Urea cycle

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

I. Removal of α-amino group of amino acids and formation of ammonia:

1. Transamination to glutamate
2. Oxidative deamination of glutamate

II. Blood transport of ammonia into liver:

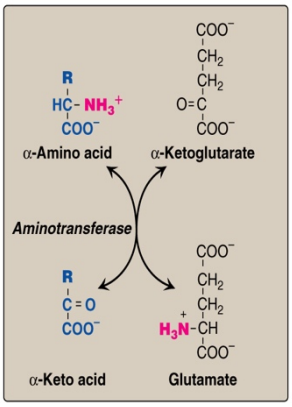
1. **in the form of glutamine (most tissue)**
2. **in the form of alanine (muscle)**

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

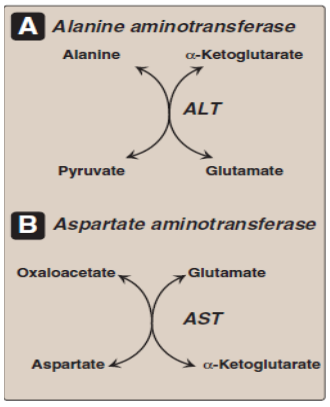
- Amino groups of amino acids are funneled to glutamate (Why?) **by transamination reactions with α-ketoglutarate**
- **Glutamate is unique. It is the only amino acid that undergoes rapid oxidative deamination**
- Oxidative deamination of glutamate will release NH_3 and re-generate α-ketoglutarate

Transamination

Transamination

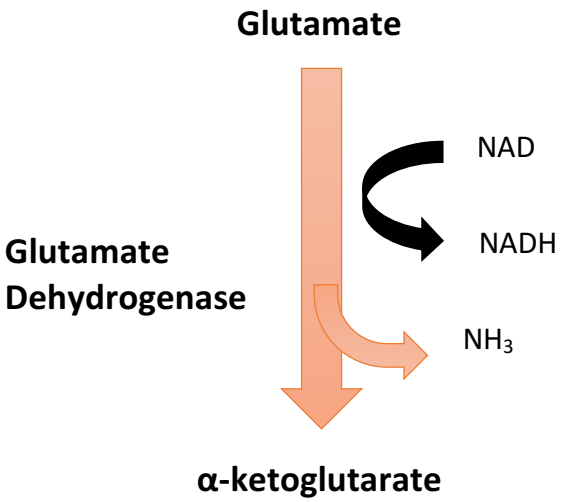


Transamination by ALT & AST



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

Oxidative Deamination



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 NH3 must be kept very low, otherwise, hyperammonemia and CNS toxicity will occur **(NH3 is toxic to CNS)**
- **To solve this problem, NH3 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

From most peripheral tissues:	From the muscle:
NH3 is transported Into the liver through forming glutamine by **glutamine synthetase .**	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**

Release of ammonia from glutamine and alanine 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.**

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

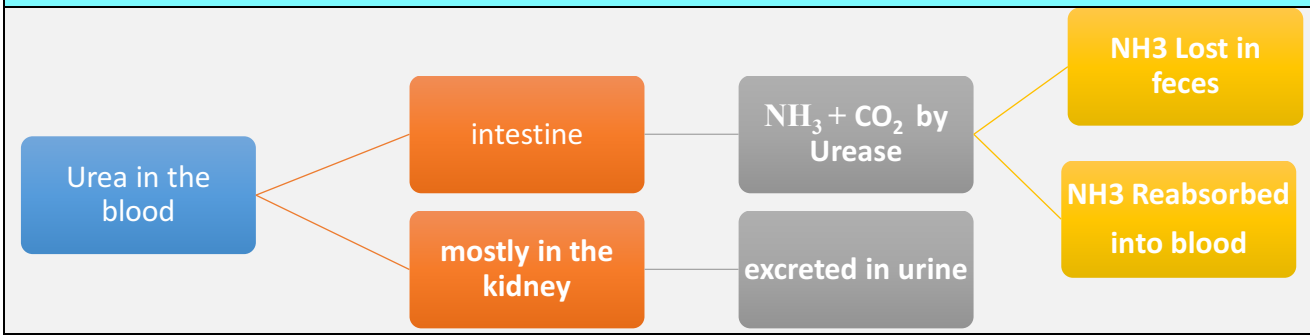
The five enzymes of urea cycle:

1. **Carbamoyl phosphate synthetase I**
2. **Ornithine transcarbamoylase (OCT)**
3. Argininosuccinate synthase
4. Argininosuccinate lyase
5. Arginase

Urea Cycle: Regulation (IMP)

- **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**

Fate of Urea



The action of intestinal urease to form NH_3 is clinically significant in renal failure:

Renal failure → ↑ blood urea → ↑ urea in the intestine → $urease$ → ↑ NH3 blood level (acquired hyperammonemia)

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

Hyperammonemia

Acquired hyperammonemia:	Inherited hyperammonemia:
1. Liver diseases: Acute: Viral hepatitis or hepatotoxic Chronic: Cirrhosis by hepatitis or alcoholism **2. Renal failure**	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 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)

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