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**

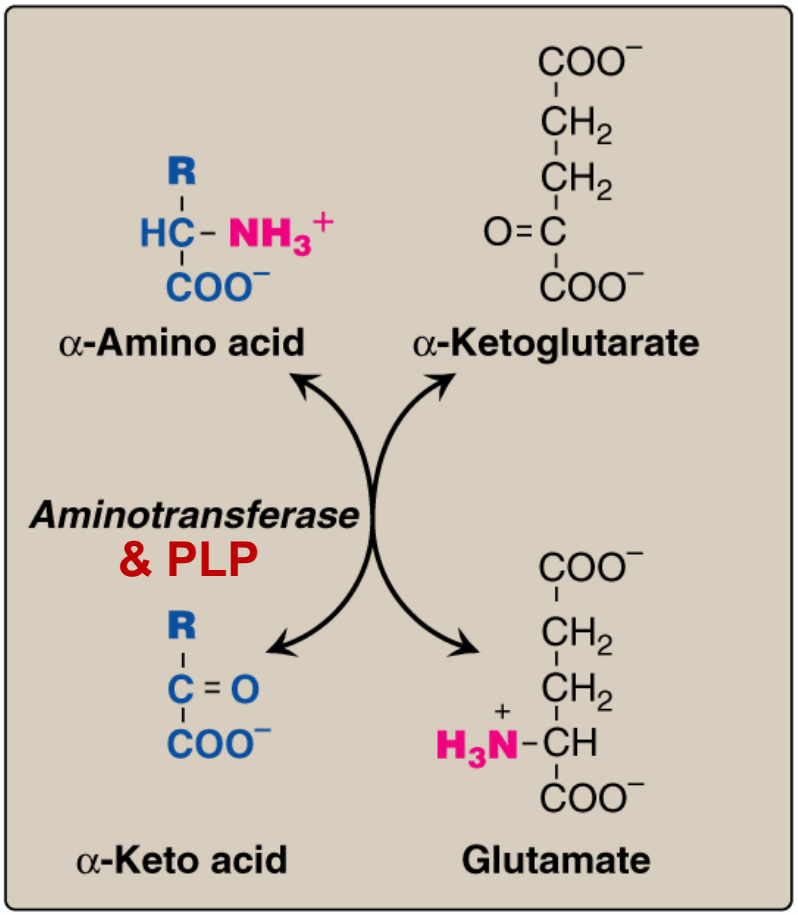
B: Blood transport of ammonia into liver:

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

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

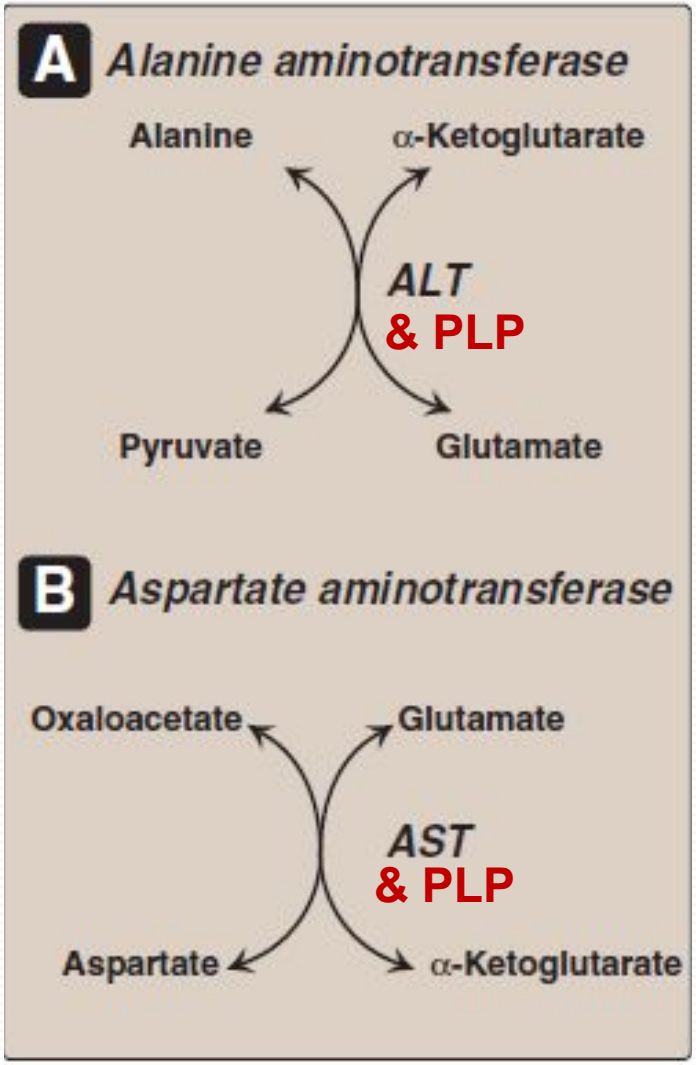
- Amino groups of amino acids are funneled to glutamate (Why?) by transamination reactions with α-ketoglutarate
- Glutamate is unique. It is the only amino acid that undergoes rapid oxidative deamination
- Oxidative deamination of glutamate will release NH_3 and re-generate α-ketoglutarate

Transaminaton

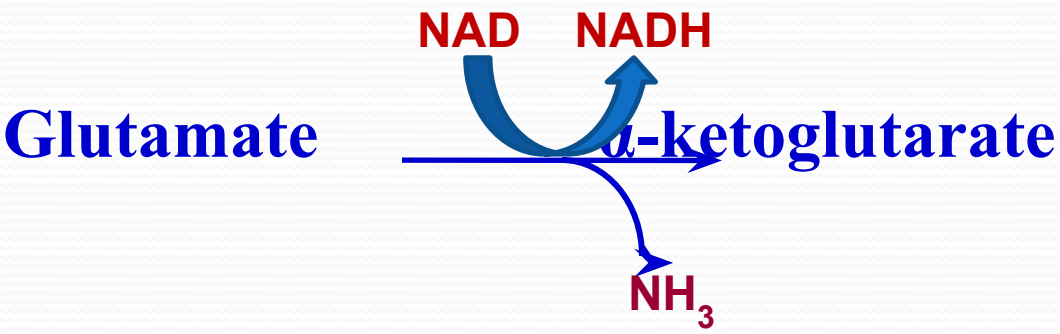


PLP: Pyridoxal phosphate, a co-enzyme that is derived from vitamin B6

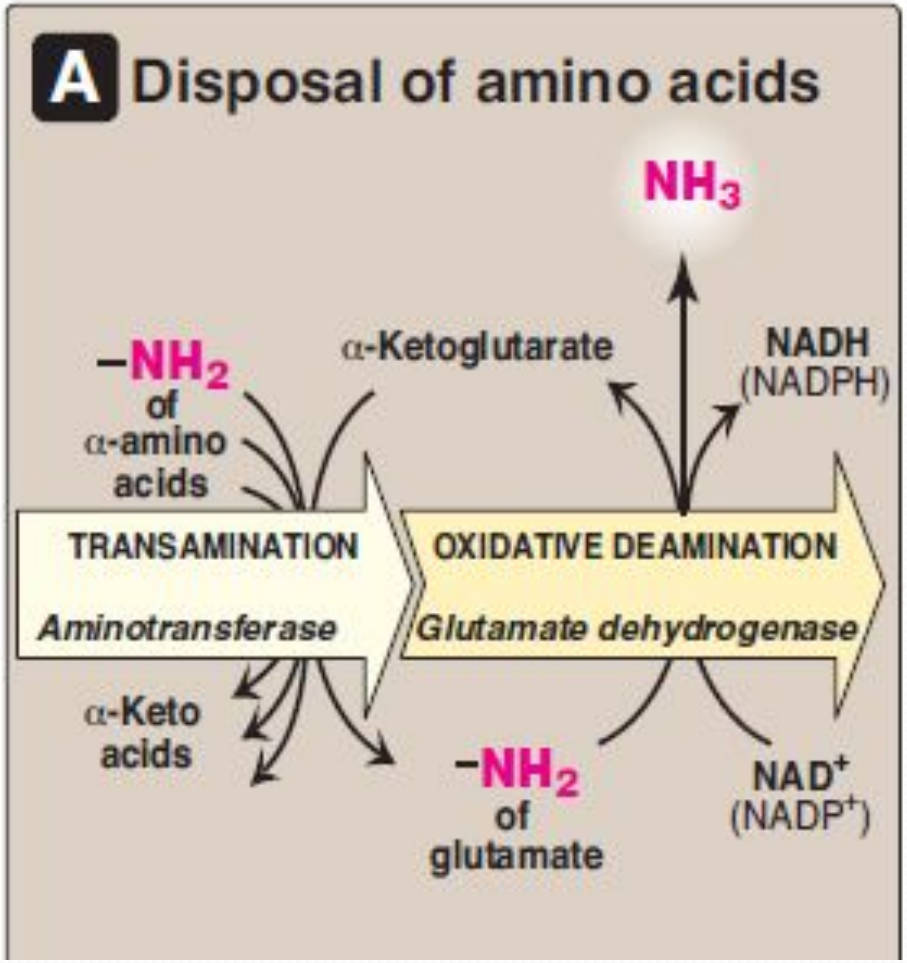
Transaminations by ALT & AST



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:

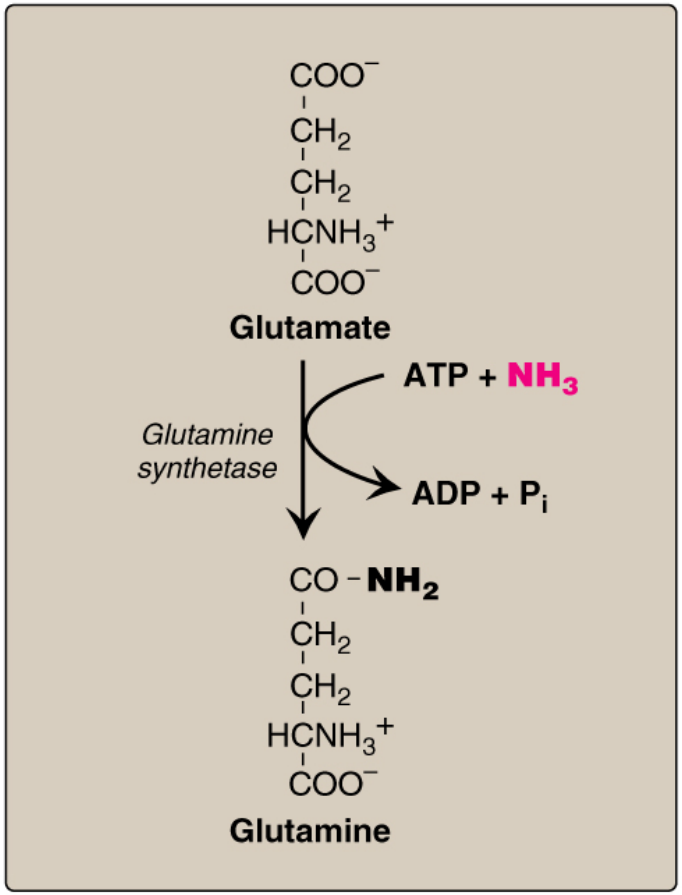
  Glutamine (most tissues)

  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



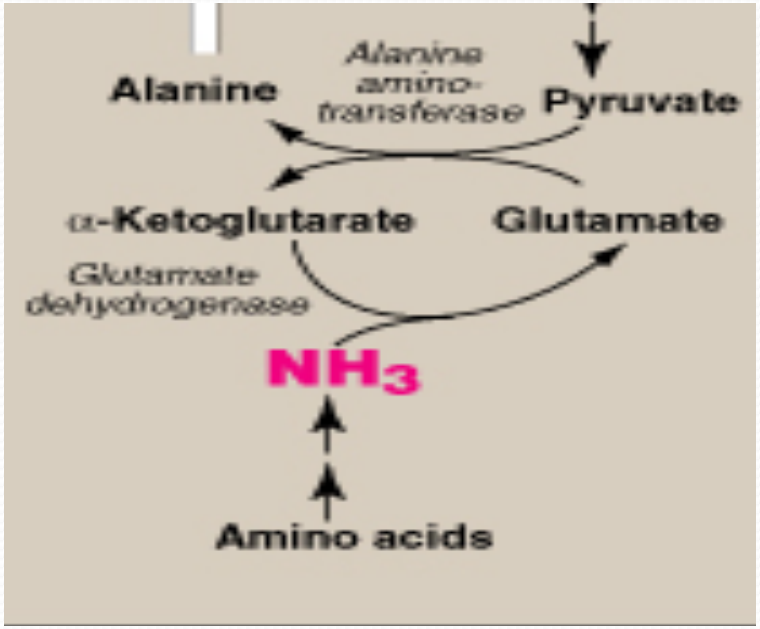
Transport of NH_3 from peripheral tissues into the liver Cont'D

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



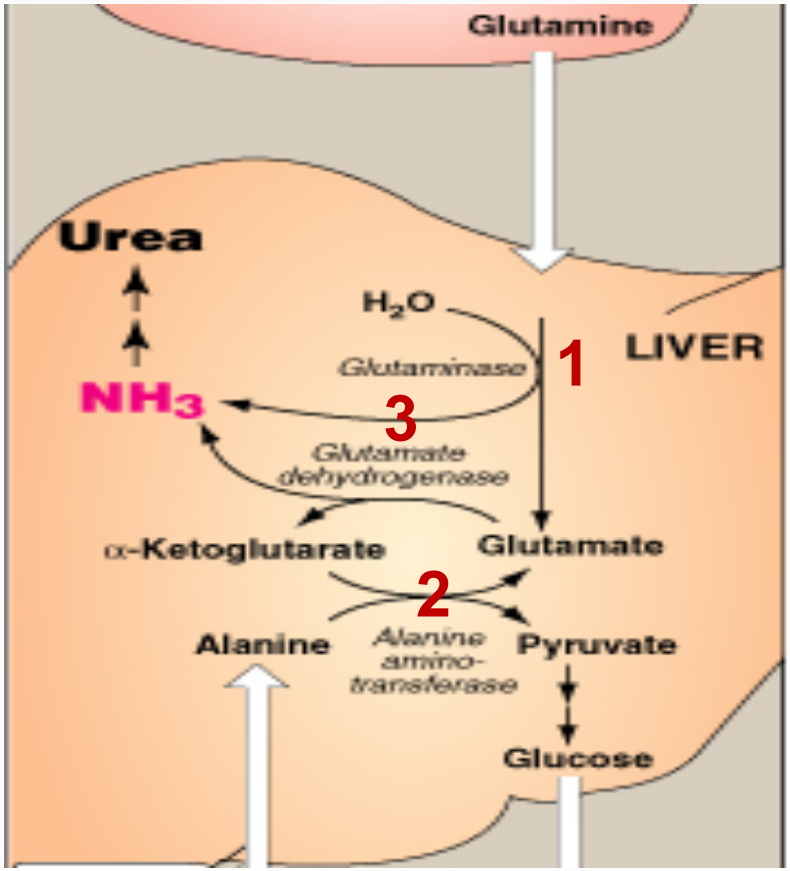
Release of ammonia from glutamine and alanine in the liver

In the Liver:

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

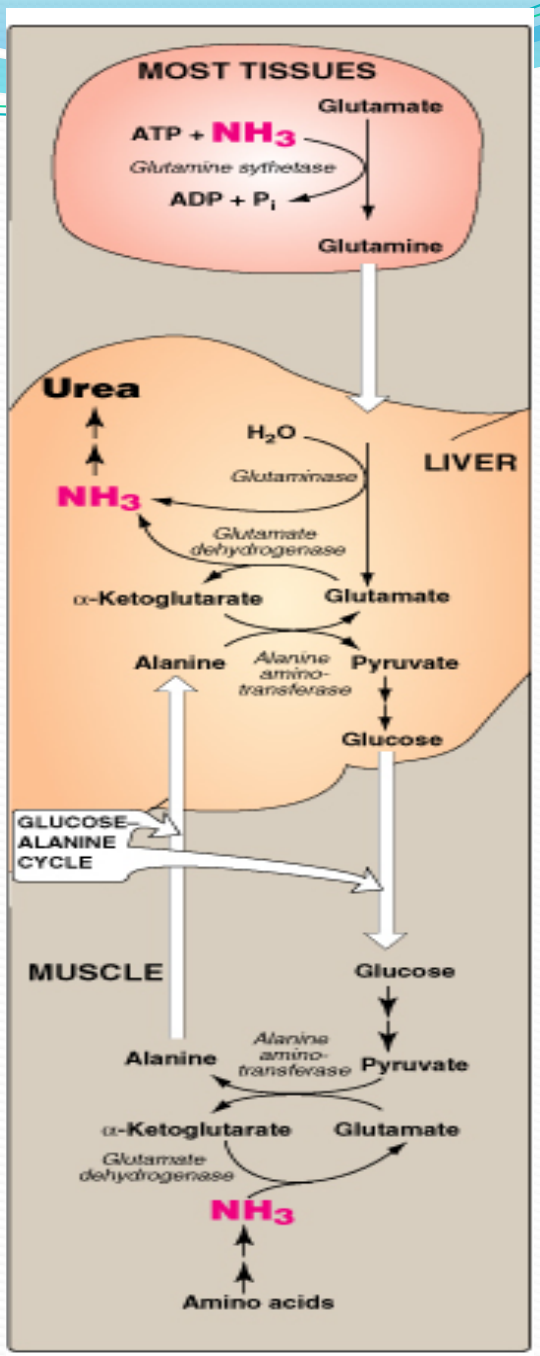
2. ***Alanine*** **will give its amino group to α-ketoglutarate to form glutamate by ALT.**

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:

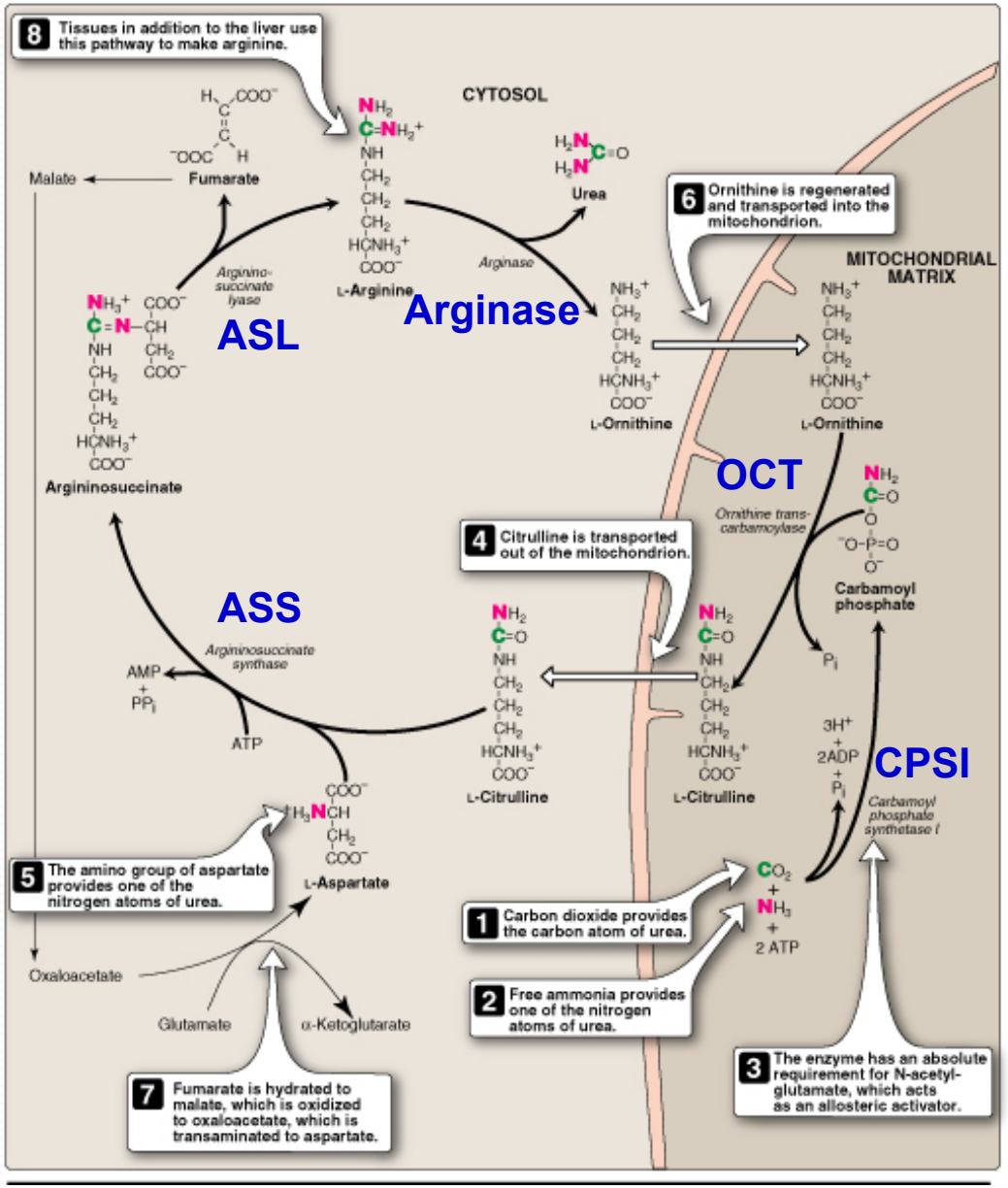
Carbamoyl phosphate synthetase I

Ornithine transcarbamoylase (OCT)

Argininosuccinate synthase

Argininosuccinate lyase

Arginase



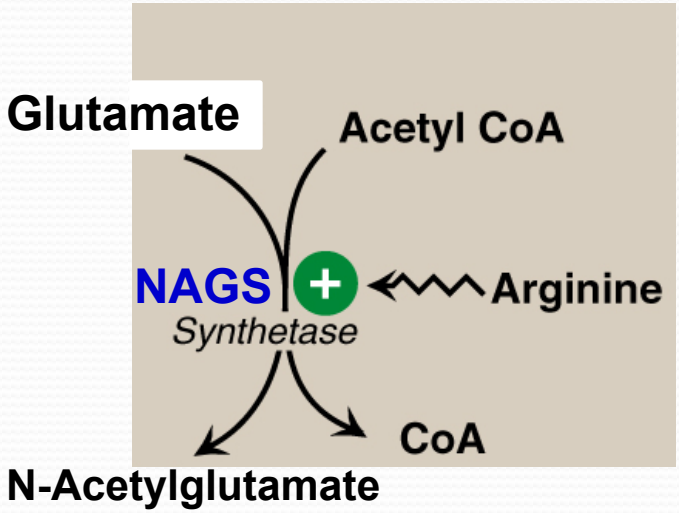
Urea Cycle: Regulation

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

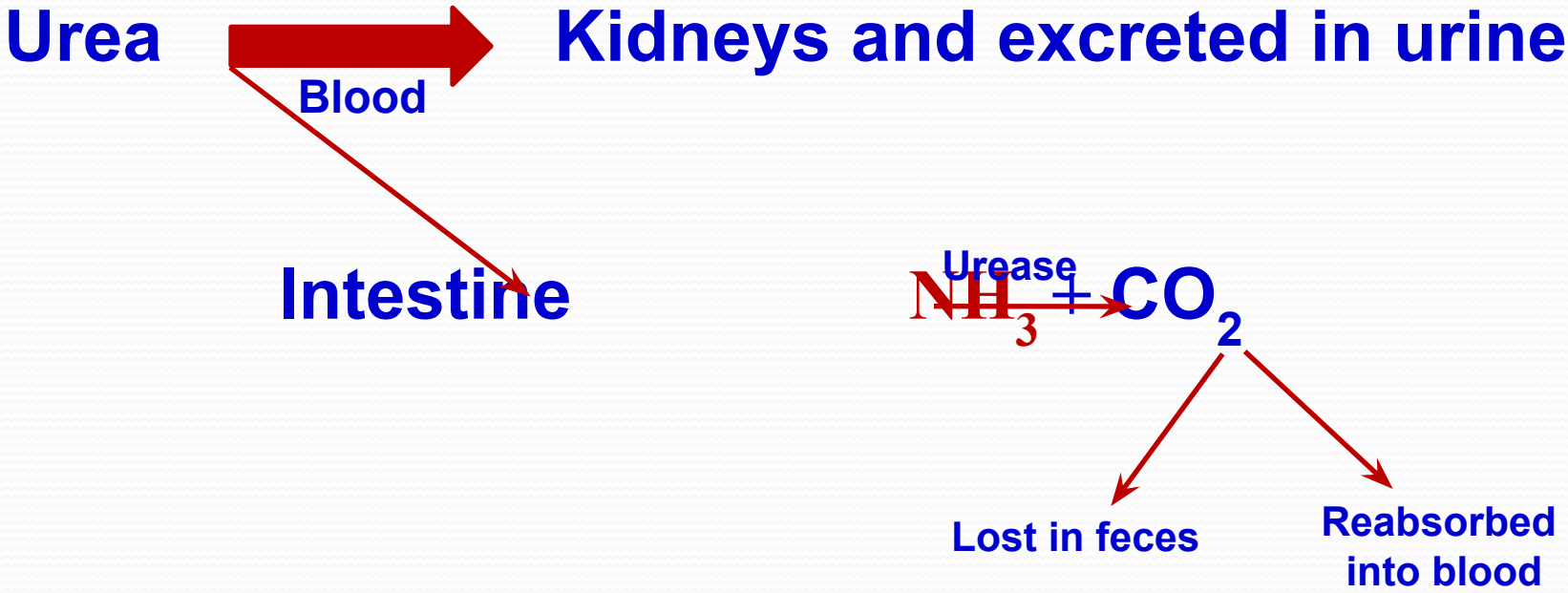
Allosteric activator of CPSI:
N-Acetylglutamate

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

NAGS deficiency is efficiently treated with Carbaglu, a CPS1 activator

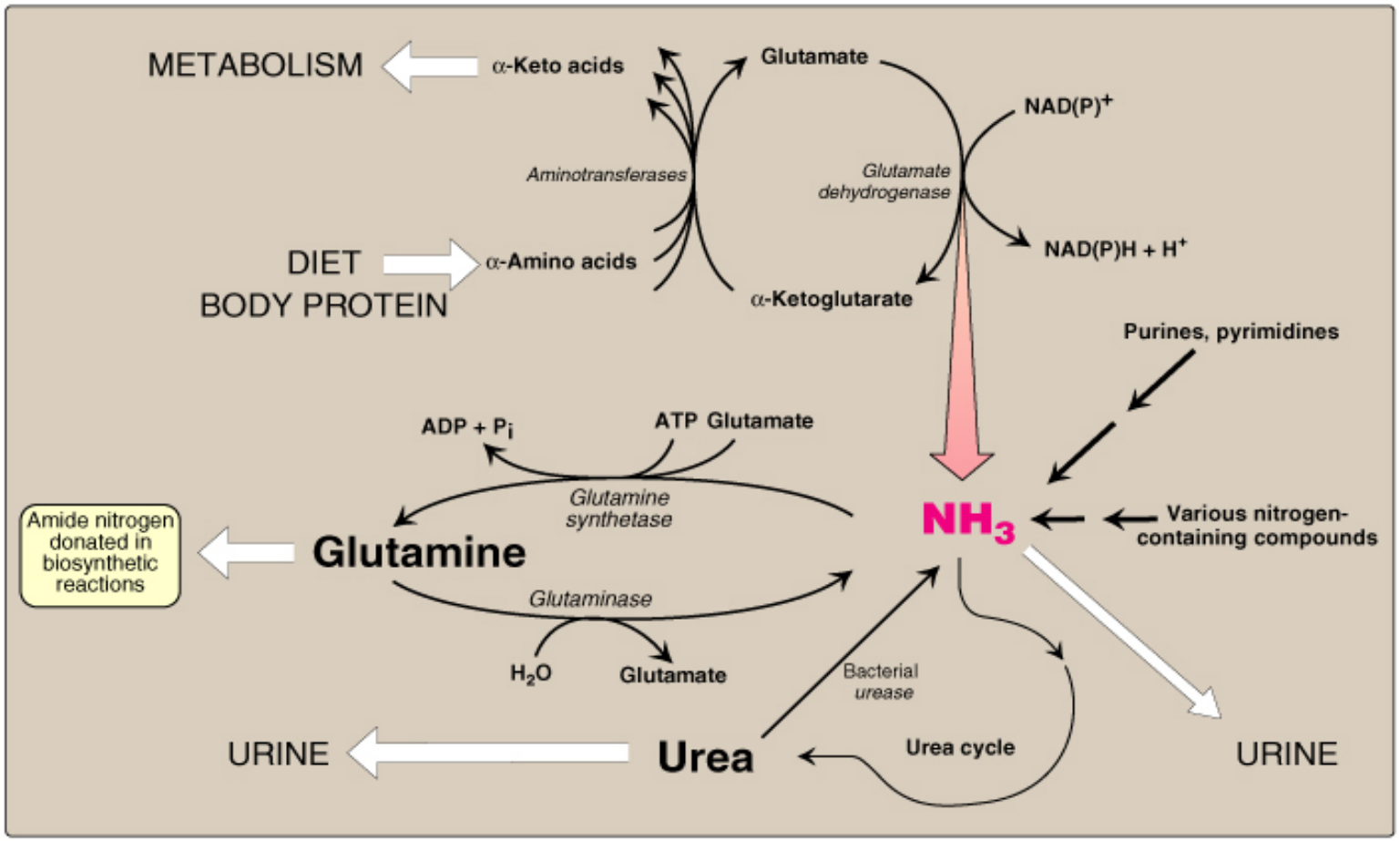


Fate of Urea



The action of intestinal urease to form 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:

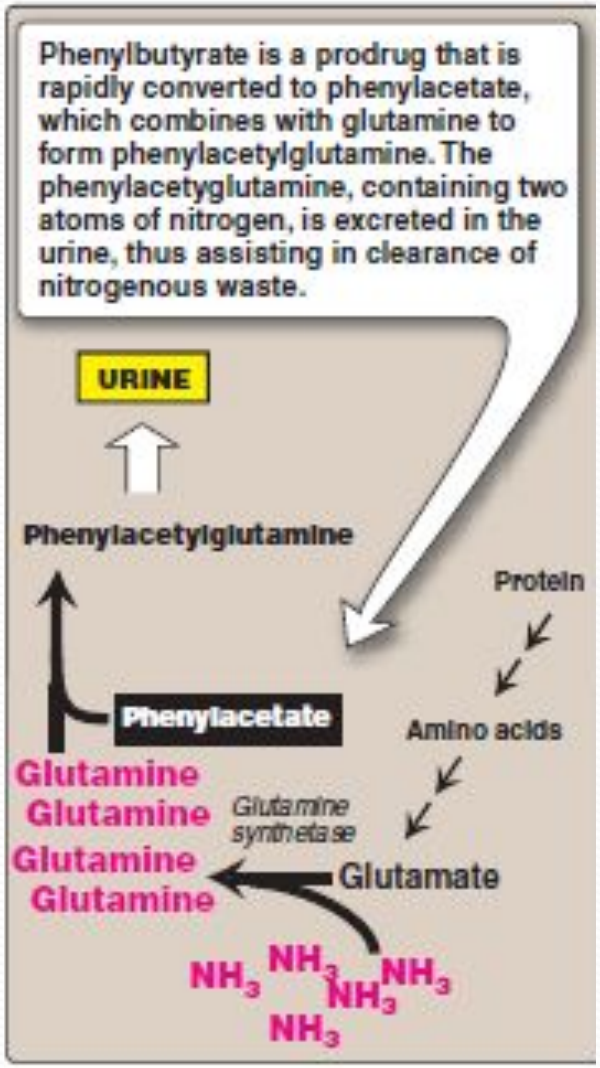
1. I.V. Sodium phenylacetate & sodium benzoate (Ammonul)
2. Oral sodium phenyl butyrate (Buphenyl)
3. I.V. Arginine: for all UCDs except UCD due to arginase deficiency (argininemia)

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

Sodlum 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