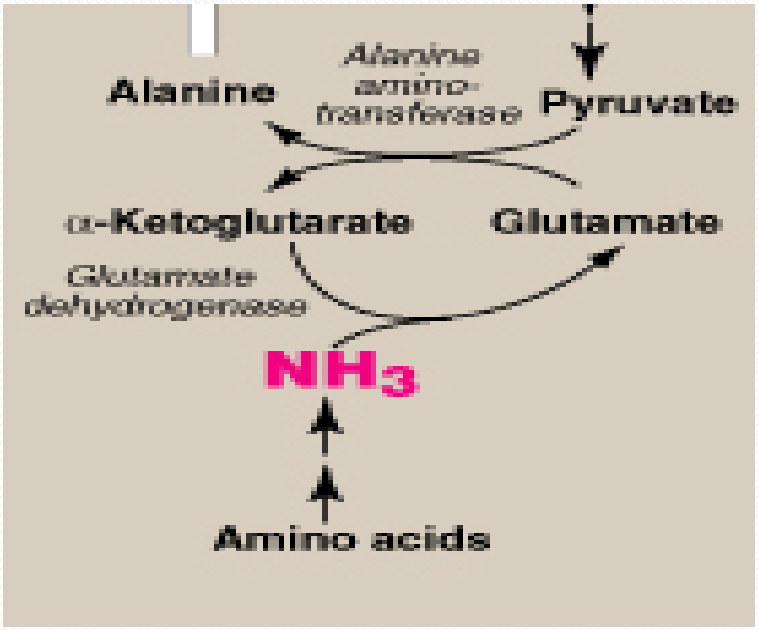
Transport of NH_3 from peripheral tissues into the liver Cont'D

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



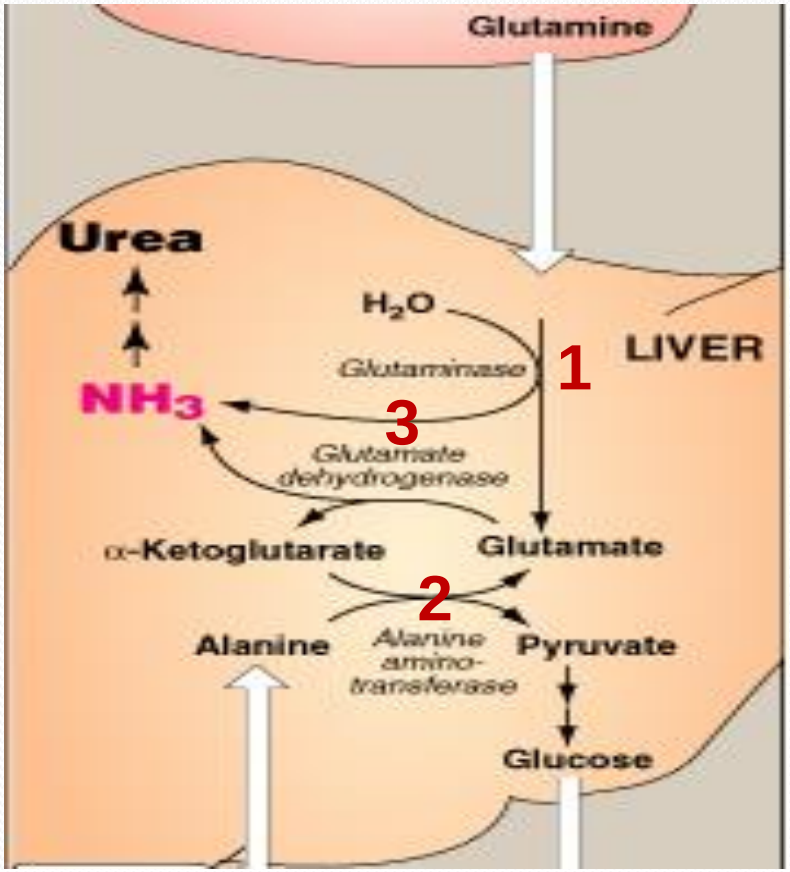
Release of ammonia from glutamine and alanine in the liver

In the Liver:

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

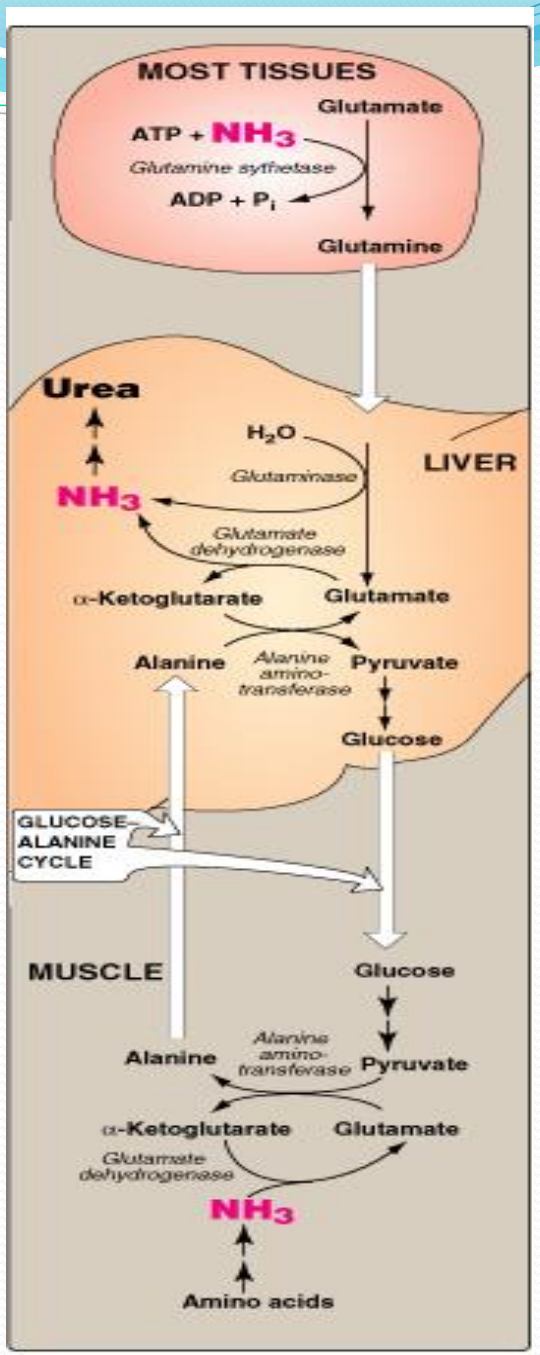
2. ***Alanine*** **will give its amino group to α-ketoglutarate to form glutamate by ALT.**

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:

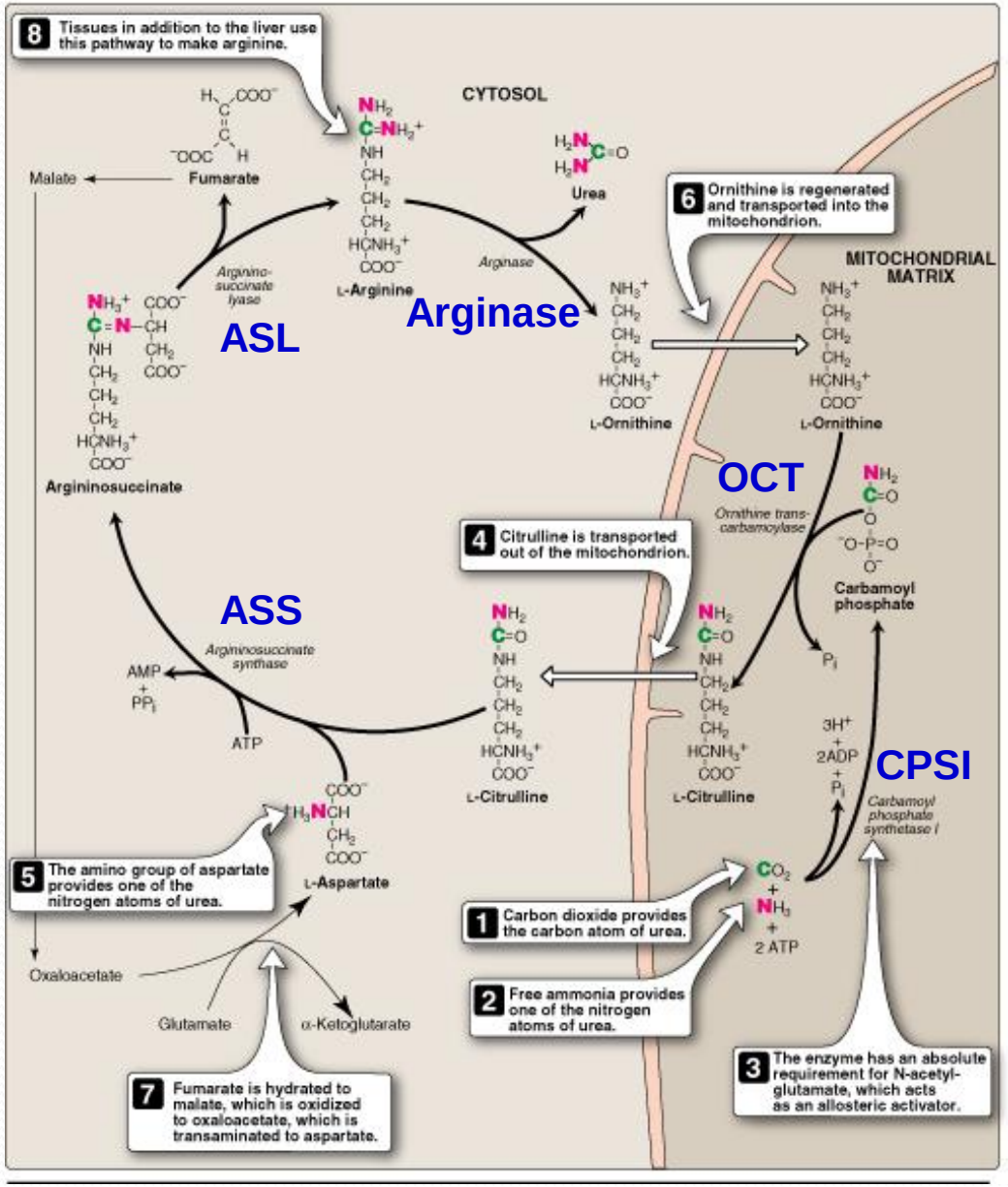
Carbamoyl phosphate synthetase I

Ornithine transcarbamoylase (OCT)

Argininosuccinate synthase

Argininosuccinate lyase

Arginase



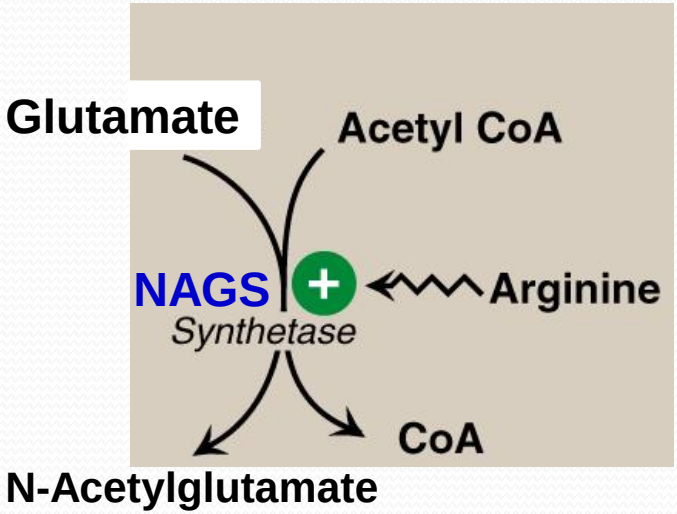
Urea Cycle: Regulation

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

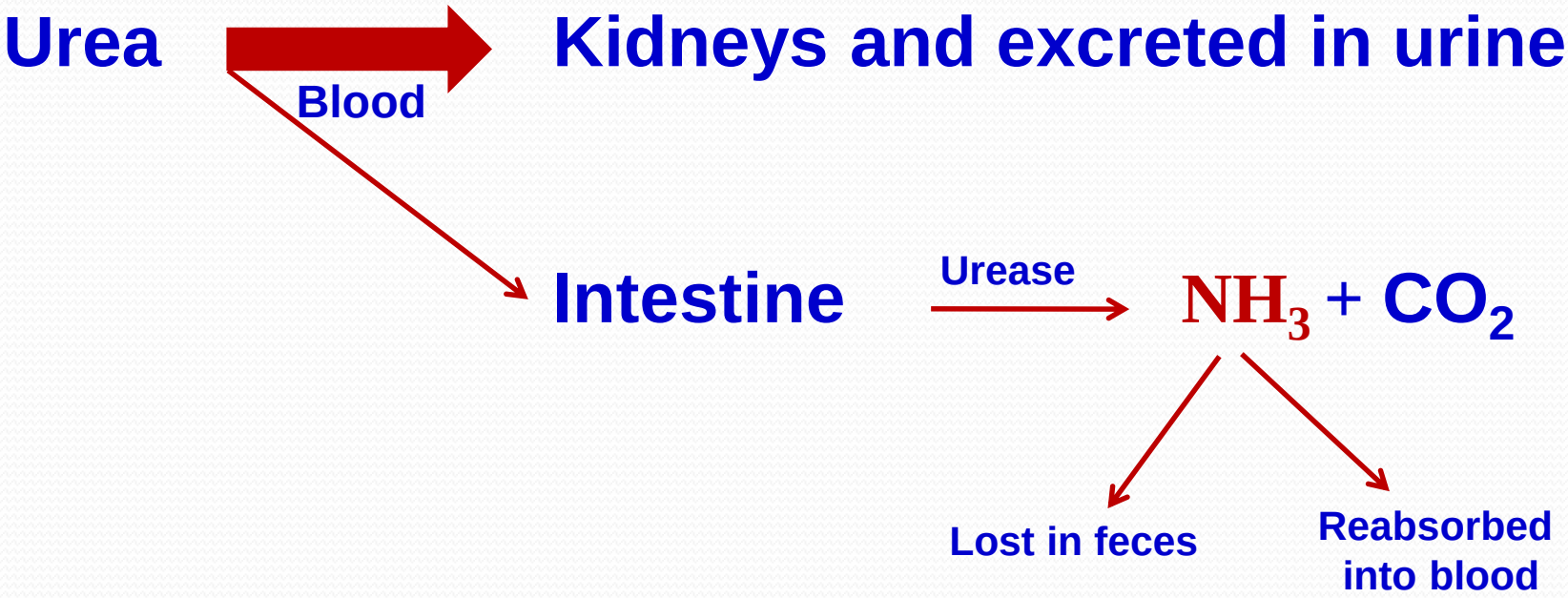
Allosteric activator of CPSI:
N-Acetylglutamate

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

NAGS deficiency is efficiently treated with Carbaglu, a CPS1 activator

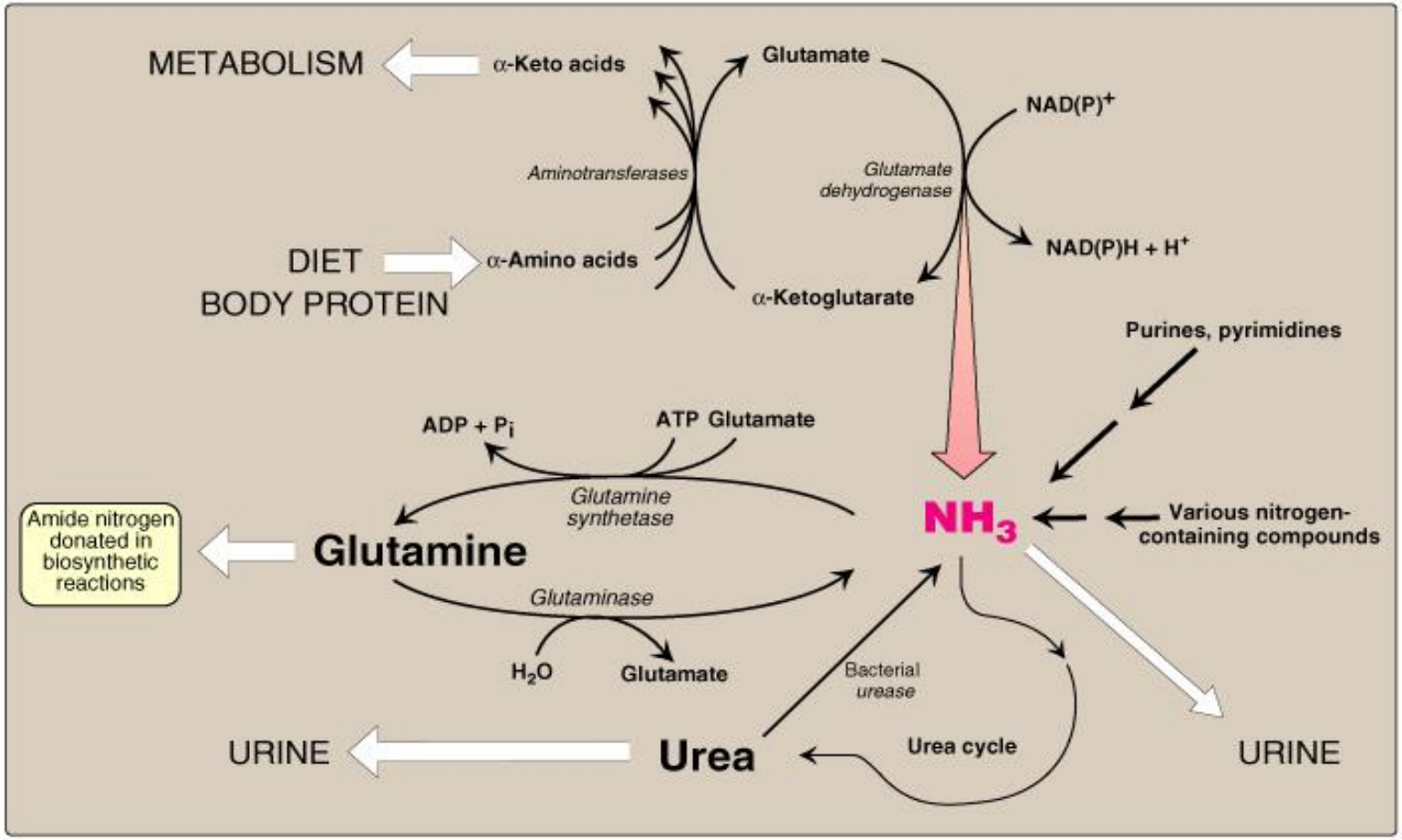


Fate of Urea



The action of intestinal urease to form NH_3 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 deficency:**
  - **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

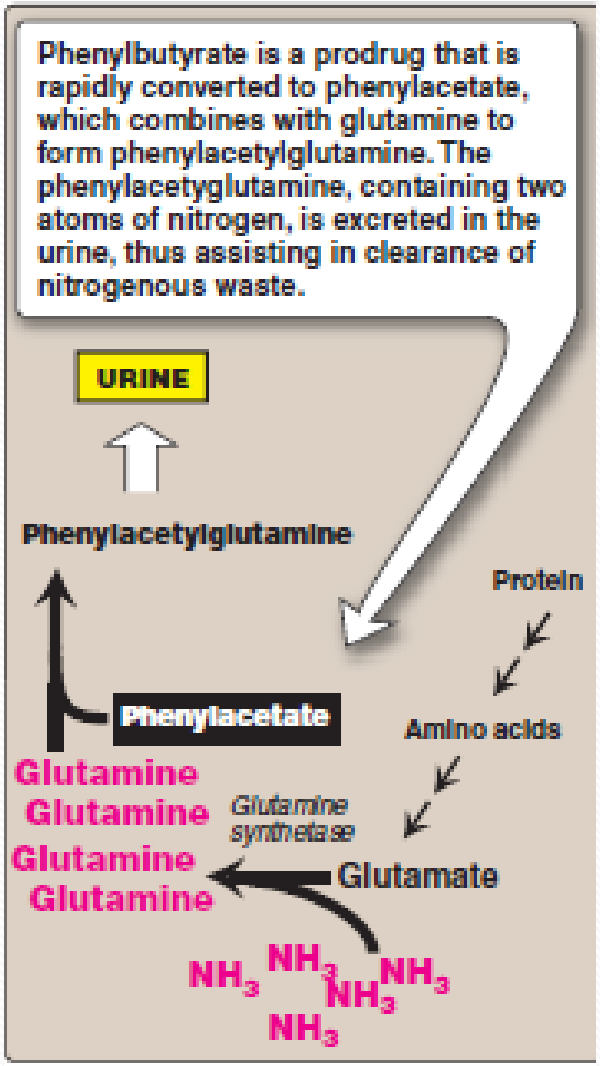
A. Drugs that scavenge ammonia by creating an alternate pathway to excrete N_2- precursors:
   1. I.V. Sodium phenylacetate & sodium benzoate (Ammonul)
   2. Oral sodium phenyl butyrate (Buphenyl)
   3. I.V. Arginine: for all UCDs except UCD due to arginase deficiency (argininemia)

B. Activators to CPSI (Carglumic acid "Carbaglu"): For hyperammoniemia 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



Thank You