Protein Metabolism and it's Disorders

(Course : M.Sc. Zoology)

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Important facts of the Protein Metabolism

•Proteins metabolism referred as synthesis of protein from Amino acids (Anabolism) and breakdown of proteins (Catabolism).

•In the Unit II, we discussed the synthesis (Anabolism) of various form of the proteins from different amino acids.

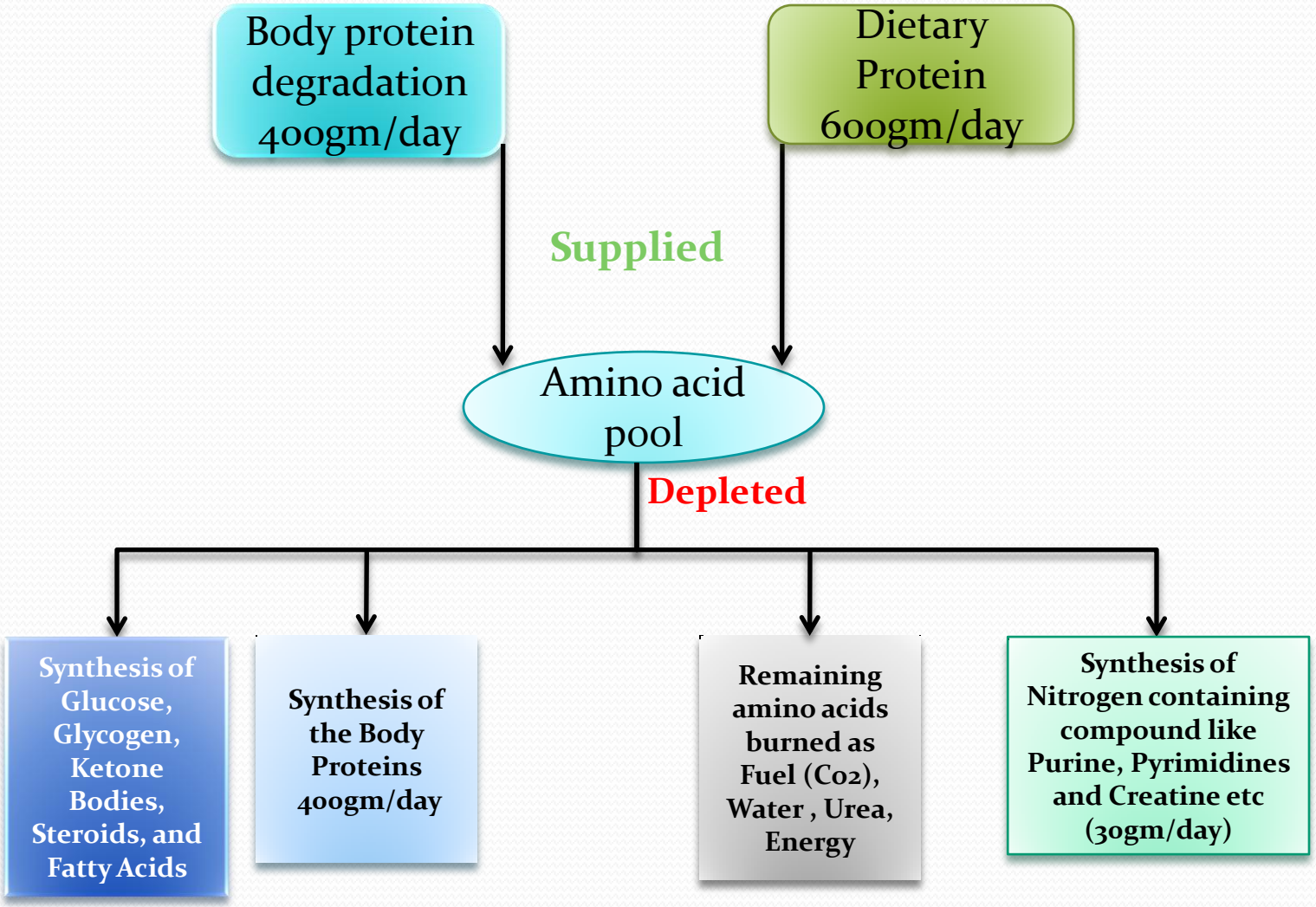
• Here we mainly focused on the Catabolism of the protein, which is integral part of metabolism of the **nitrogen-containing molecules.**

• Nitrogen enters in to the body in various form of compounds that is present in food, the most important is amino acids (as dietary food).

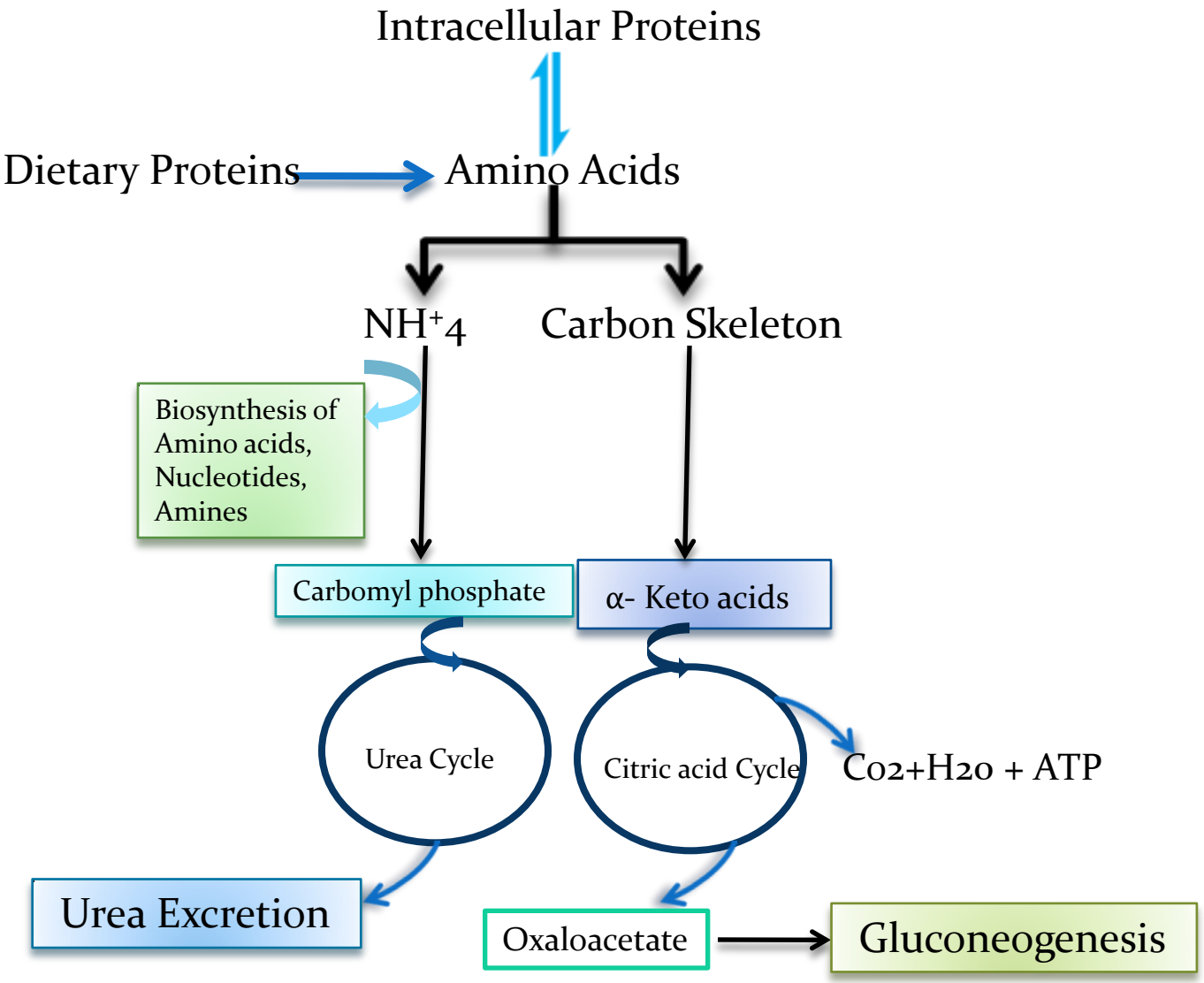
• During Protein/amino acid metabolism (Catabolism), Nitrogen leaves the body as urea, ammonia, and in form of other derivatives.

• The Catabolism of the protein depends on **the amino acid pool and protein turnover** (the rate of protein synthesis and degradation is equal).

• The amino acids present in through out of the body (cells, blood, and the extracellular fluids etc) is called **amino acid pools**. It is maintained by following factors as represented in below diagram:



Fate of Amino acids Catabolism in Mammals



Catabolism Steps of the Amino acids

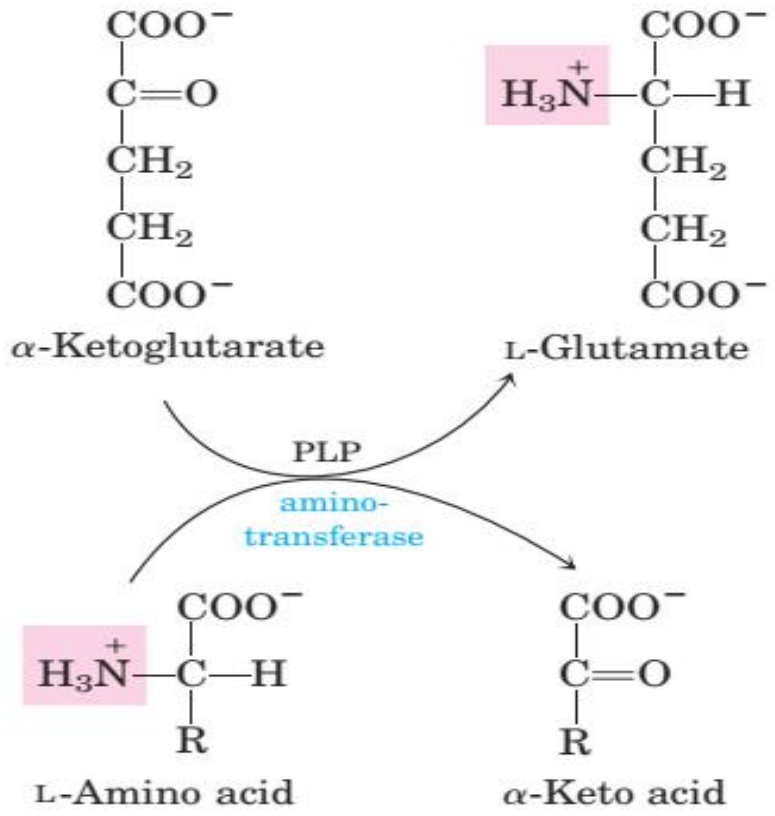
Step1: Transport of amino acids in to the cells: The transport of amino acids occurs from the extracellular fluids in to the cells by **active transport systems, driven by the hydrolysis of ATP.** There are seven different transport systems are known for amino acids in the cells .

Step 2: Transamination: It is a very crucial steps of the catabolism, removing of the α-amino group is essential for producing energy from any amino acid after that removal of remaining carbon skeletons is being metabolized .

Mechanism:

A. The first step in the catabolism of most amino acids is the transfer of their **α-amino group** to **α-ketoglutarate** .

B. The products are an **α-keto acid** (derived from the original amino acid) and **glutamate**.



Note:

PLP(Pyridoxal Phosphate) act as cofactor . Pyridoxal phosphate functions as an intermediate carrier of amino groups at the active site of aminotransferases.

Aminotransferases: It is a enzyme of tranamination reaction requires a prosthetic group PLP (the coenzyme form of pyridoxine, or vitamin B6).

Fig. Enzyme Catalyzed Transamination reaction

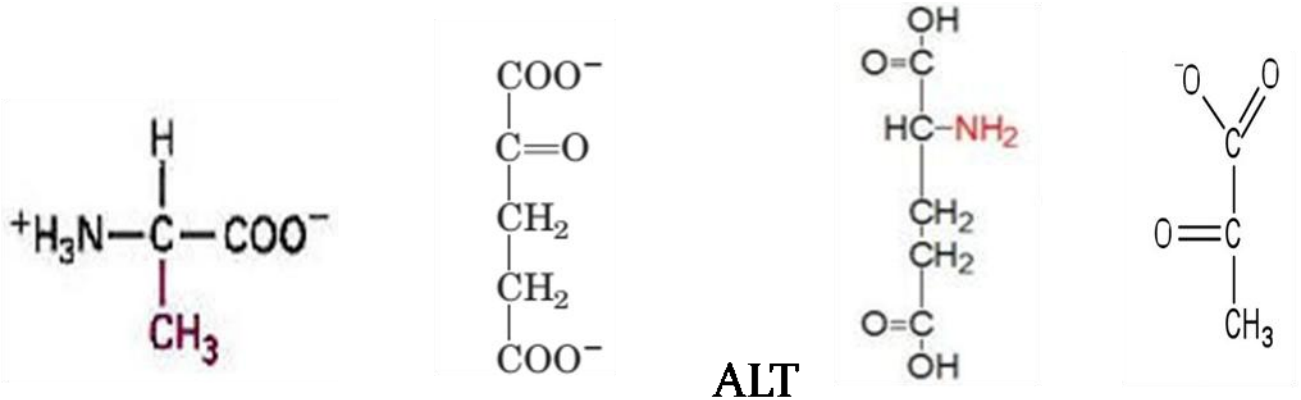
Important facts about Aminotransferases

• There are two most important aminotransferases: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) using substrate alanine and aspartate respectively that catalyzed **transamination** reactions.

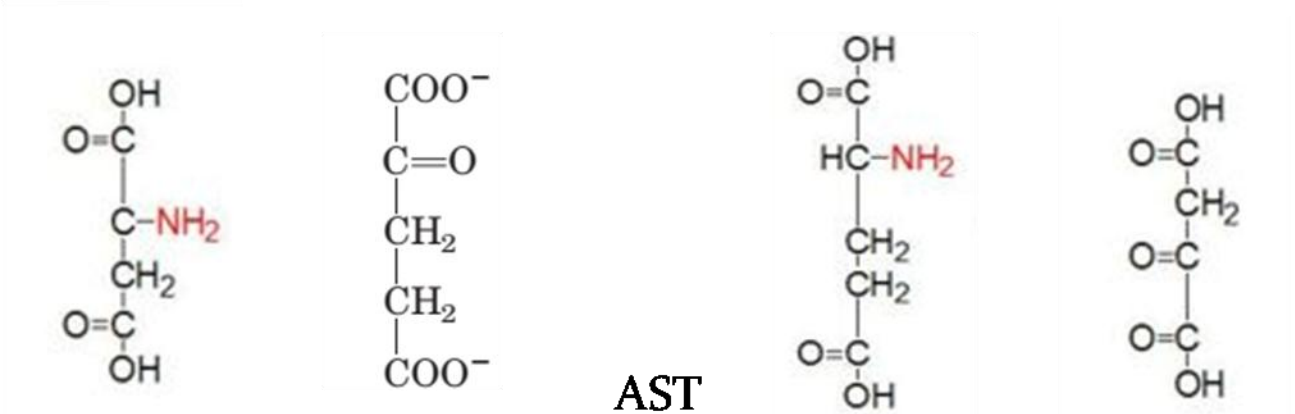
•**Alanine aminotransferase (ALT)** is earlier called **glutamate-pyruvate transaminase,** present in many tissue. It transfer amino group of alanine to α-ketoglutarate, resulting in the formation of pyruvate and glutamate. ALT is normally found inside **liver** cells .

Aspartate aminotransferase (AST) is earlier called **glutamate-oxaloacetate transaminase,** AST transfers amino groups from aspartate to glutamate , forming to oxaloacetate. Glutamate is used as important source of nitrogen in the urea cycle. AST is found in the **liver**, heart, skeletal muscle, kidneys, brain, and red blood cells

• Both ALT and AST have lots of clinical significance . The high level of plasma concentration indicates liver dysfunction, myocardial infarction and muscle disorders. Moreover, ALT is more specific than AST for liver disease because normally found inside **liver** cells.



Alanine + α- Ketoglutarate ⇌ Glutamate + Pyruvate



Aspartate + α- Ketoglutarate ⇌ Glutamate + Oxaloacetate

Step3. Oxidative deamination:

• After the transamination reactions that transfer amino groups, oxidative deamination occurs by **glutamate dehydrogenase** results in the liberation of the amino group as free ammonia from Glutamate. This reaction is occurs in the liver.

• The α-keto acids enter the central pathway of energy metabolism and ammonia in urea synthesis, liberated after oxidative deamination.

•**Glutamate** is a unique amino acid that only undergoes rapid oxidative deamination, that is catalyzed by **glutamate dehydrogenase**.

•The glutamate dehydrogenase of mammalian liver has the unusual capacity to use either NAD^+ or $NADP^+$ as cofactor.

Mechanism of Oxidative deamination:

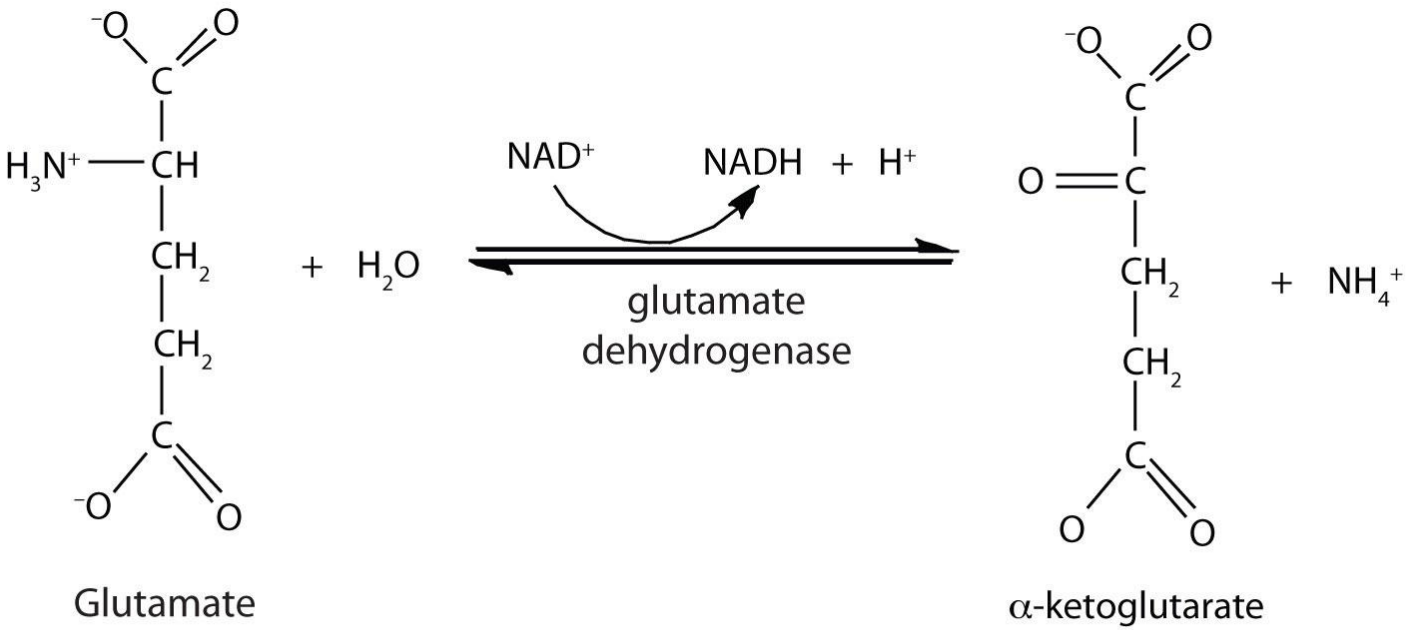


Fig. Reaction is catalyze by enzyme glutamate dehydrogenase

Note# D-Amino acid oxidase: In addition to the glutamate dehydrogenase , the D-Amino acid oxidase is an FAD-dependent peroxisomal enzyme that catalyzes the oxidative deamination of these amino acid isomers, which are found in plants. D-Amino acids are found in plants and in the cell walls of microorganisms.

Mechanism of Transport of ammonia to the Liver

• Since the ammonia is highly toxic in nature which is liberated through oxidative deamination, and can't transport directly to the liver alone.

• Therefore, there are two mechanisms are available in humans for the transport of ammonia from peripheral tissues to the liver for conversion to urea.

•**The first:** it is found in most tissues, where uses glutamine synthetase to combine ammonia with glutamate to form Glutamine (a nontoxic transport form of ammonia).
• Then the glutamine is transported from blood to the liver, where it cleaved by Glutaminase to produce glutamate and free ammonia.

•**The second**: In form of Alanine in muscle, where pyruvate (the end product of aerobic glycolysis) involves transamination reaction to form alanine. The tranaport of ammonia in muscle pathway is called the **glucose-alanine cycle.**

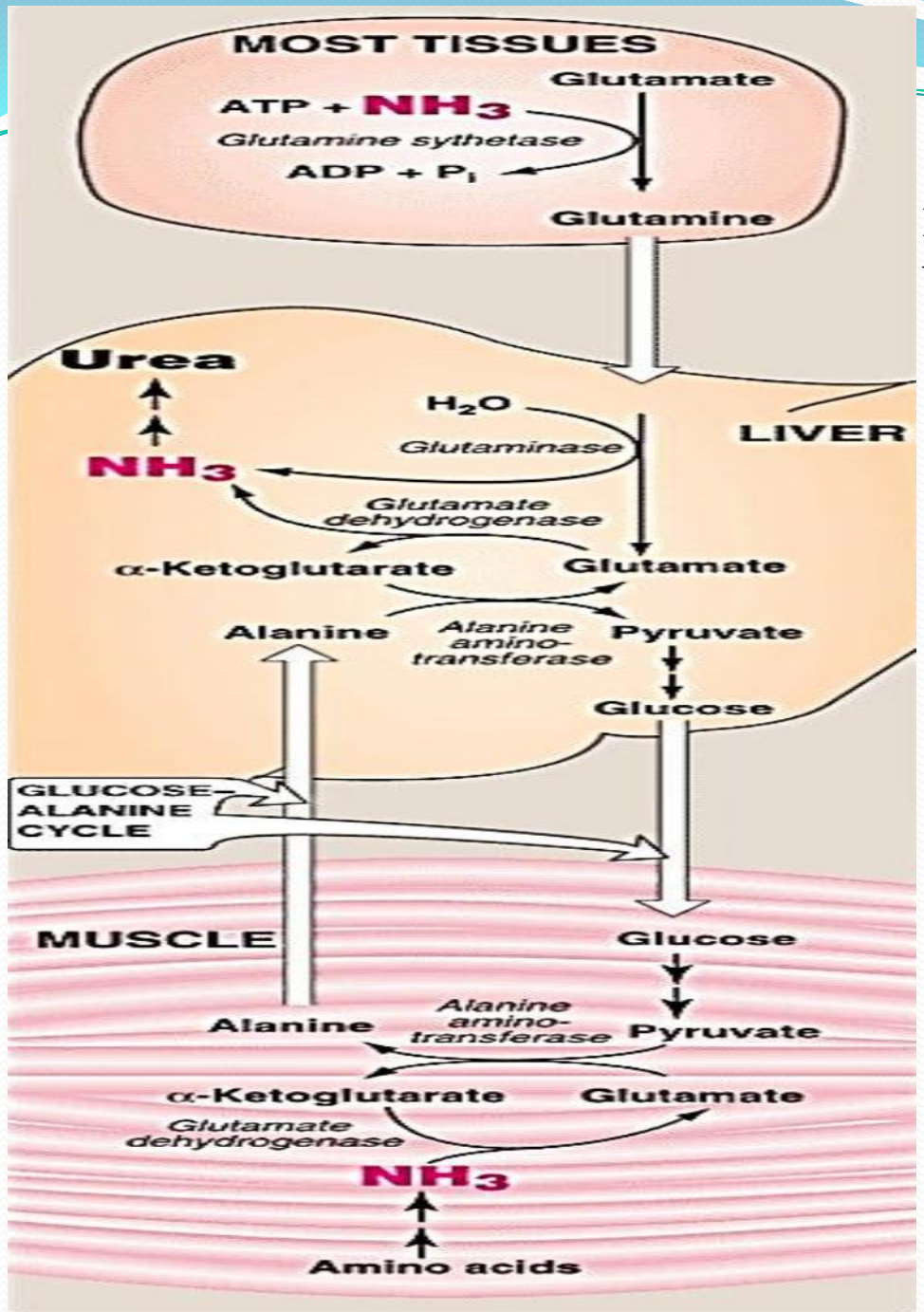


Fig: Transport of ammonia from peripheral tissues to the liver

Urea Cycle

There are different mode of nitrogen excretion in different organisms:

Ammonotelic: Excreting amino nitrogen as ammonia ex. Most aquatic species .

•**Uricotelic :** Excreting amino nitrogen in the form of uric acids in birds and reptiles .

•**Ureotelic** : Excreting amino nitrogen in the form of urea in terrestrial animals.

• So in ureotelic organisms, first ammonia deposited in the mitochondria of hepatocytes and get converted to urea is called **Urea cycle**.

• This pathway was discovered in 1932 by Hans Krebs and Kurt Henseleit.

•Urea production occurs almost exclusively in the liver and ultimately excreted through kidneys in form of urine.

There are fives steps in the Urea Cycle:

1- Formation of carbamoyl phosphate
2-Formation of citrulline
3- Formation of argininosuccinate
4- Formation of arginine and fumarate
5-Formation of urea and ornithine

Mitochondria of liver Cells

Cytosol of liver Cells

Note#

•**Carbamoyl phosphate synthetase I (CPSI);** Involves in the formation of carbamoyl phosphate that requires two molecules of ATP . It is rate limiting steps. Carbamoyl phosphate synthetase I requires **N-acetylglutamate (NAG)** as a positive allosteric activator.

•N-acetylglutamate is synthesized from acetyl coenzyme A and glutamate by **N-acetylglutamate synthase.** The level of NAG is controlled by protein-rich meal/less protein rich meal.

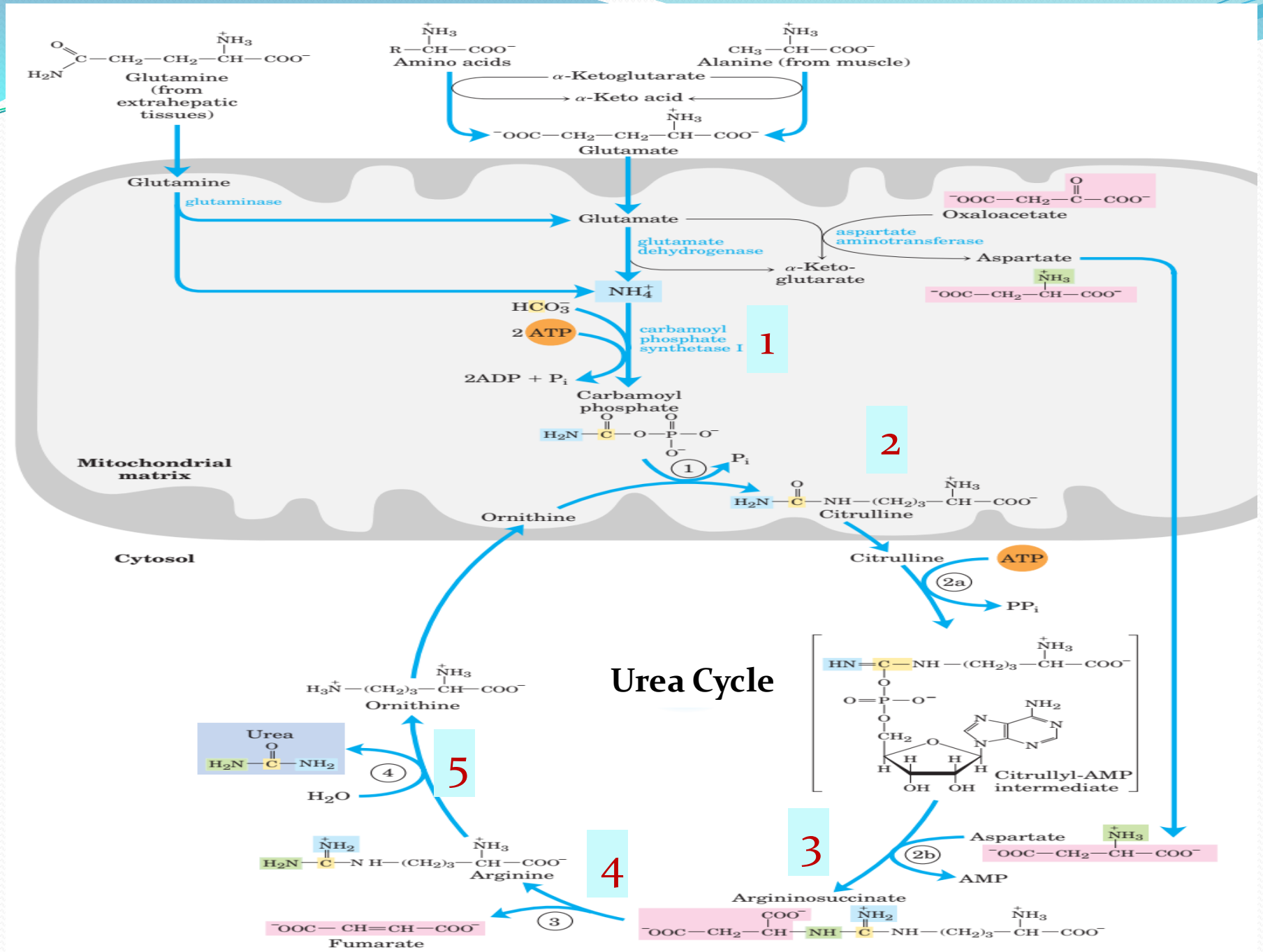


Fig. Urea cycle (Adopted from Lehninger (Principles of Biochemistry) , page -666)

Important facts of the Urea Cycle

•Condensation of CO_2, ammonia, and ATP to form **carbamoyl phosphate** is catalyzed by mitochondrial **carbamoyl phosphate synthase I.**

• **Four high-energy phosphates (ATP)** are consumed in the synthesis of each molecule of urea: two ATP to restore two ADP to two ATP to restore AMP. Therefore, the synthesis of urea is irreversible, with a large, negative ΔG.

•The major metabolic role of **ornithine, citrulline,** and **argininosuccinate** in mammals is urea synthesis.

•One nitrogen of the urea molecule is supplied by free NH_3, and the other nitrogen by aspartate .

•Carbamoyl Phosphate Synthase I is the Pacemaker Enzyme of the Urea Cycle.

•Urea diffuses from the liver to blood to the kidneys, where it is filtered and excreted in the urine.

Important Disorders Related to Protein Metabolism

•**Hyperammonemia:** When the level of urea get elevated in blood than Normal level of ammonia (5–50 µmol/L), due genetic defects of the urea cycle, or liver disease Called **Hyperammonemia. Its emergency medical situation** because ammonia has a direct neurotoxic effect on the CNS. At high concentrations, ammonia can cause coma and death.

• **Neural Dysfunction**: High level of ammonia Impaired neural transmission process due to **increased formation of GABA**(gamma amino butyric acid) from glutamate.

•**Hyperargininemia**: In this defects elevated level of arginine is found in blood and cerebrospinal fluid .

• Clinical symptoms are common to all urea cycle disorders include vomiting, avoidance of high-protein foods, intermittent ataxia, irritability, lethargy, and mental retardation .

Thank You