The Urea Cycle

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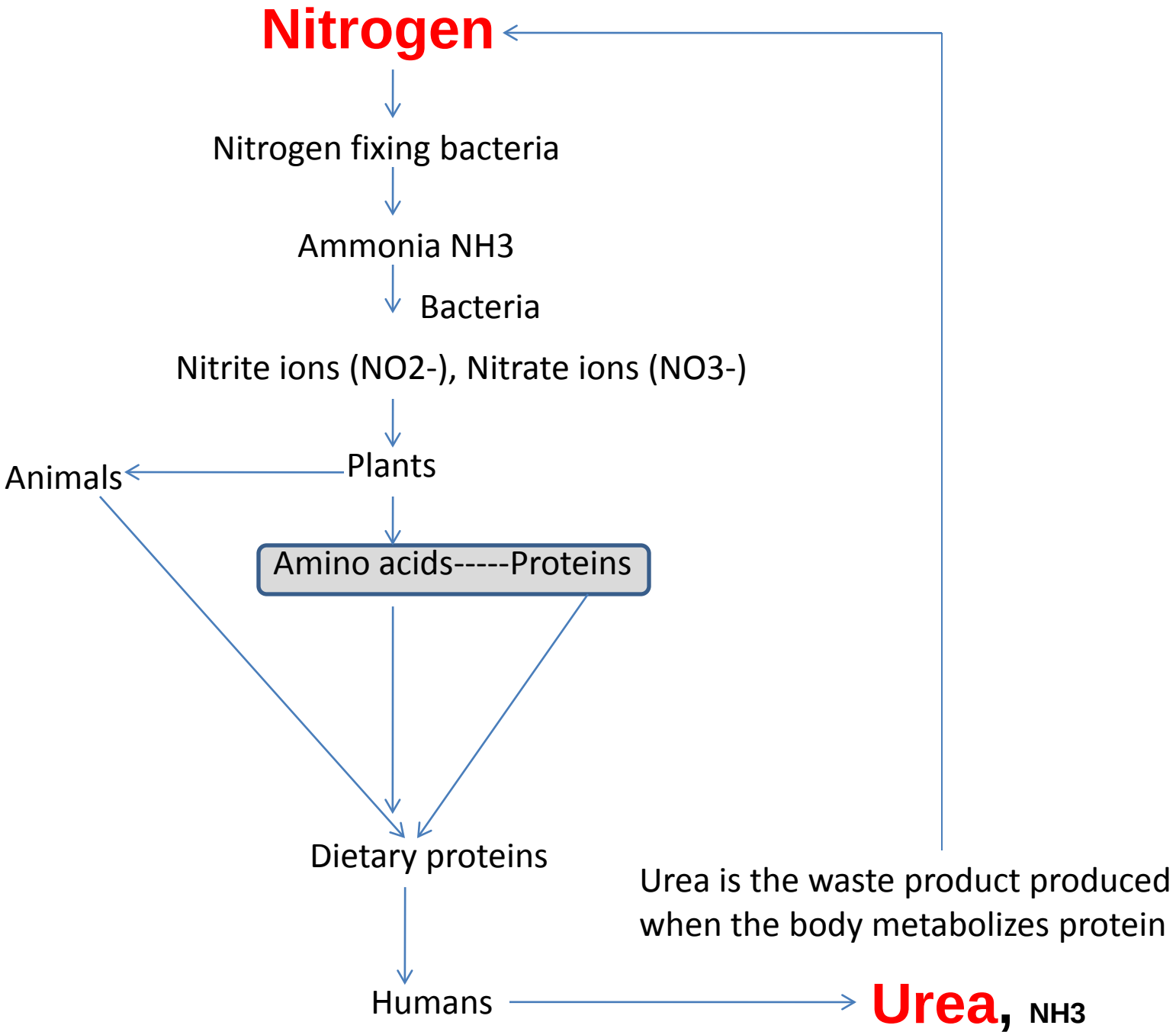

Nitrogen
Nitrogen fixing bacteria
Ammonia NH3
Bacteria
Nitrite ions (NO2-), Nitrate ions (NO3-)
Plants
Animals
Amino acids-----Proteins
Dietary proteins
Humans
Urea is the waste product produced when the body metabolizes protein
Urea, NH3

Amino acids

Generated

* Degradation of body proteins
* Degradation of dietary proteins
* Synthesis of non-essential amino acids from simple intermediates of metabolism

depleted

* Synthesis of body proteins
* Consumed as precursors of essential nitrogen-containing small molecules
* Conversion of amino acids to glucose, fatty acids or CO_2

Degradation of body/cellular proteins

Pathways of protein degradation:

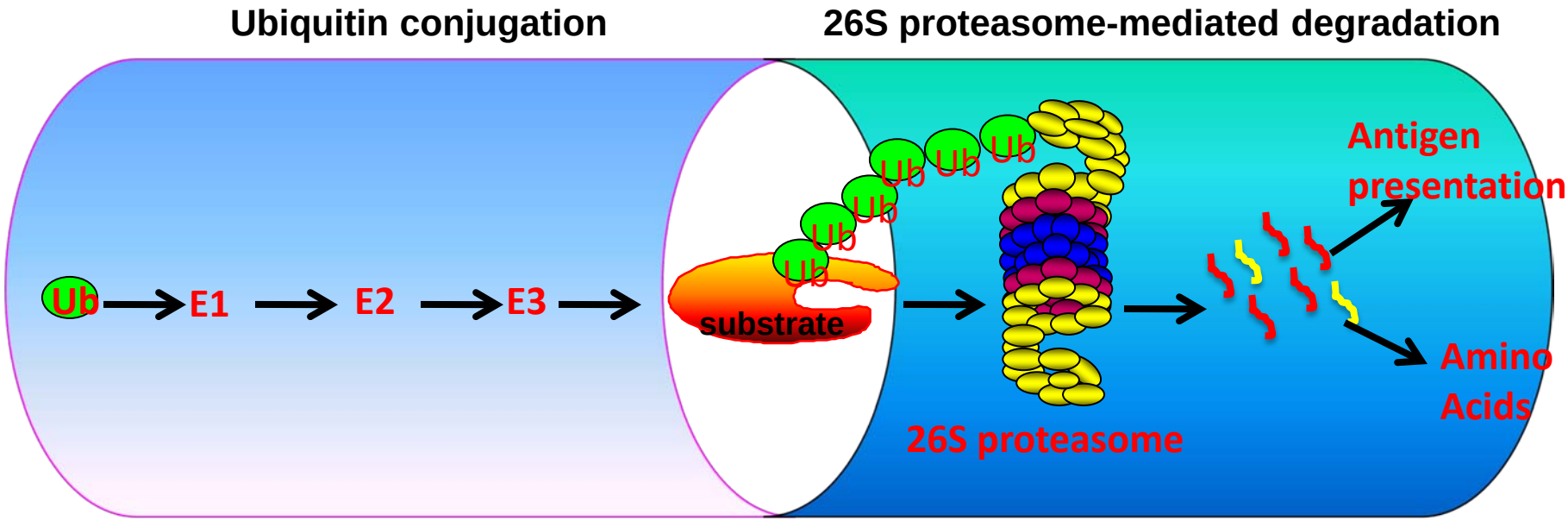
Ubiquitin/26S proteasome

Lysosome

- **Microautophagy**
- **Macroautophagy**
- **Chaperone-mediated microautophagy**

Ubiquitin/26S proteasome pathway

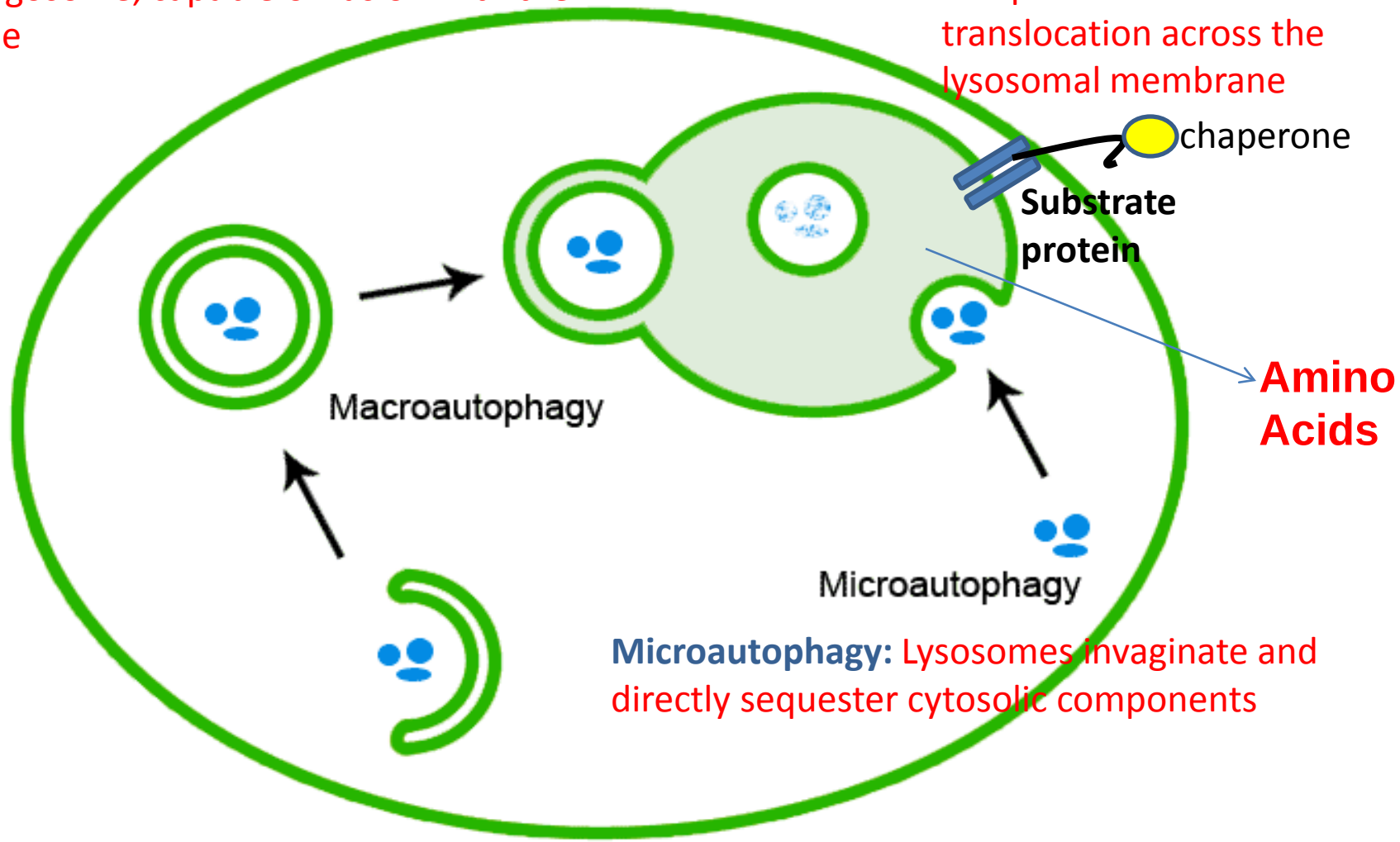
Degradation of a target substrate by the ubiquitin pathway involves two steps:



Autophagy

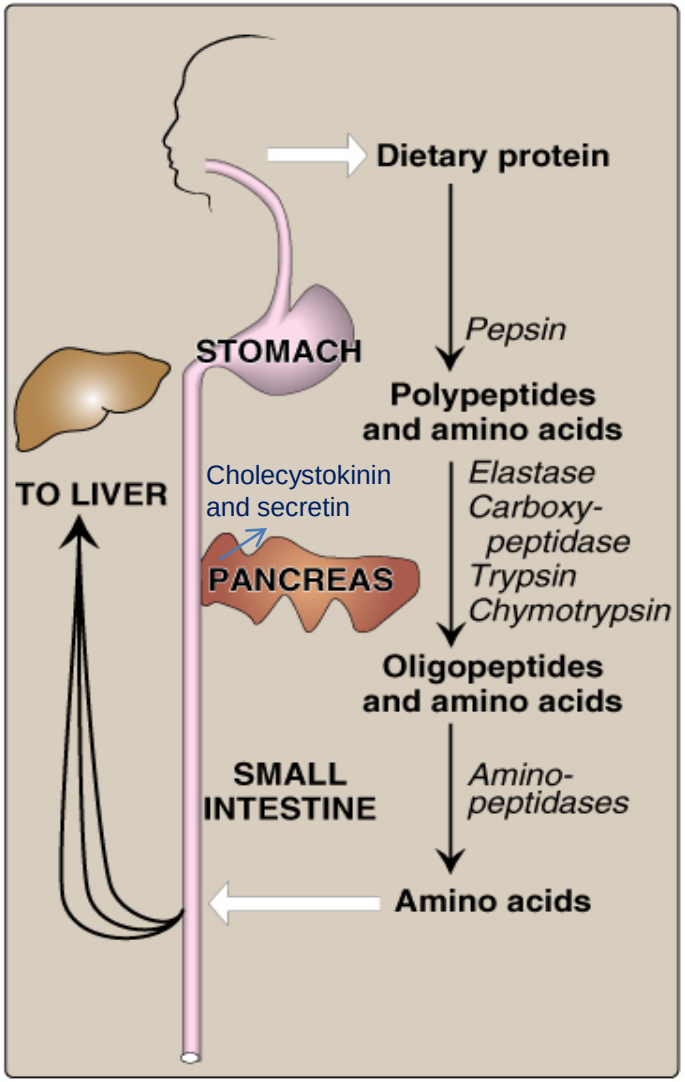
Macroautophgay: Involves the formation of a crescent-shaped structure (the phagophore) that expands to form the double-membrane autophagosome, capable of fusion with the lysosome

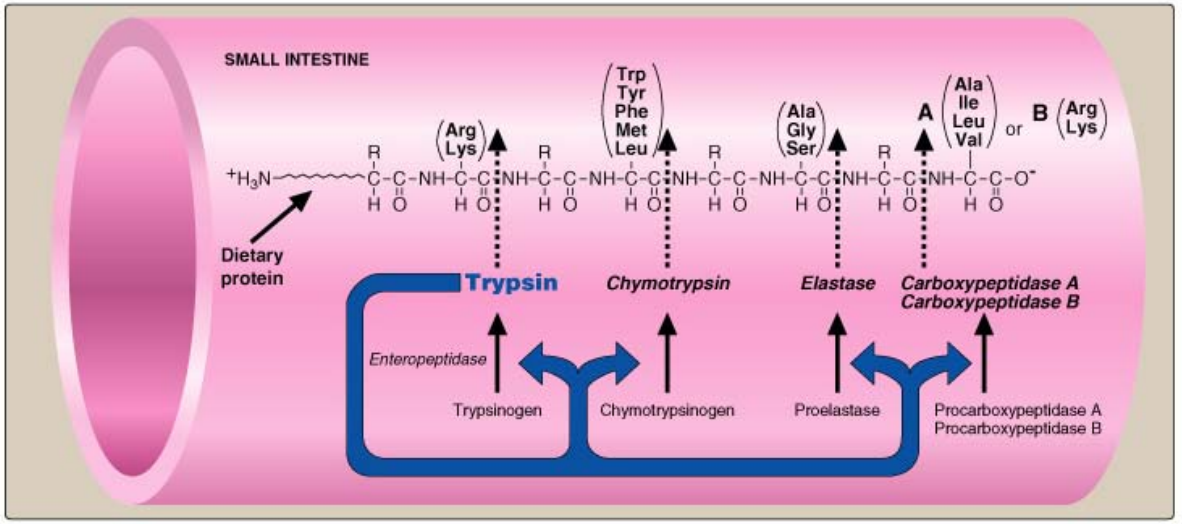
CMA: Involves degradation of selected proteins that have a consensus peptide sequence which is recognized by the binding of a hsc70-containing chaperone/co-chaperone complex for their translocation across the lysosomal membrane



Microautophagy: Lysosomes invaginate and directly sequester cytosolic components

Fate of Dietary Protein





A. Digestion of proteins by gastric secretions

B. Digestion of proteins by pancreatic enzymes

*****Specificity

*Release of zymogens by Cholecystokinin and secretin

*Activation of zymogens

* Abnormalities in protein digestion

C. Digestion of oligopeptides by enzymes of the small intestine

D. Absorption of amino acids and dipeptides

Free amino acids are taken into the enterocytes up by a Na+-linked secondary transport systems. Di and tripeptides are taken up by H+-linked transporters.

Transport of AA into cells

Seven different transport systems are known that have overlapping specificity for different Amino acids.

The small intestine and proximal tubule of the Kidney have common transport systems for amino acid uptake.

Cystinuria------ defective reabsorption of **C**ystine and also **O**rnithine, **A**rginine and **L**ysine.

Hartnup disorder-------caused due to the transport of tryptophan.

Essential *versus* Nonessential Amino Acids

Essential	Nonessential
Arginine[a]	Alanine
Histidine	Aspartate
Isoleucine	Cysteine
Leucine	Glutamate
Lysine	Glycine
Methionine[b]	Proline
Phenylalanine[c]	Serine
Threonine	Tyrosine
Tryptophan	
Valine	

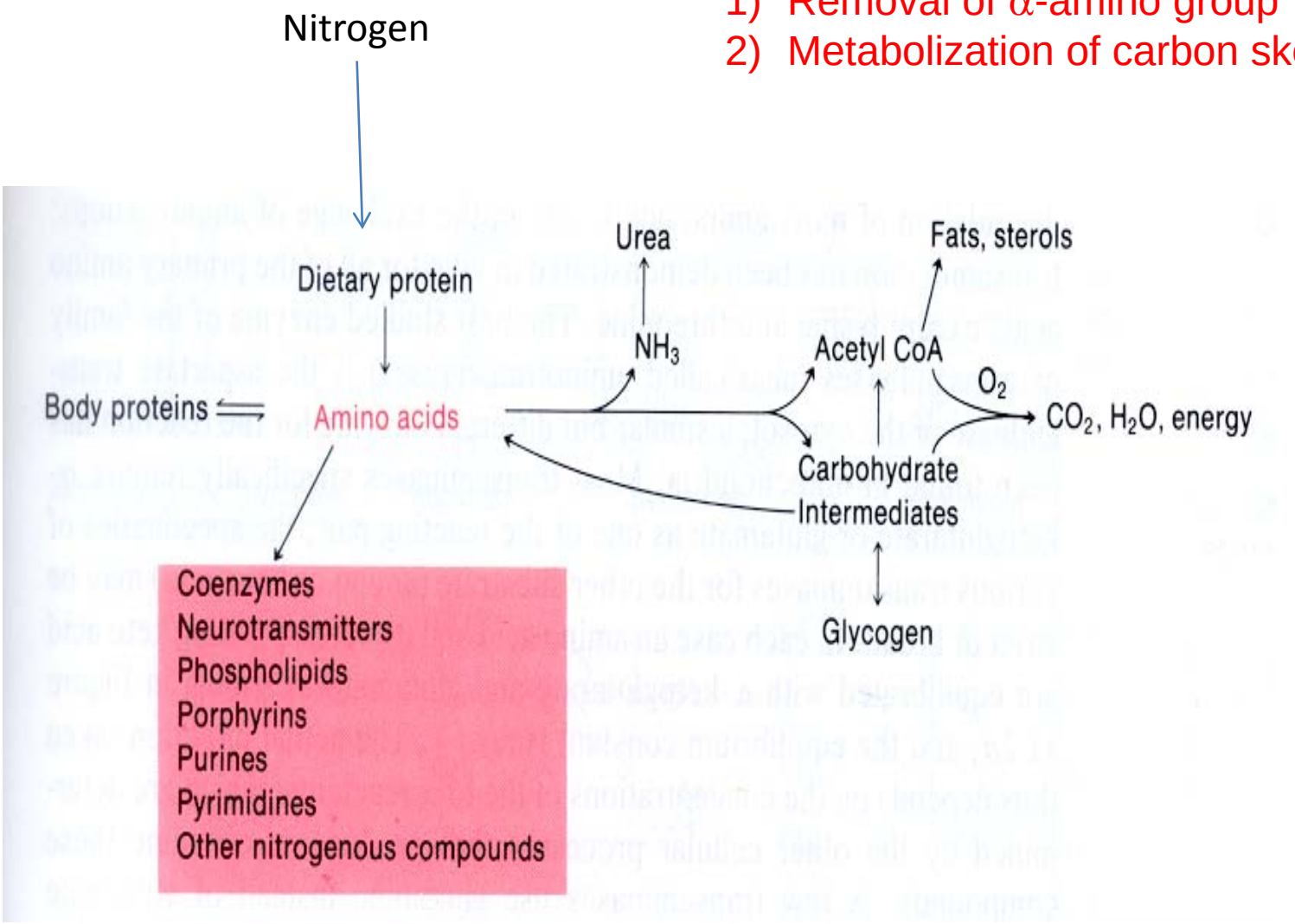
[a] Arginine is synthesized by mammalian tissues, but the rate is not sufficient to meet the need during growth.

[b] Methionine is required in large amounts to produce cysteine if the latter is not supplied adequately by the diet.

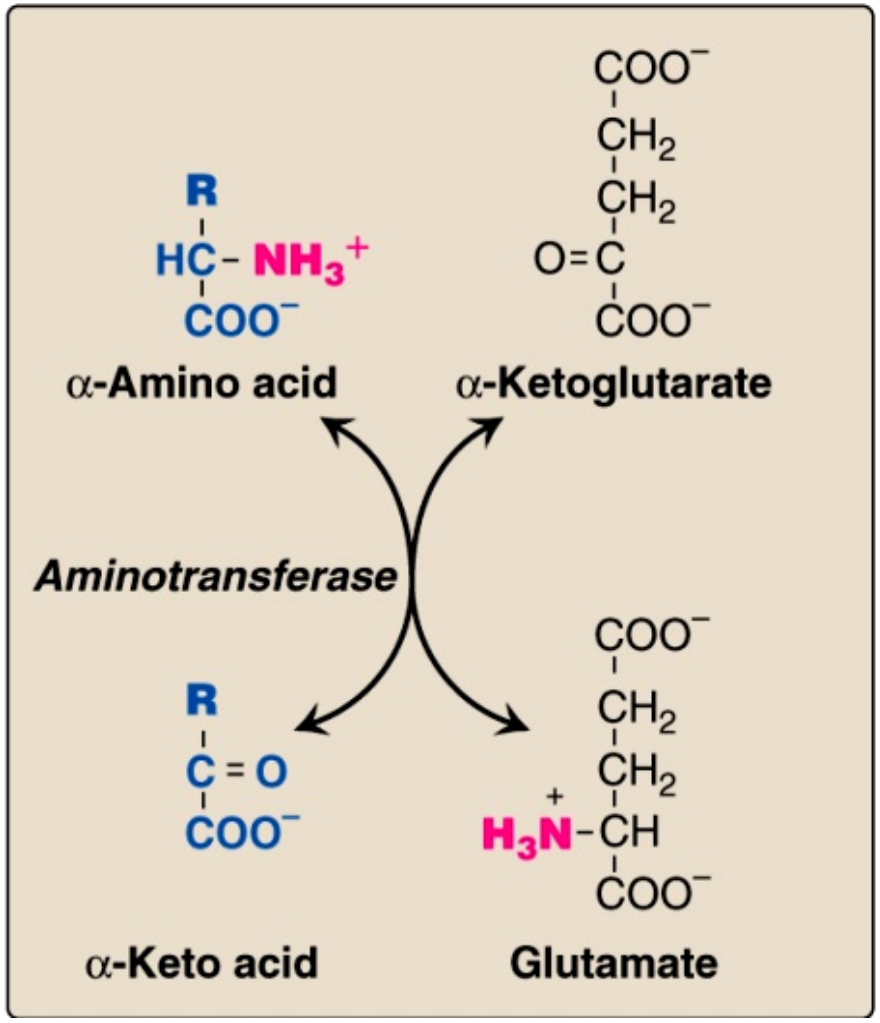
[c] Phenylalanine is needed in larger amounts to form tyrosine if the latter is not supplied adequately by the diet.

Amino Acid Catabolism

1) Removal of α-amino group
2) Metabolization of carbon skeleton



Transamination: the funneling of amino groups to glutamate



Transfer of amino groups to α-ketoglutarate

Almost all amino acids undergo transamination, except, lysine and threonine.

Aminotransferase

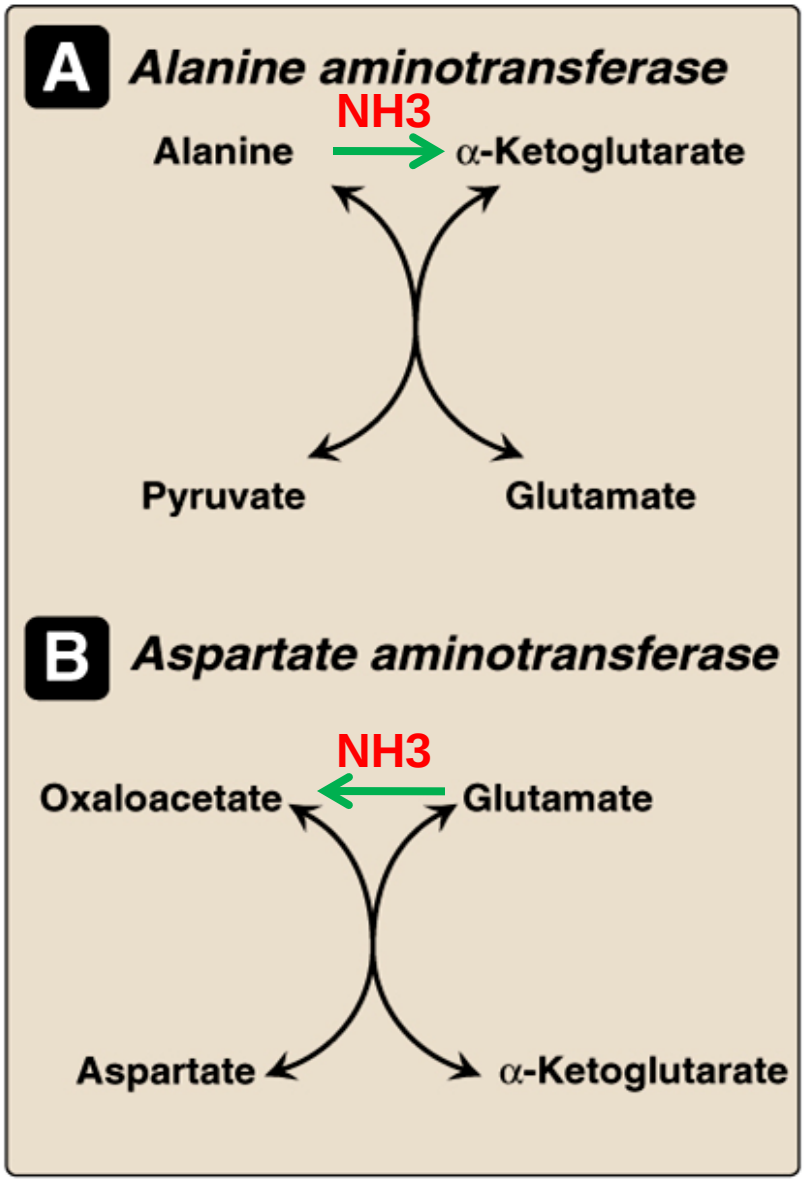
•Substrate Specific-

•Alanine aminotransferase (ALT)

• Aspartate aminotransferase (AST)

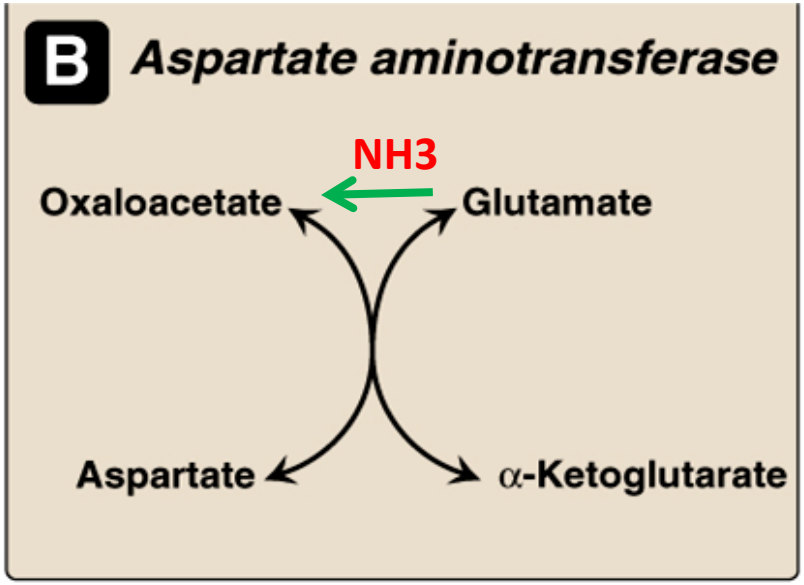
↑ AST and ALT - Liver diseases
Nonhepatic diseases

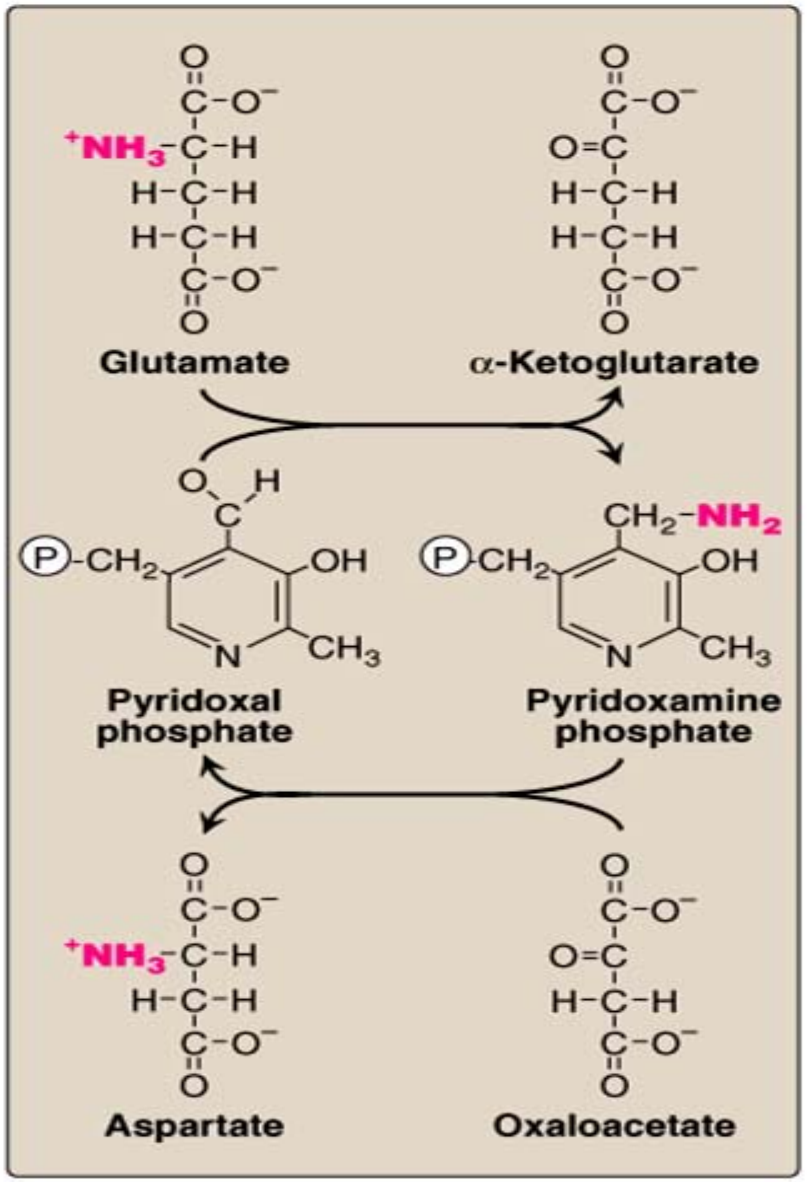
Source of nitrogen in the Urea cycle ←



Mechanism of action of aminotransferase

1) Transfer amino groups to PLP
2) Resulted pyridoxamine phosphate formed reacts with a-keto acid to form amino acid and aldehye form of PLP

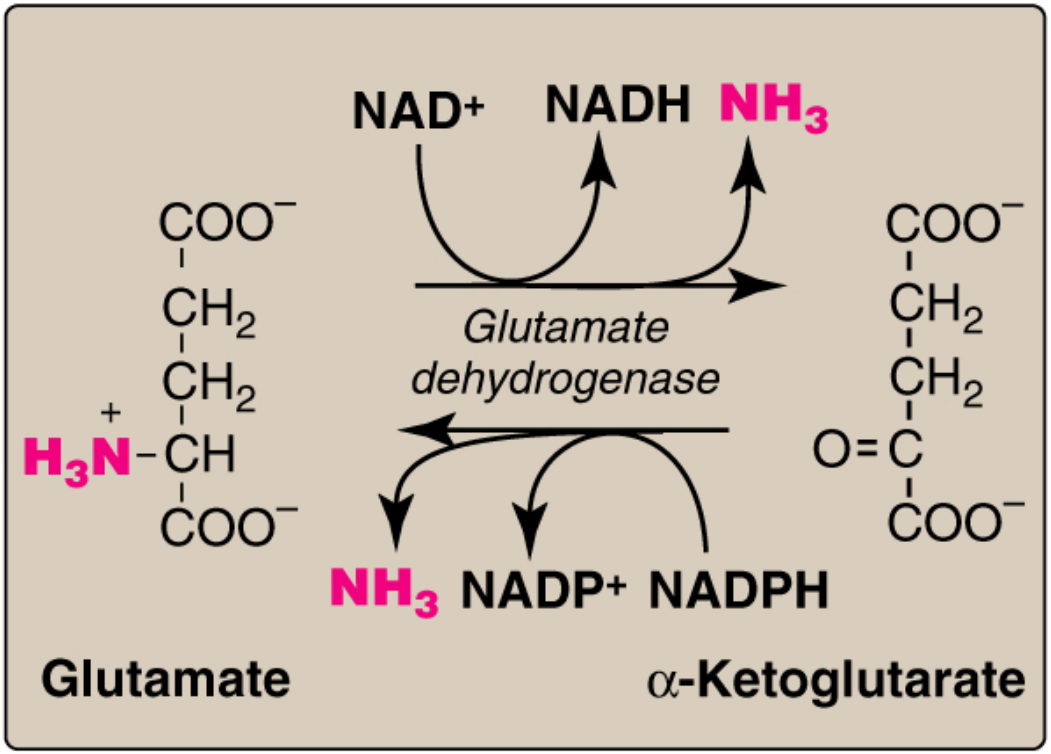




Glutamate dehydrogenase: The oxidative deamination of amino acids

(Liver and Kidney)

Transamination: Transfer of amino groups
Deamination: Liberation of amino group as ammonia



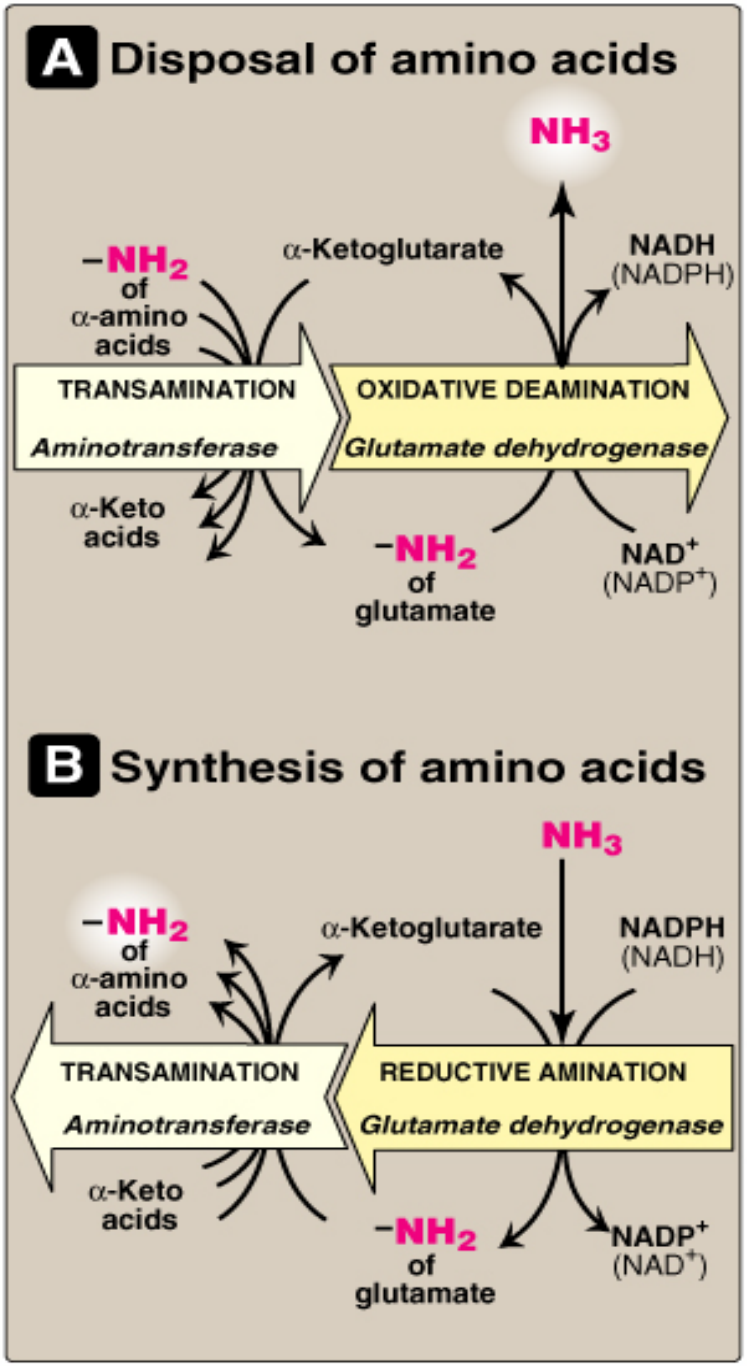
Co-enzymes: NAD+ and NADP+

Directions: Depends on the levels of Glutamate , α-ketoglutarate

Allosteric inhibitors: GTP is an inhibitor
ADP is an activator

Amino Acid Catabolism

Amino acid Metabolism



D-amino acids

•Present in our diet

* Present in plants

* Not used for mammalian protein synthesis

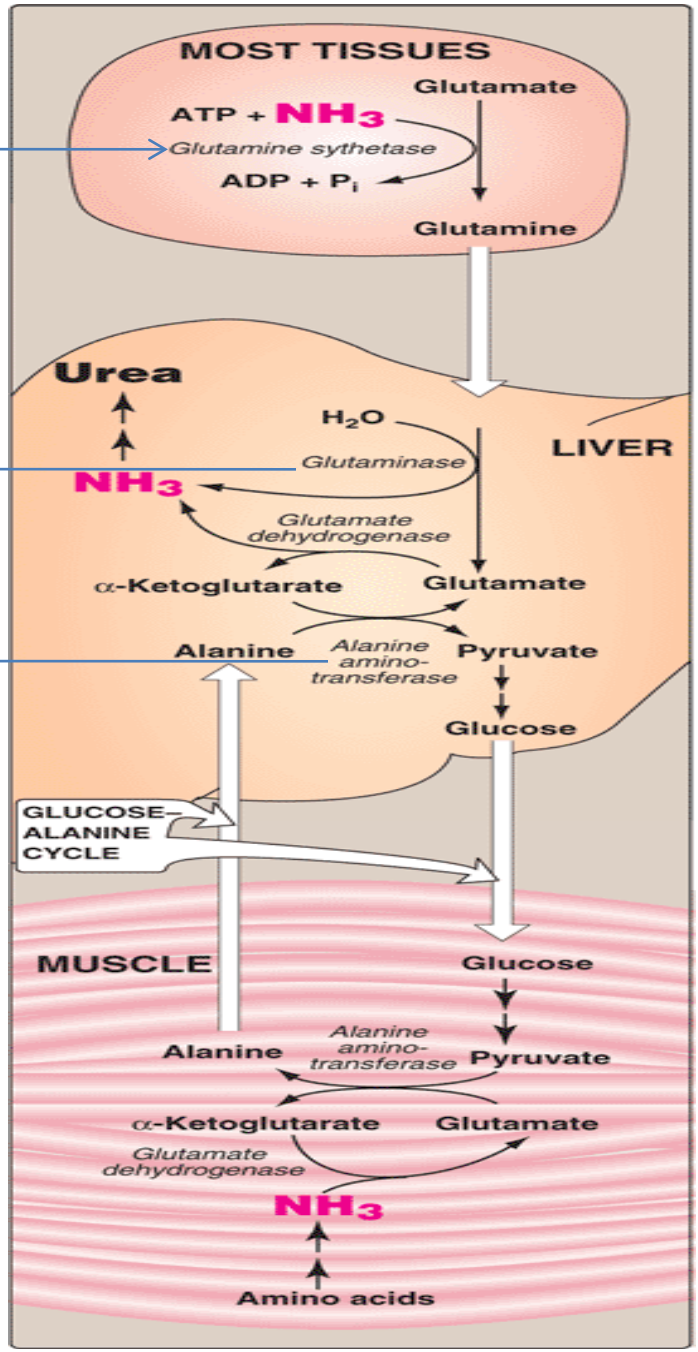
* D-amino acid oxidase enzyme catalyzes deamination of D-AA

Transport of ammonia to the liver

Glutamine Synthatase

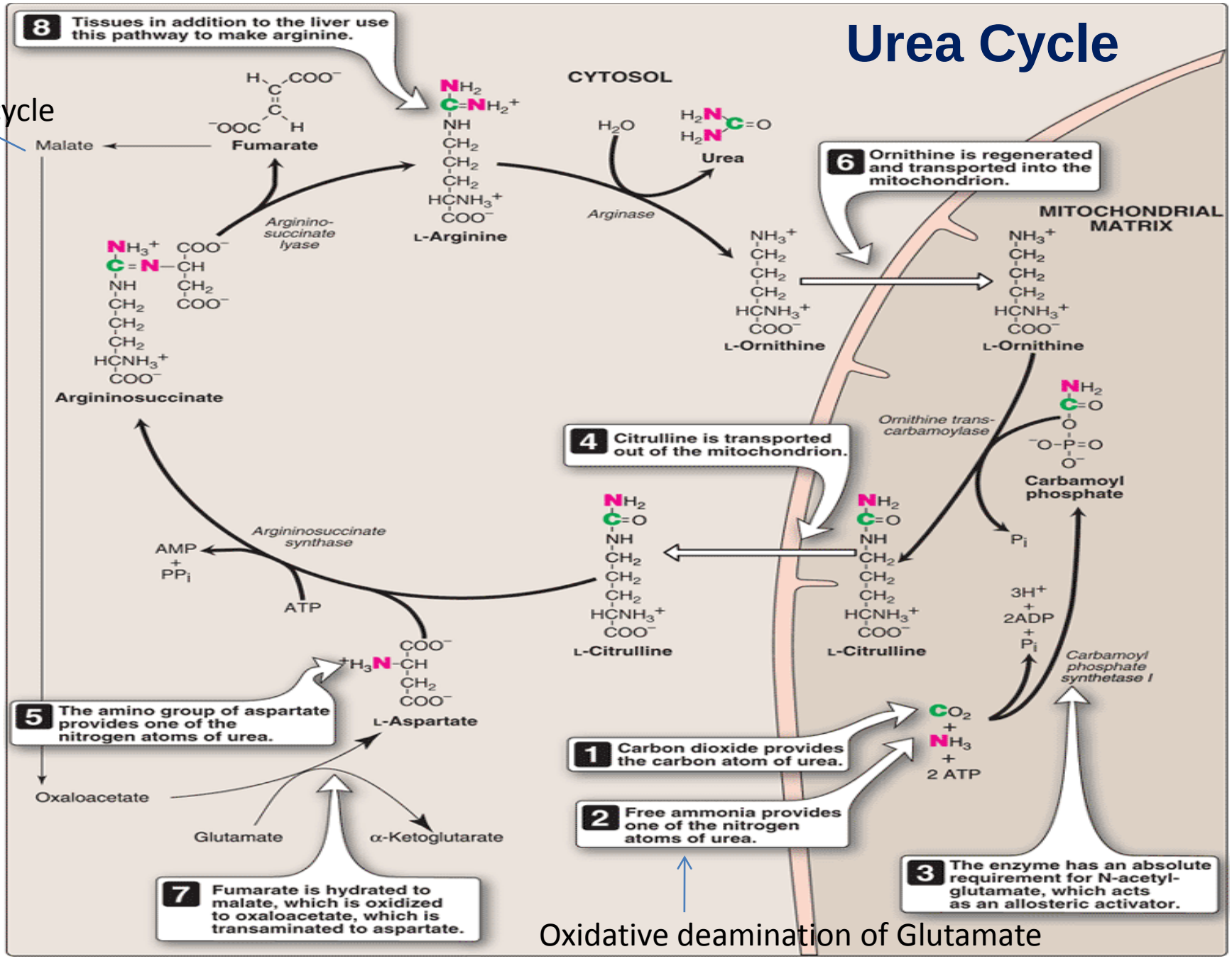
Gutaminase

ALT



Glucose-Alanine cycle serves two purposes:

1) Recycles carbon skeletons between muscle and liver
2) Transports NH3 to the liver and is converted into urea.



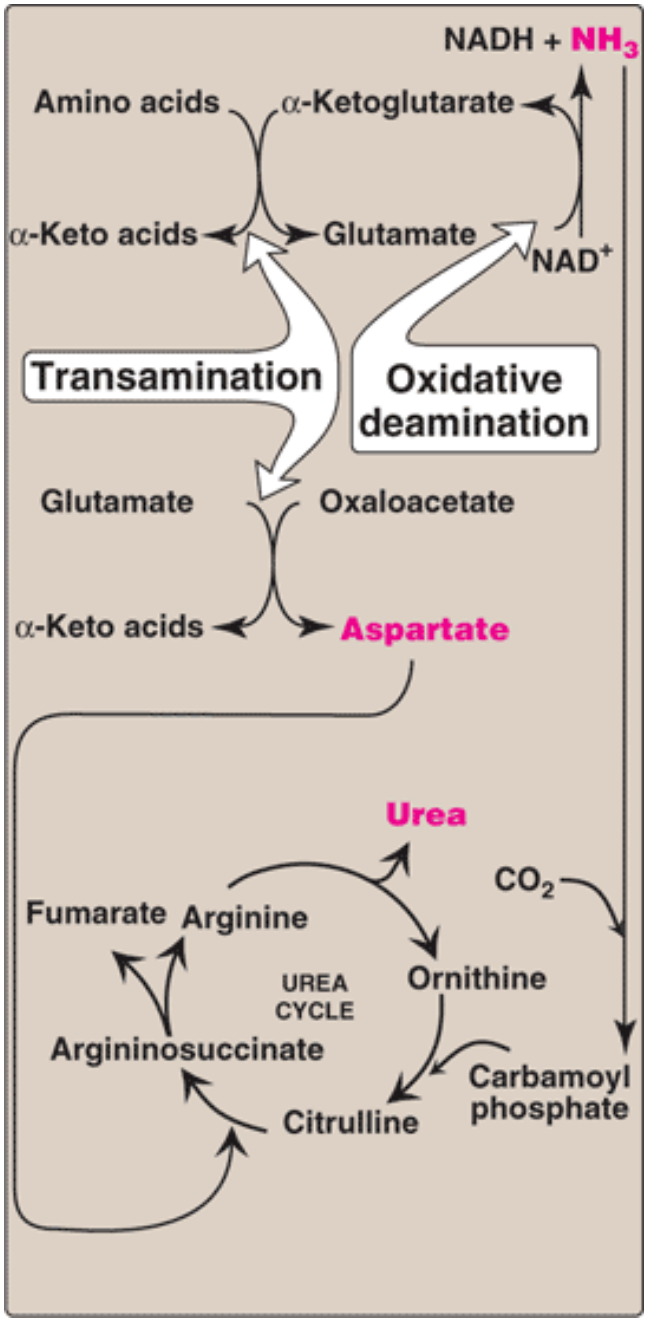
Oxidative deamination of Glutamate
By mitochondrial glutamate dehydrogenase

Summary of the Urea Cycle

* The urea cycle consists of five reactions: two mitochondrial and three cytosolic.
* The cycle converts two amino groups, one from NH_4^+ and one from Asp, and a carbon atom from CO2.
  to the relatively nontoxic excretion product urea.
* Requires four "high-energy" phosphate bonds.

Step	Reactants	Products	Catalyzed by	Location
1	NH3 + Co2 + 2 ATP	Carbamoyl Phosphate + 2ADP + pi	Carbamoyl phoshate Synthetase I	Mitochondria
2	Carbamoyl Phosphate + Ornithine	Citrullin + Pi	Ornithine trascarbamoylase	Mitochondria
3	Citrullin + Aspartate + ATP	Argininosuccinate + AMP + PPi	Argininosuccinate synthase	Cytosol
4	Argininosuccnate	Arginine + Fumarate	Argininosuccinate lyase	Cytosol
5	Arginine + H2O	Ornithine + Urea	Arginase	Cytosol

Flow of Nitrogen from amino acids



One Nitrogen of Urea is supplied by ammonia

Second Nitrogen of Urea is supplied by Aspartate

Carbon and oxygen of Urea is derived from CO2

Overall stoichometry of the urea cycle

Aspartate + NH3 + CO2 + 3 ATP ⟶

Urea + fumarate +2ADP +AMP + 2 Pi + Ppi + 3H2O

Sources of Ammonia

From Amino acids----------in liver by transdeamination reaction

From glutamine----------in kidneys by the action of renal glutaminase and glutamine dehydrogenase

From urea----------Bacterial urease action in the intestine which is then transported into the liver to make urea

From amines----------by the action of amine oxidase
(Amines from diet
Neurotransmitters
Monoamines)
From purines and pyrimidines---------amino groups are released as ammonia

Fate of Urea

Ammonia

Liver

Blood

Kidney

Excreted in Urine

Diseases caused due to the Urea metabolism/catabolism

Hyperammonemia

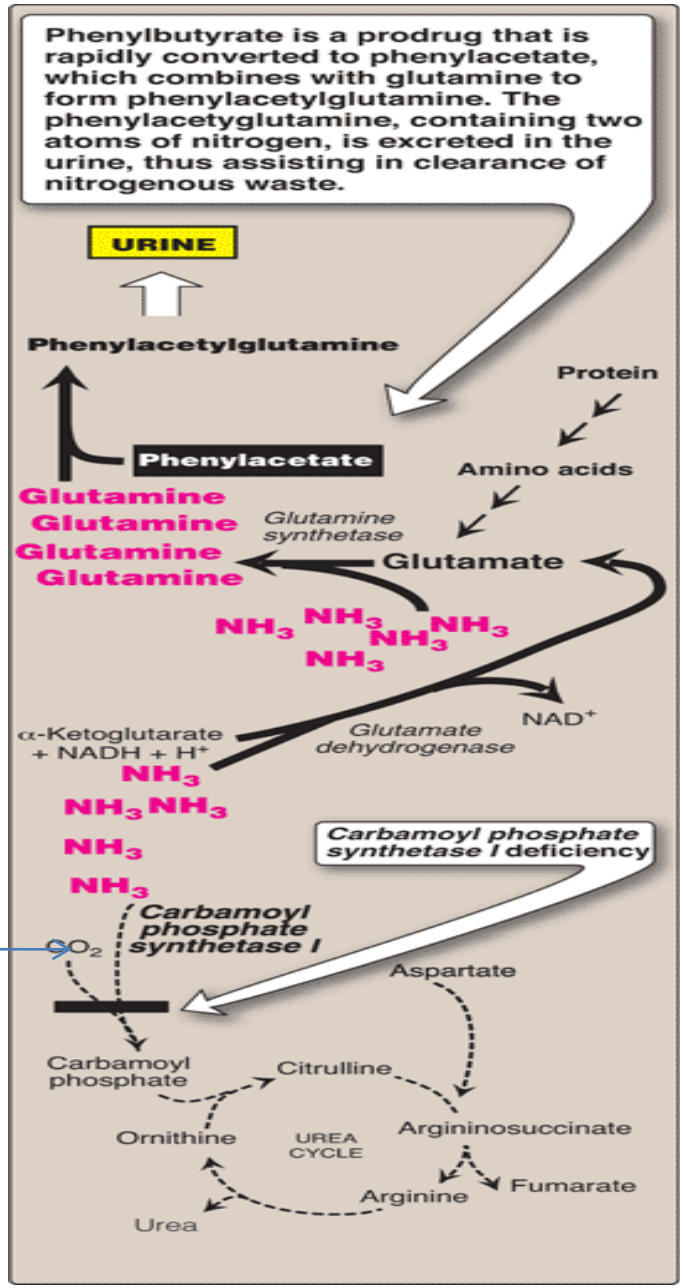
↓

Due to the Liver diseases
Blood level of ammonia is increased

↓

Affects CNS and could cause death

Patients with carbamoyl Phosphate synthatase I



Amino acid pool

is defined as

All the free amino acids in cells and extracellular fluids

are **produced** by

- **Degradation of body protein**
  - is regulated by
    - Ubiquitin
    - N-Terminal amino acids
    - PEST sequences
  - occurs in
    - Proteasome
    - Lysosome
    - Cytosol via nonspecific proteases
- **Synthesis of nonessential amino acids**
  - requires
    - α-Keto acids and ammonia
- **Degradation of dietary protein**
  - involves
    - Proteolytic enzymes of the GI tract and pancreas

are **consumed** by

- Simultaneous synthesis and degradation — leads to → **Protein turnover**
- **Synthesis of body protein**
  - is regulated by
    - Transcription and translation factors
- **Amino acids used in biosynthesis**
  - involves
    - Biosynthetic pathways
- **Metabolism of amino acids**
  - involves
    - Intermediary metabolism

Removal of nitrogen from amino acids

occurs because

Amino acids cannot directly participate in energy metabolism

therefore

Amino groups are removed

mediated by

Two sequential reactions

first

1 Transaminases — elevated serum levels can detect → **Liver damage**

- due to
  - Hepatitis
  - Cirrhosis
  - Heptotoxic drugs
  - Defects in enzymes of the urea cycle

result in

Amino groups transferred to α-keto acids forming:

- **Aspartate**
- **Glutamate**

followed by

2 Glutamate dehydrogenase

results in

Glutamate oxidatively deaminated to:

- **α-Ketoglutarate**
- **NH_3** — can be stored and transported as → **Glutamine**

Glutamine can release ammonia

enters

Urea cycle

- may have
  - **Inherited enzyme deficiencies**
    - characterized by
      - Hyperammonemia
      - Mental retardation
    - treated by
      - Drug therapy
      - Reduction of protein intake
- results in
  - **Nitrogen of asparate, CO_2, and NH_3 incorporated into**
  - **Urea**