- Thus far, you have studied various pathways including, Glycolysis, Gluconeogenesis, synthesis and degradation of fatty acids, Pentose phosphate pathway, glycogen synthesis and degradation, Monosaccharides etc. Now we will study the metabolism of amino acids which contribute significantly to the generation of metabolic energy. carnivores 90% herbivores very little. First lets begin by understanding how we get rid of Nitrogen from our bodies, so lets look at the Urea cycle.

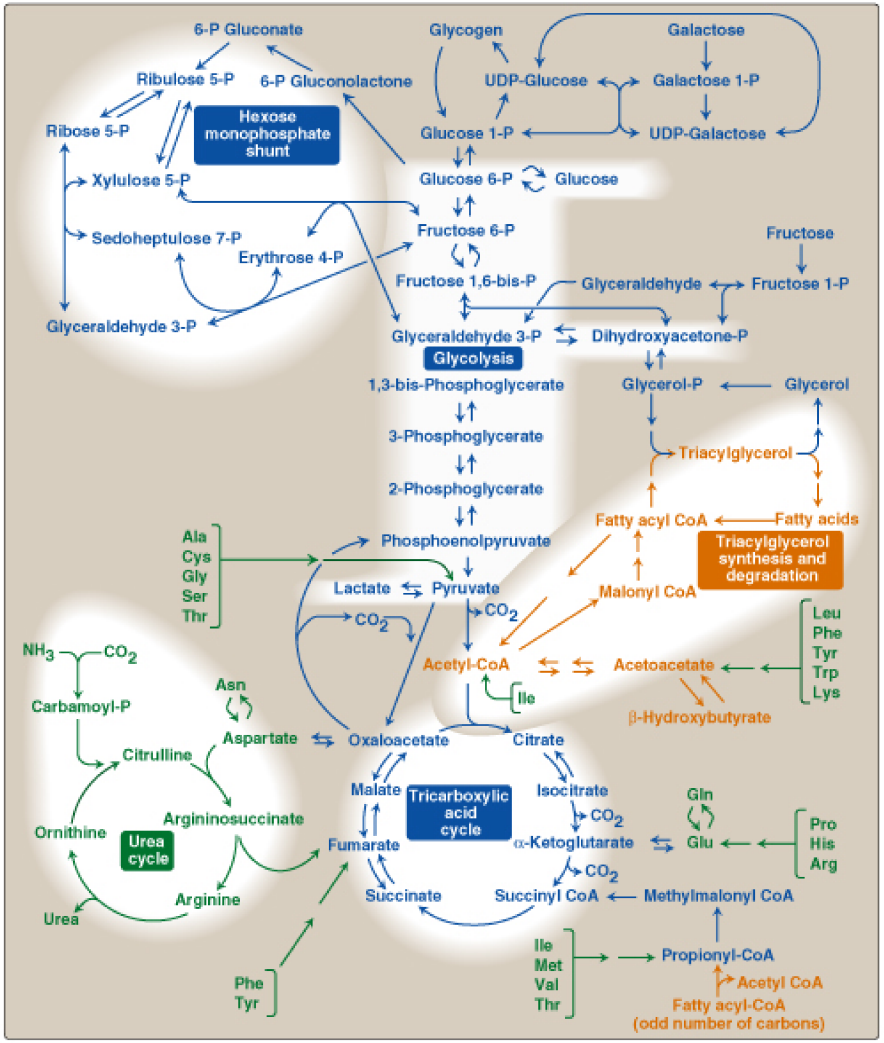


Figure 8.2
Important reactions of intermediary metabolism. Several important pathways to be discussed in later chapters are highlighted. Curved reaction arrows (⟲) indicate forward and reverse reactions that are catalyzed by different enzymes. The straight arrows (⇆) indicate forward and reverse reactions that are catalyzed by the same enzyme. Key: Blue text = intermediates of carbohydrate metabolism; brown text = intermediates of lipid metabolism; green text = intermediates of protein metabolism.

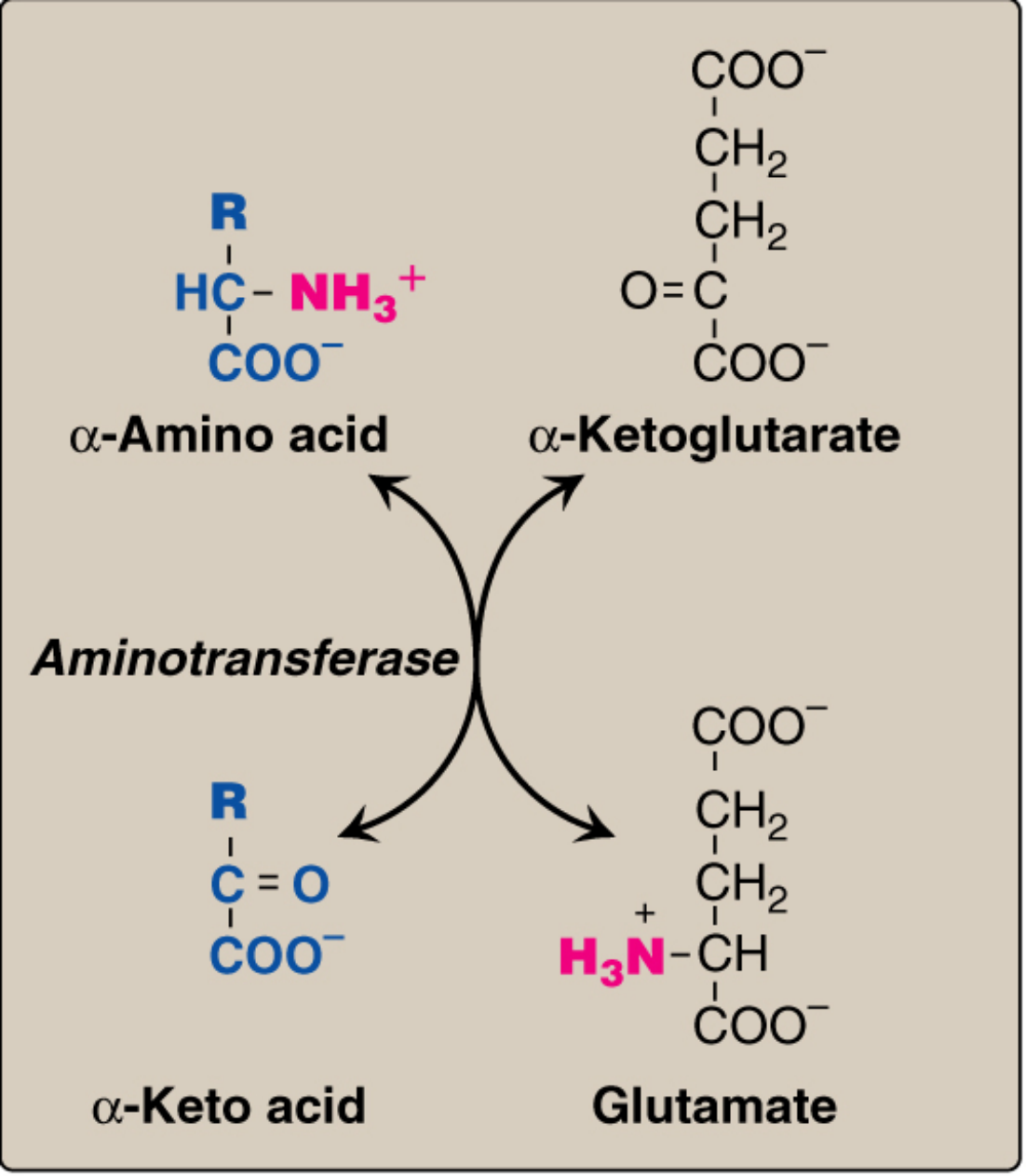


Figure 19.7

Aminotransferase reaction using α-ketoglutarate as the amino-group acceptor.

α Amino group keeps amino acids safe from oxidative breakdown. Removal of this group is essential for energy production it is an obligatory step for catabolism. Nitrogen can then be incorporated or excreted.This is done through transamination or oxidative deamination, provide amonia and aspartate sources for the Urea cycle.

Transamination is funneled through glutamate. This is done through the transfer of the α amino group to α ketoglutarate. Product α-keto acid and glutamate. Alanine to pyruvate and aspartate to oxaloacetate all amino acids except lysine and threonina (lose the α amino through deamination.

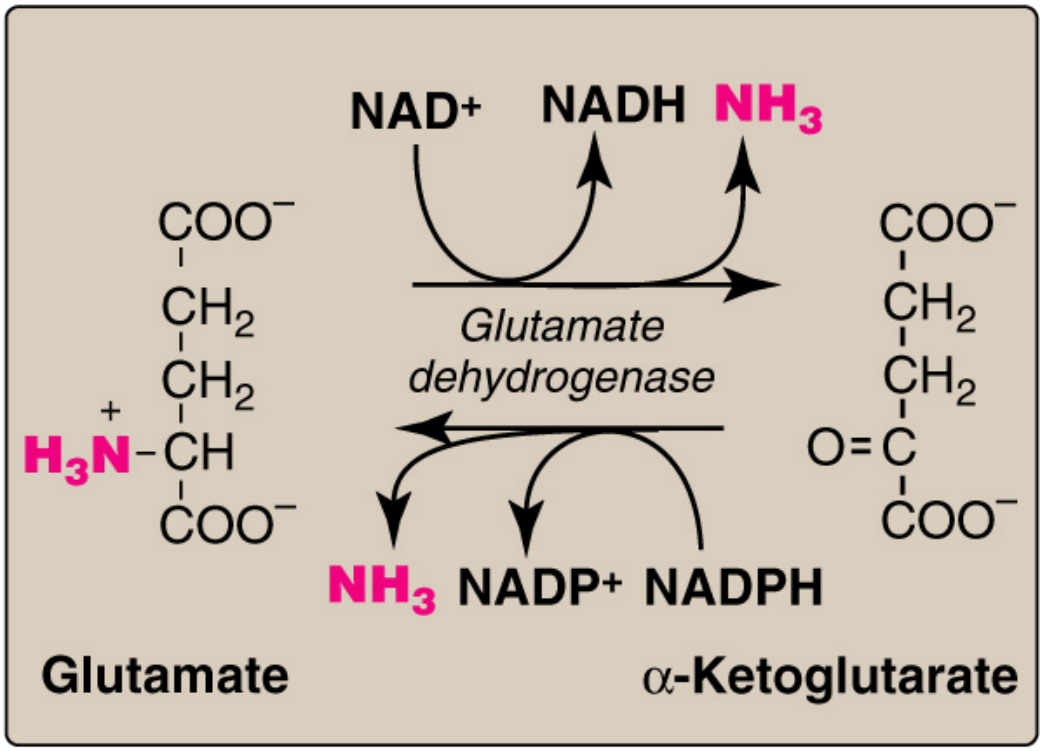


Figure 19.11
Oxidative deamination by *glutamate dehydrogenase*.

Glutamate dehydrogenase the oxidative deamination

Glutamate only amino acid that undergoes rapid oxidative deamination (glutamate dehydrogenase NH3 + NADH), where amino groups are released as ammonia. After a meal rich in protein the levels of glutamate in liver are increased favoring amino acid degradation and formation of ammonia. Activators of this enzyme are ADP and GDP while ATP and GTP are inhibitors. This reaction occurs in the mitochondria.

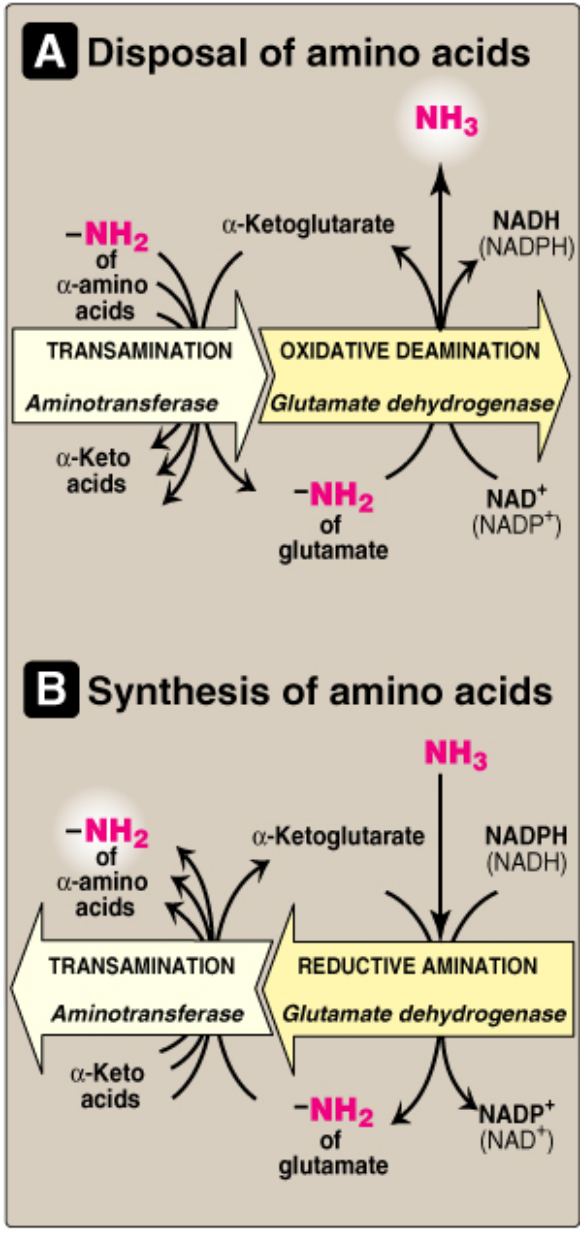
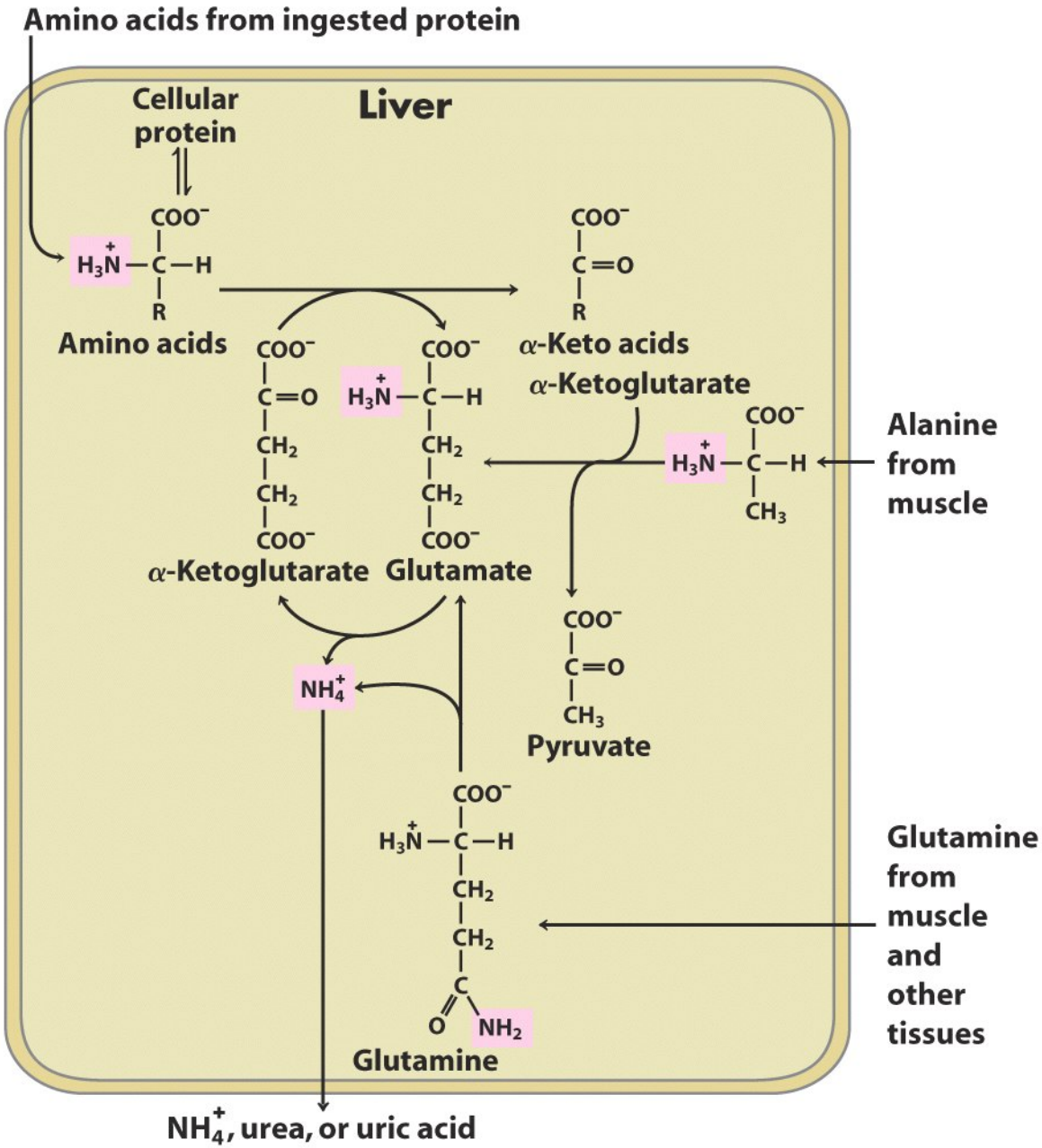


Figure 19.12
Combined actions of *aminotransferase* and *glutamate dehydrogenase* reactions.


Amino acids from ingested protein
Liver
Cellular protein
Amino acids
α-Keto acids
α-Ketoglutarate
Alanine from muscle
α-Ketoglutarate
Glutamate
Pyruvate
Glutamine from muscle and other tissues
Glutamine
NH4+, urea, or uric acid

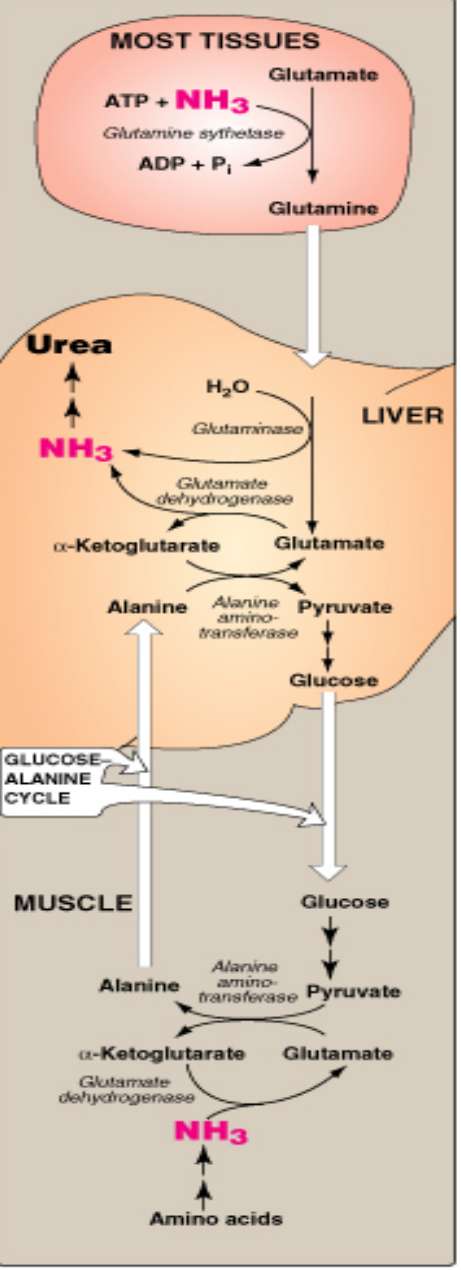


Figure 19.13
Transport of ammonia from peripheral tissues to the liver.

Ammonia can be transported to the liver from other tissues through two mechanisms that reduce the toxicity of ammonia. One through Glutamine (most tissues through, glutamine synthetase). In the liver the glutamine is converted back to glutamate (Fig. 19.17) by glutaminase. The second mechanism is used by muscle, is the transamination of pyruvate to form alanine (alanine aminotransferase). In the Liver alanine is converted again to pyruvate by the same enzyme. Pyruvate then can be used to form glucose and this could be used then by muscles in the glucose-alanine cycle.

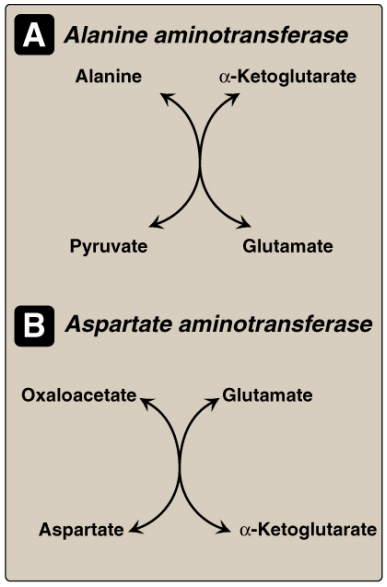
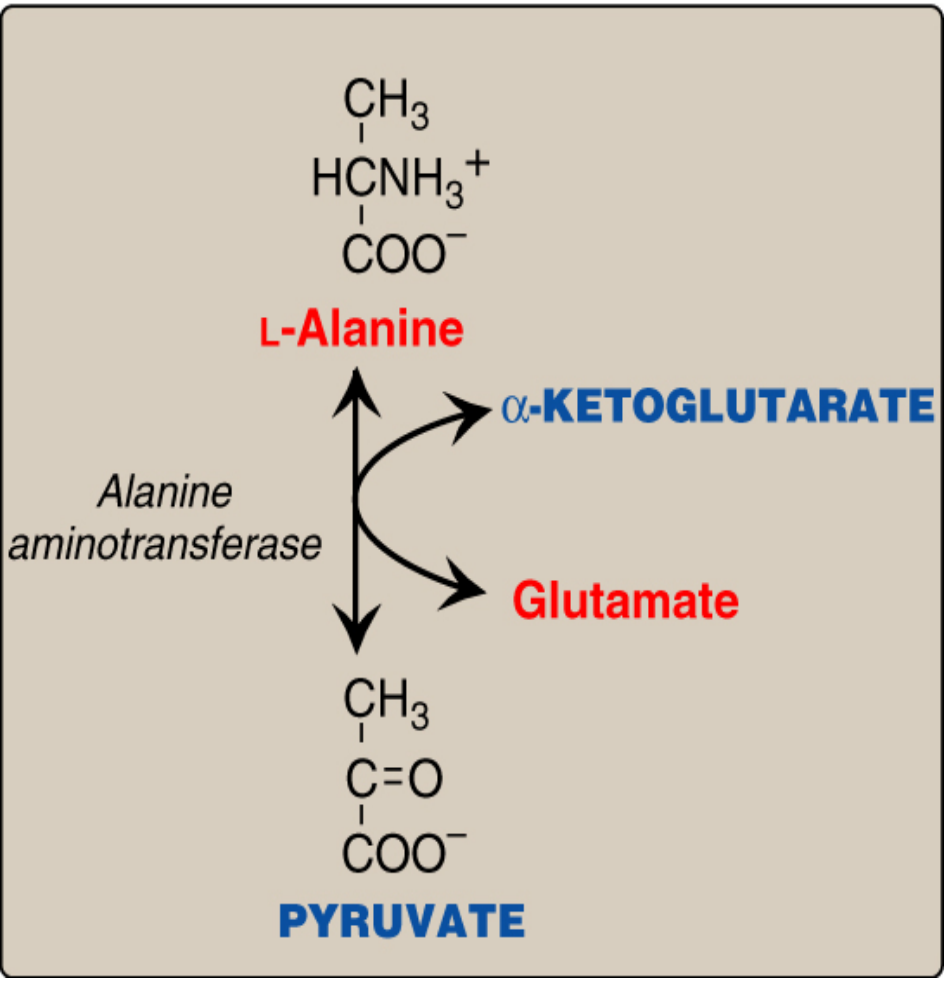


Figure 19.8
Reactions catalyzed during amino acid catabolism. A. *Alanine aminotransferase.* B. *Aspartate aminotransferase.*

Amino acids that form pyruvate



- Alanine loses its amino group by transamination to form pyruvate.

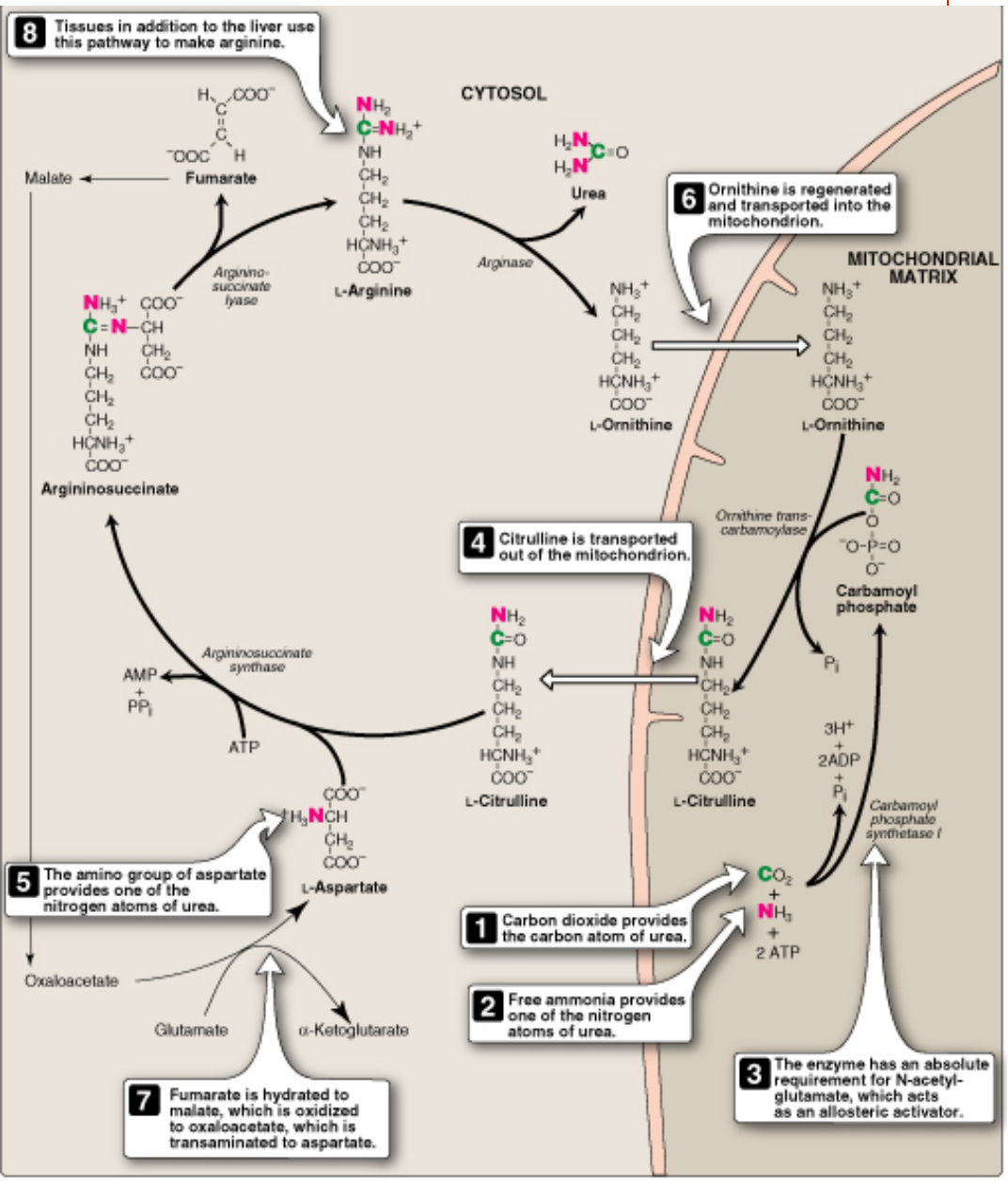


Figure 19.14
Reactions of the urea cycle.

- Reactions of the Urea cycle The formation of carbamoyl phosphate (CO_2 provides the Carbon for Urea and free ammonia provides one of the nitrogen atoms of urea forming the previous compound Carbamoyl phosphate synthetase 1) uses an ATP. This step requires N-acetylglutamate as activator of the enzyme. Carbamoyl phosphate synthetase 2 does not require the activator and is used in biosynthesis of pyrimidines. Citrulline is then formed from L-Ornithine (these two amino acids are not incorporated into proteins). Ornithine is regenerated in each cycle similar to oxaloacetate. The formation of citrulline liberates an inorganic phosphate. Notice that these rxs occur in mitochondrion. Arginosuccinate is then synthesized from aspartate in the cytosol as it condenses with citrulline, the amino group of aspartate provides 2nd nitrogen of Urea. Cleavage of arginosuccinate to yield Arginine & fumarate (arginosuccinate lyase). Arginine is the precursor of urea, fumarate is hydrated to malate (TCA,

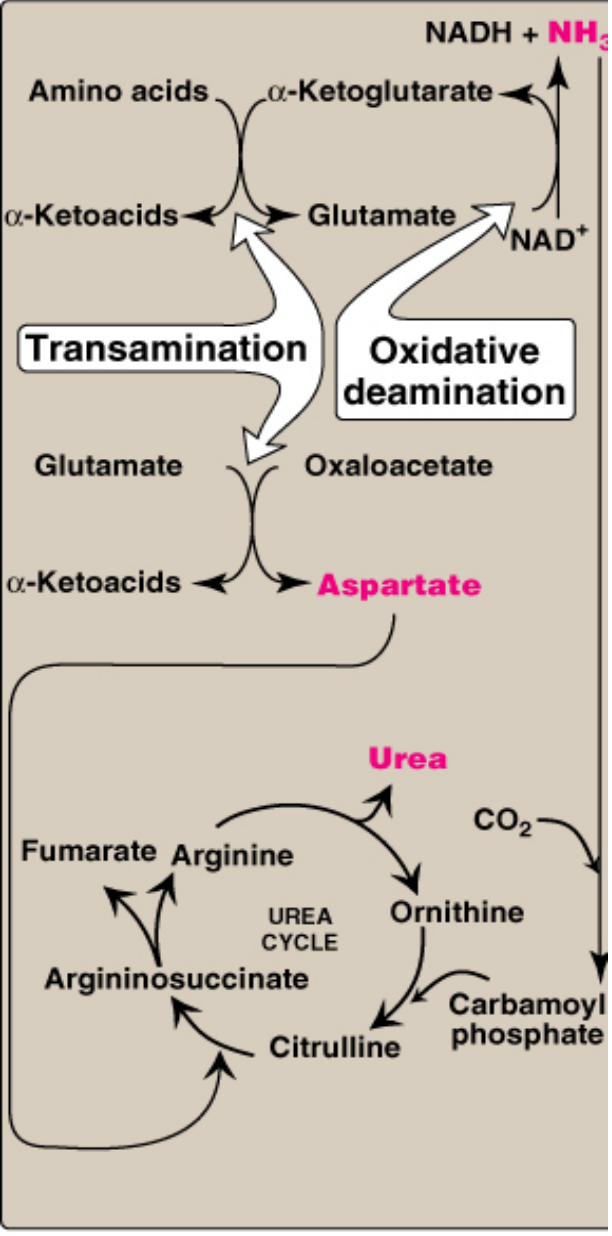


Figure 19.15
Flow of nitrogen from amino acids to urea. Amino groups for urea synthesis are collected in the form of ammonia and aspartate.

- OAX to aspartate) Cleavage of arginine to ornithine and urea (arginase) this occurs almost exclusively in liver. Urea diffuses the liver and transported to the kidneys. Some go into the intestine where it is cleaved to NH3 and CO2 by bacterial urease. In patients with kidney failure we find high levels of NH3 in blood (hyperammonemia) due to reabsorption for which an antibiotic neomycin is given. (important why treatment with antibiotics) A summary of the cycle can observed in this slide. Oxidative deamination of glutamate provides the NH3 and transamination provides aspartate with the other Nitrogen.

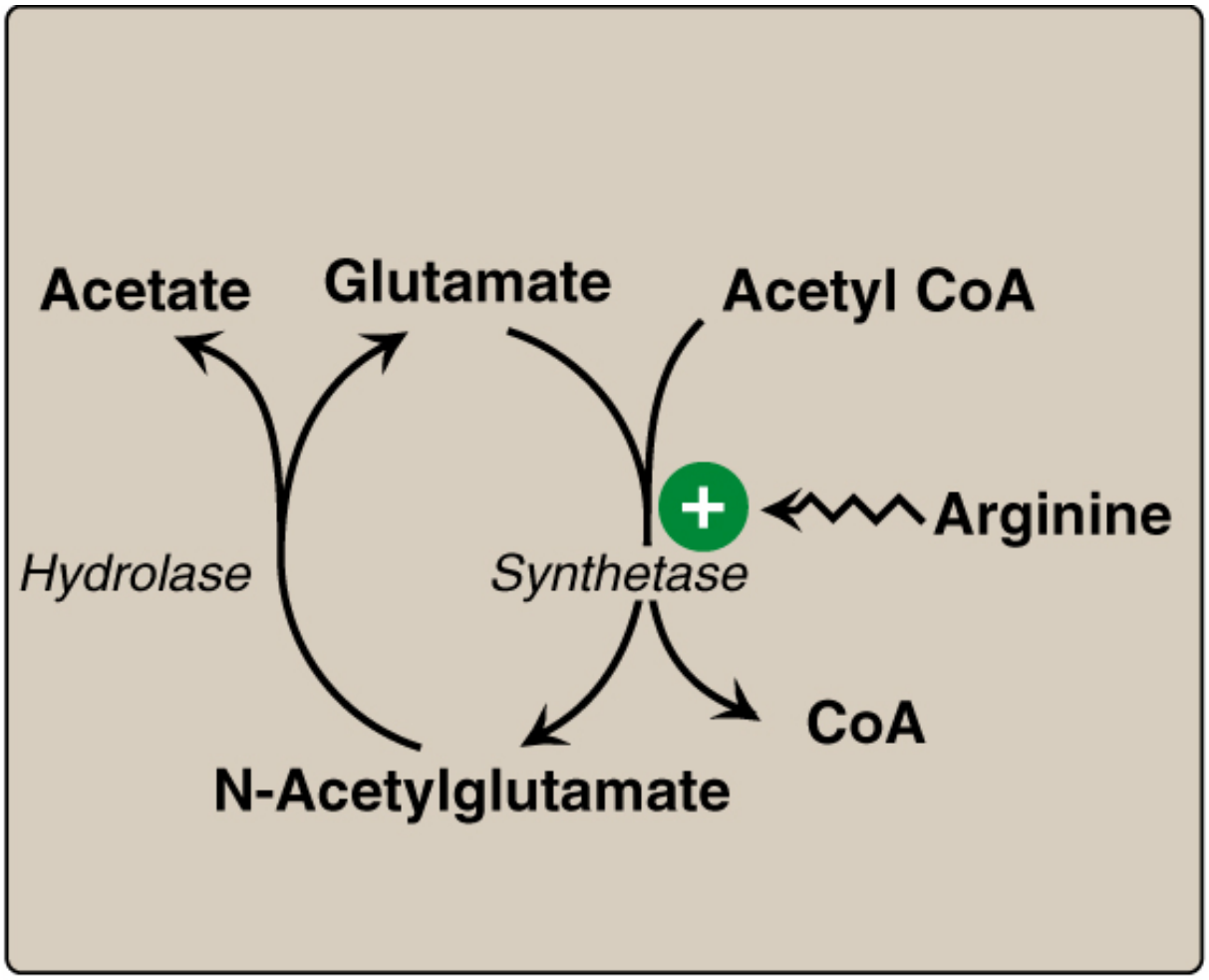


Figure 19.16

Formation and degradation of N-acetylglutamate, an allosteric activator of *carbamoyl phosphate synthetase I*.

This is the rate limiting step of the urea cycle since it could be regulated. N-acetylglutamate is synthesized from acetyl CoA and glutamate. Arginine is an activator. A protein rich meal will lead to an increase rate of urea synthesis. This drives the formation of carbamoyl phosphate and urea production.

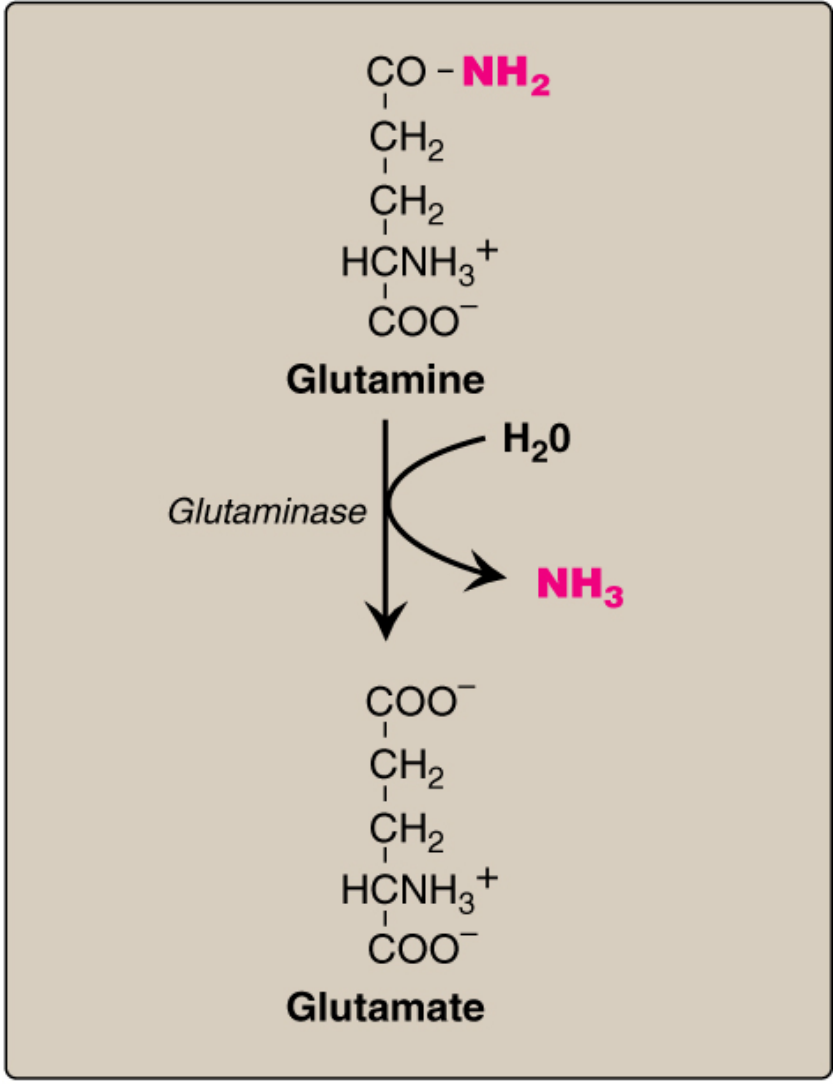


Figure 19.17
Hydrolysis of glutamine to form ammonia.

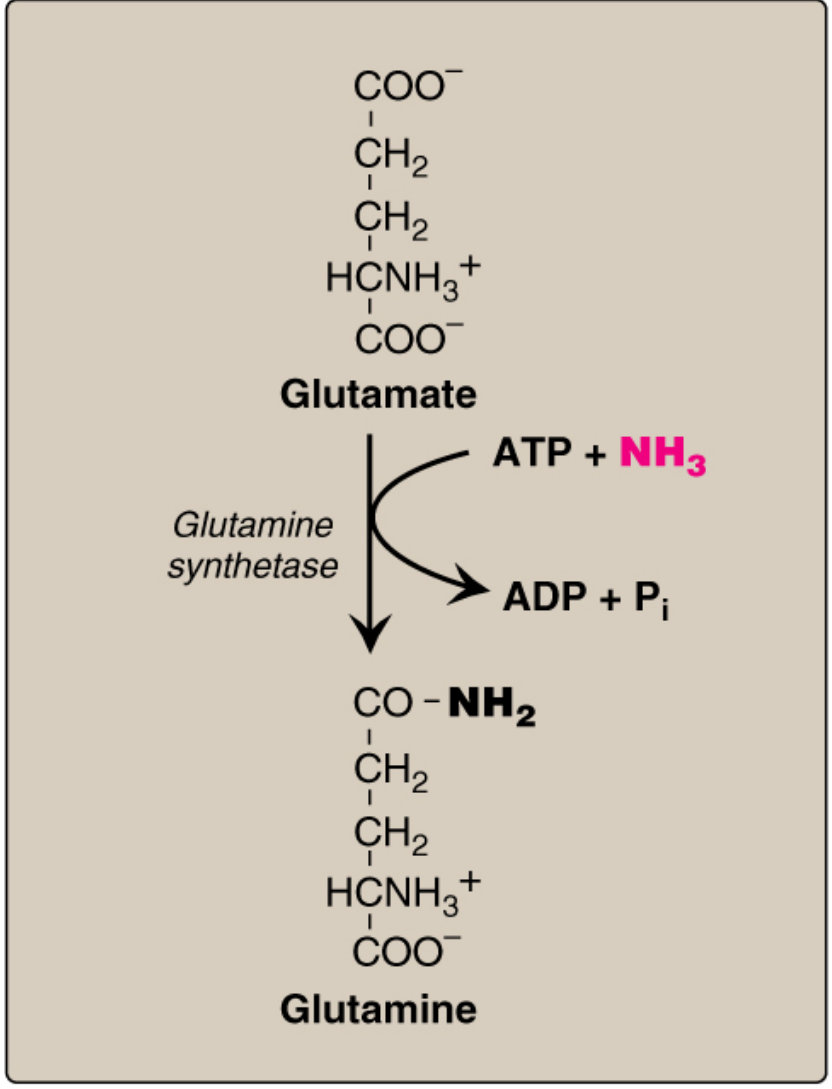


Figure 19.18
Synthesis of glutamine.