METABOLISM OF PROTEIN

PROTEIN METABOLISM

- Amino acid catabolism is part of the larger process of the metabolism of nitrogen-containing molecules. Nitrogen enters the body in a variety of compounds present in food, the most important being amino acids contained in dietary protein. Nitrogen leaves the body as urea, ammonia, and other products derived from amino acid metabolism. The role of body proteins in these transformations involves two important concepts: the amino acid pool and protein turnover.

A. Amino acid pool

- Free amino acids are present throughout the body, for example, in cells, blood, and the extracellular fluids. For the purpose of this discussion, envision all these amino acids as if they belonged to a single entity, called the amino acid pool.
- This pool is supplied by three sources:

1) amino acids provided by the degradation of body proteins,

2) amino acids derived from dietary protein, and

3) synthesis of nonessential amino acids from simple intermediates of metabolism.

- Conversely, the amino pool is reduced by three routes:

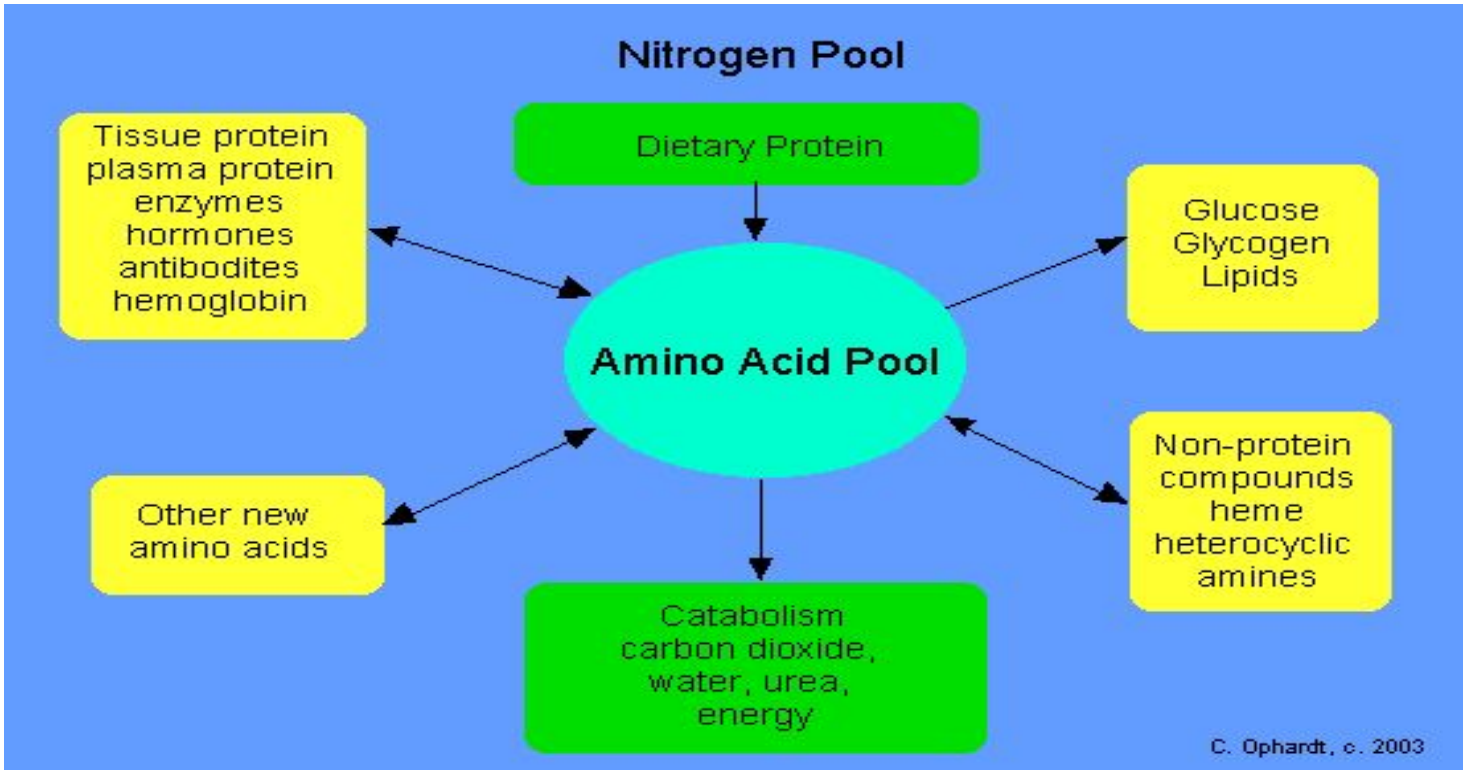
1) synthesis of body protein,

2) amino acids consumed as precursors of essential nitrogen-containing small molecules, and

3) conversion of amino acids to glucose, glycogen, fatty acids, ketone bodies, or CO_2 + H_2O.

B. PROTEIN TURNOVER

- Most proteins in the body are constantly being synthesized and then degraded, permitting the removal of abnormal or unneeded proteins. For many proteins, regulation of synthesis determines the concentration of protein in the cell, with protein degradation assuming a minor role. For other proteins, the rate of synthesis is constitutive, that is, relatively constant, and cellular levels of the protein are controlled by selective degradation.



DIGESTION OF DIETARY PROTEINS

A. Digestion of proteins by gastric secretion
   1) Hydrochloric acid,
   2) Pepsin
B. Digestion of proteins by pancreatic enzymes
   1) Specificity,
   2) Release of zymogens,
   3) Activation of zymogens,
   4) Abnormalities in protein digestion
C. Digestion of oligopeptides by enzymes of the small intestine
D. Absorption of amino acids and small peptides

AMINO ACID DEAMINATION

- The first reaction in the breakdown of an amino acid is almost always removal of its alphaamino group with the object of excreting excess nitrogen and degrading the remaining carbon skeleton or converting it to glucose. Urea, the predominant nitrogen excretion product in terrestrial mammals, is synthesized from ammonia and aspartate. Both of these latter substances are derived mainly from glutamate, a product of most deamination reactions.
- Most amino acids are deaminated by transamination, the transfer of their amino group to an alpha-keto acid to yield the alpha-keto acid of the original amino acid and a new amino acid,in reactions catalyzed by aminotransferases.

1. Oxidative deamination

   Oxidative deamination is the liberation of free ammonia from the amino group of amino acids coupled with oxidation. This takes place mostly in liver and kidney. The purpose of oxidative deamination is to provide NH3 for urea synthesis and D-keto acids for a variety of reactions, including energy generation.

2. Non-oxidative deamination

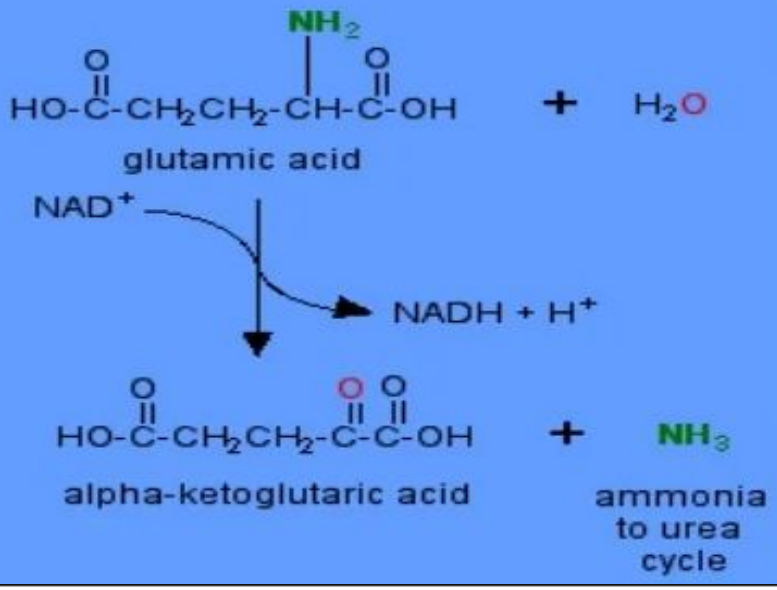
   Some of the amino acids can be deaminated to liberate NH3 without undergoing oxidation, eg.

   (a) Amino acid dehydrases

   (b) Amino acid desulfhydrases

   (c) Deamination of histidine

Oxidative Deamination

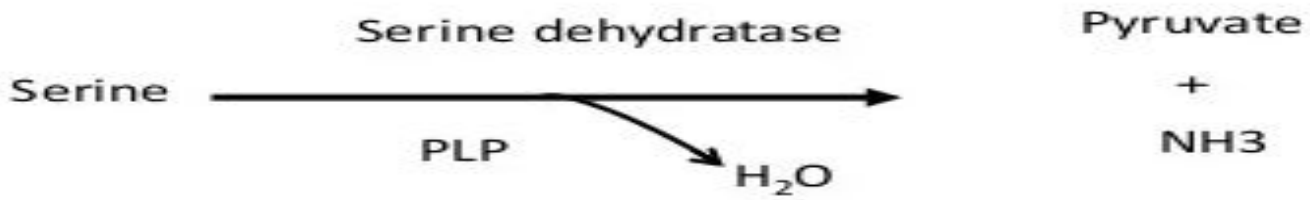


Nonoxidative deamination

Removal of the α amino group of amino acid as free ammonia without oxidation of the amino acid

Dehydratase

Acts on hydroxyl amino acids to remove ammonia



TRANSAMINATION

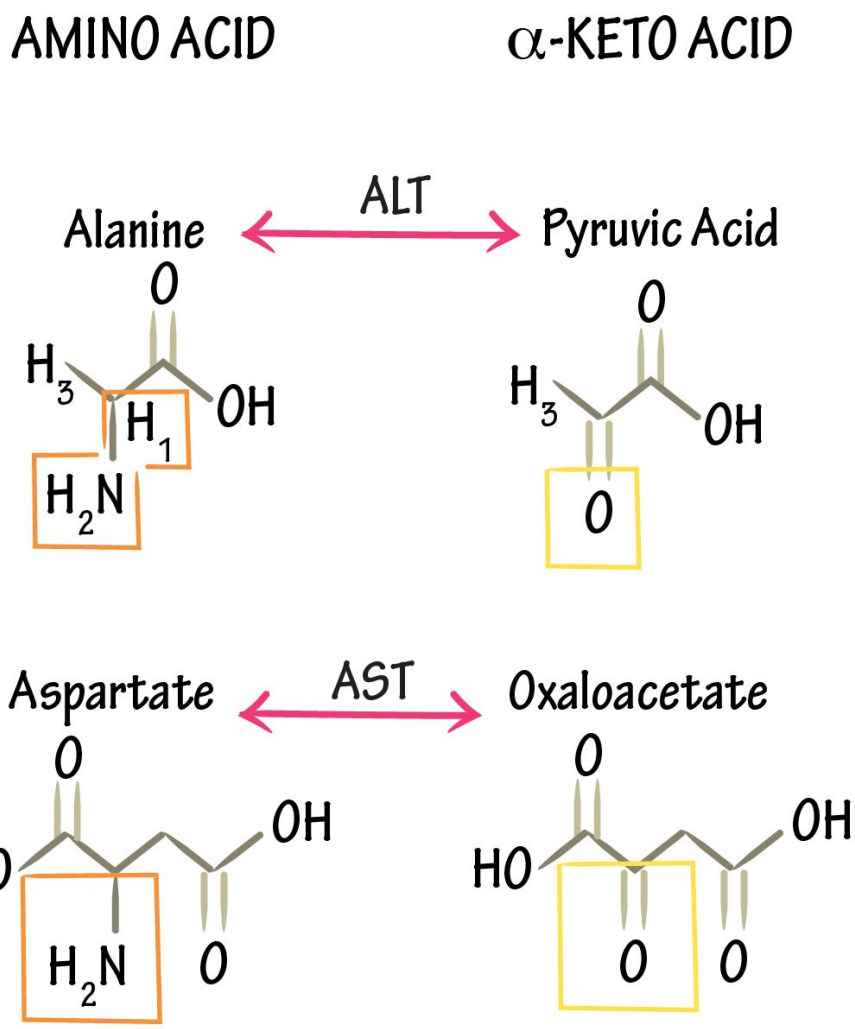
- The transfer of an amino (NH_2) group from an amino acid to a keto acid is known as transamination. This process involves the interconversion of a pair of amino acids and a pair of keto acids, catalysed by a group of enzymes called transaminases (recently, aminotransferases).
- Transamination occurs in two stages –

1. Transfer of the amino group to the coenzyme pyridoxal phosphate (bound to the coenzyme) to form pyridoxamine phosphate.
2. The amino group of pyridoxamine phosphate is then transferred to a keto acid to produce a new amino acid and the enzyme with PLP is regenerated.

- All the transaminases require pyridoxal phosphate (PLP), a derivative of vitamin B6. The aldehyde group of PLP is linked with H-amino group of lysine residue, at the active site of the enzyme forming a Schiff base (imine linkage). When an amino acid (substrate) comes in contact with the enzyme, it displaces lysine and a new Schiff base linkage is formed. The amino acid-PLP-Schiff base tightly binds with the enzyme by noncovalent forces. Snell and Braustein proposed a Ping Pong Bi Bi mechanism involving a series of intermediates (aldimines and ketimines) in transamination reaction.

Transamination Components

Aminotransferases

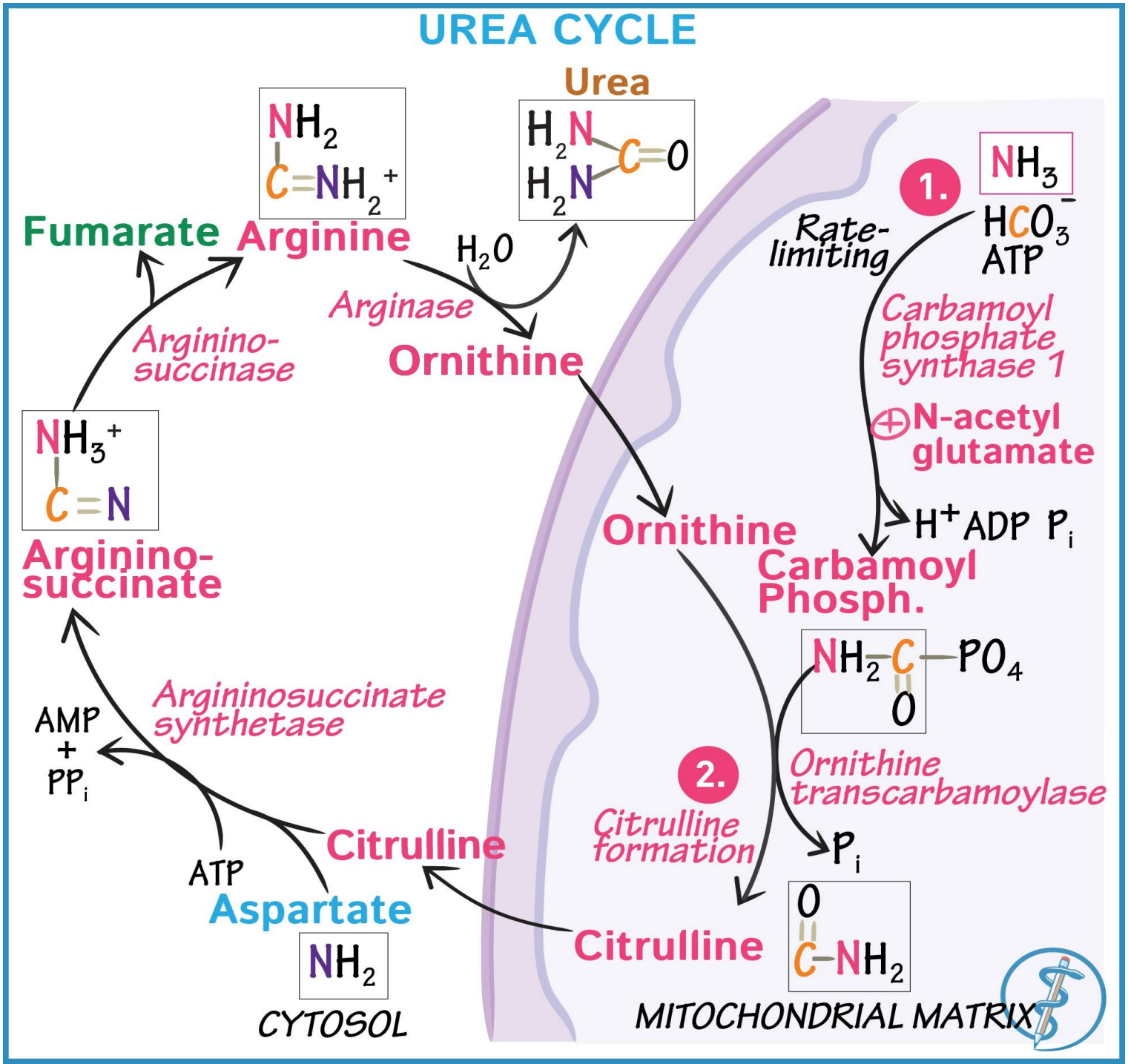


UREA CYCLE

- Urea is the major disposal form of amino groups derived from amino acids, and accounts for about 90% of the nitrogen-containing components of urine. One nitrogen of the urea molecule is supplied by free ammonia, and the other nitrogen by aspartate. The carbon and oxygen of urea are derived from CO2. Urea is produced by the liver, and then is transported in the blood to the kidneys for excretion in the urine.
- The first two reactions leading to the synthesis of urea occur in the mitochondria, whereas the remaining cycle enzymes are located in the cytosol

1. **Formation of carbamoyl phosphate:** Formation of carbamoyl phosphate by carbamoyl phosphate synthetase I is driven by cleavage of two molecules of ATP. Ammonia incorporated into carbamoyl phosphate is provided primarily by the oxidative deamination of glutamate by mitochondrial glutamate dehydrogenase.Ultimately, the nitrogen atom derived from this ammonia becomes one of the nitrogens of urea. Carbamoyl phosphate synthetase I requires N-acetylglutamate as a positive allosteric activator.
2. **Formation of citrulline:** The carbamoyl portion of carbamoyl phosphate is transferred to ornithine by ornithine transcarbamoylase (OTC) as the high-energy phosphate is released as Pi. The reaction product, citrulline, is transported to the cytosol. [Note: Ornithine and citrulline are basic amino acids that participate in the urea cycle, moving across the inner mitochondrial membrane via a cotransporter. They are not incorporated into cellular proteins because there are no codons for these amino acids.

3. **Synthesis of argininosuccinate:** Argininosuccinate synthetase combines citrulline with aspartate to form argininosuccinate. The α-amino group of aspartate provides the second nitrogen that is ultimately incorporated into urea. The formation of argininosuccinate is driven by the cleavage of ATP to adenosine monophosphate (AMP) and pyrophosphate. This is the third and final molecule of ATP consumed in the formation of urea.
4. **Cleavage of argininosuccinate:** Argininosuccinate is cleaved by argininosuccinate lyase to yield arginine and fumarate. The arginine formed by this reaction serves as the immediate precursor of urea. Fumarate produced in the urea cycle is hydrated to malate, providing a link with several metabolic pathways. For example, the malate can be transported into the mitochondria via the malate shuttle, reenter the tricarboxylic acid cycle, and get oxidized to oxaloacetate (OAA), which can be used for gluconeogenesis.Alternatively, the OAA can be converted to aspartate via transamination, and can enter the urea cycle
5. **Cleavage of arginine to ornithine and urea:** Arginase cleaves arginine to ornithine and urea, and occurs almost exclusively in the liver. Thus, whereas other tissues, such as thekidney, can synthesize arginine by these reactions, only the liver can cleave arginine and, thereby, synthesize urea.
6. **Fate of urea:** Urea diffuses from the liver, and is transported in the blood to the kidneys, where it is filtered and excreted in the urine. A portion of the urea diffuses from the blood into the intestine, and is cleaved to CO2 and NH3 by bacterial urease . This ammonia is partly lost in the feces, and is partly reabsorbed into the blood. In patients with kidney failure, plasma urea levels are elevated, promoting a greater transfer of urea from blood into the gut. The intestinal action of urease on this urea becomes a clinically important source of ammonia, contributing to the hyperammonemia often seen in these patients. Oral administration of neomycin reduces the number of intestinal bacteria responsible for this NH3 production.


UREA CYCLE
Urea
Fumarate
Arginine
H_2O
Arginase
Ornithine
Arginino-succinase
Arginino-succinate
Argininosuccinate synthetase
AMP + PP_i
ATP
Aspartate
Citrulline
CYTOSOL
Rate-limiting
1.
HCO_3^-
ATP
Carbamoyl phosphate synthase 1
⊕N-acetyl glutamate
H^+ ADP P_i
Carbamoyl Phosph.
Ornithine
2.
Citrulline formation
Ornithine transcarbamoylase
P_i
Citrulline
MITOCHONDRIAL MATRIX


THANK YOU