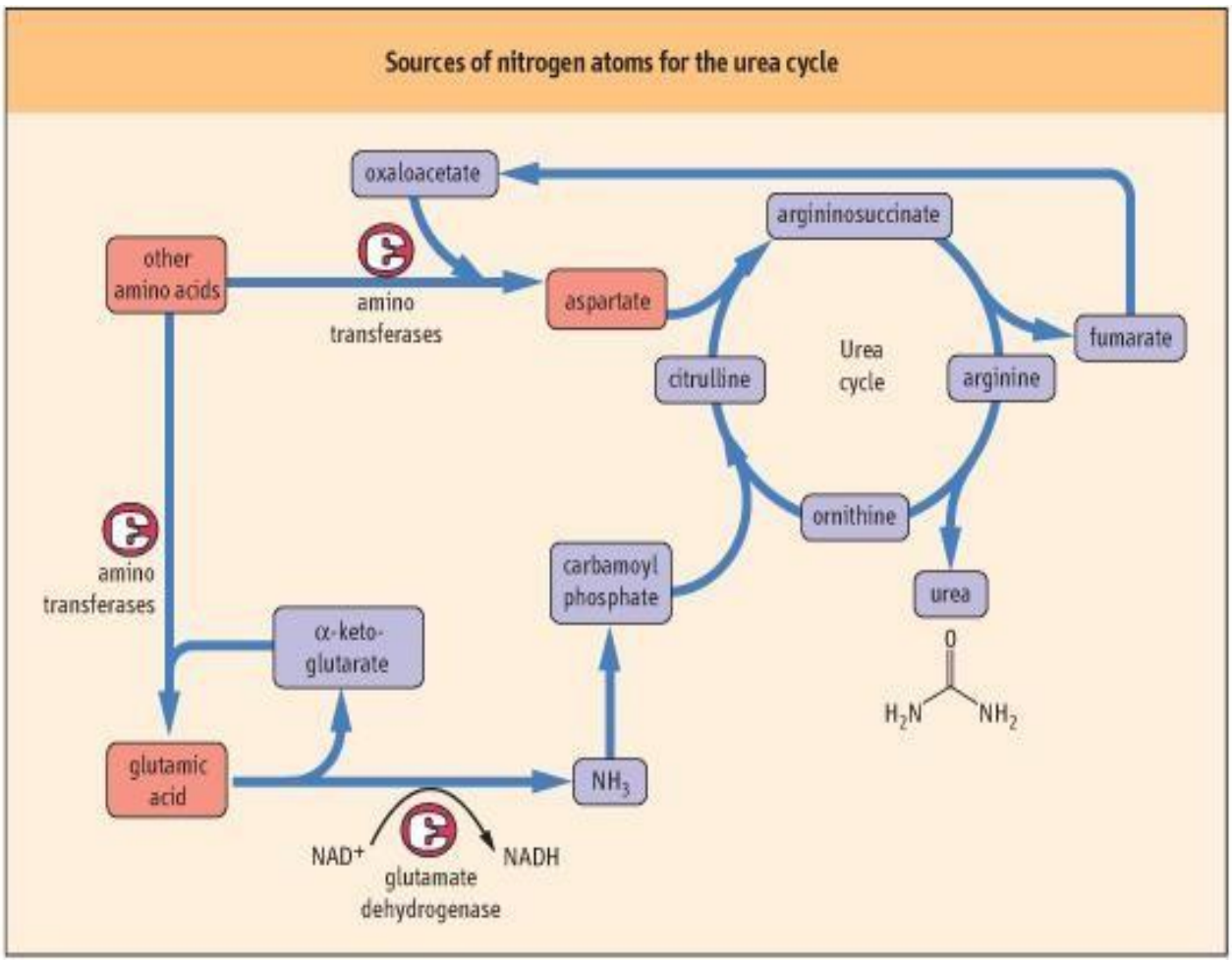
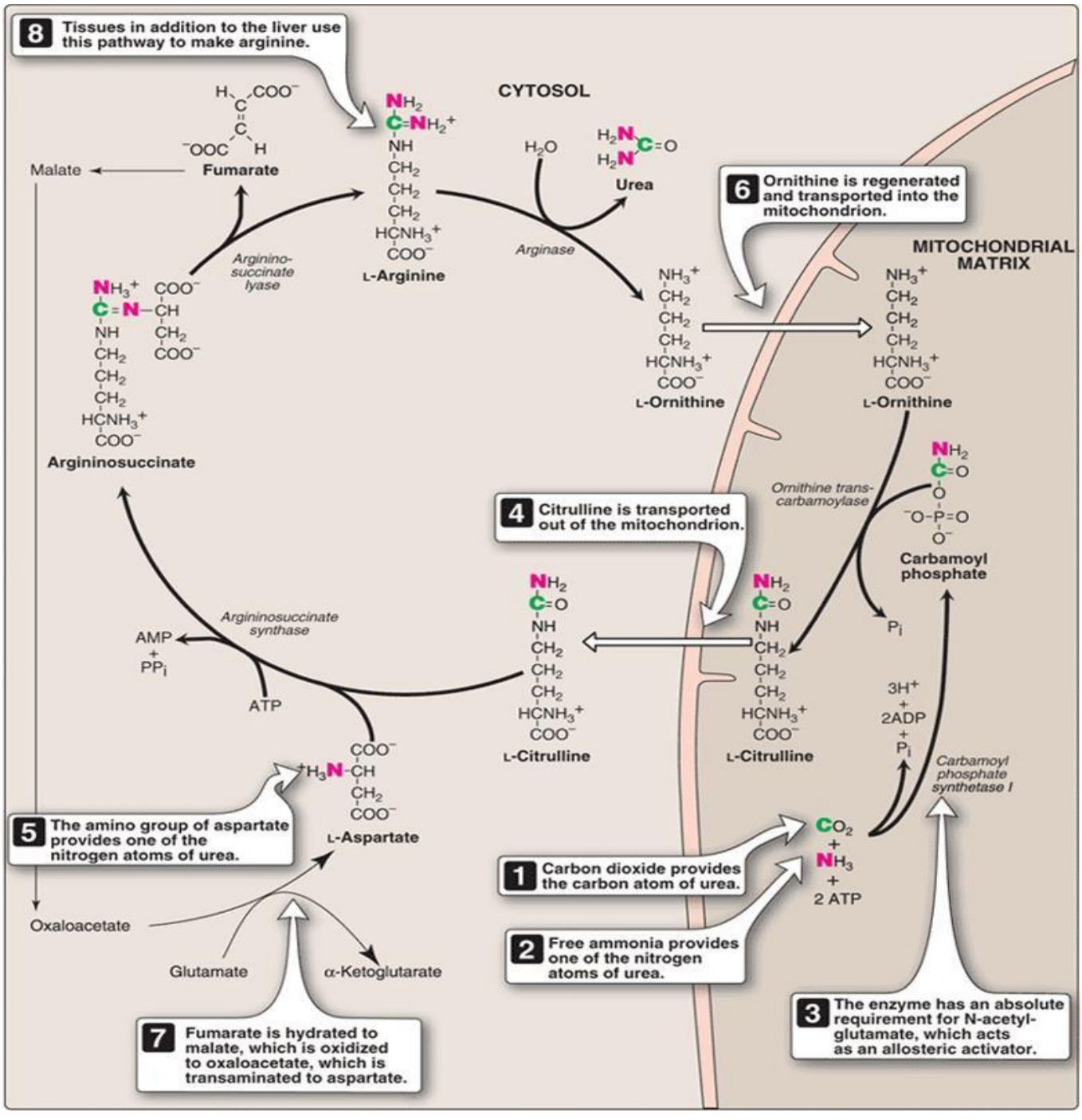
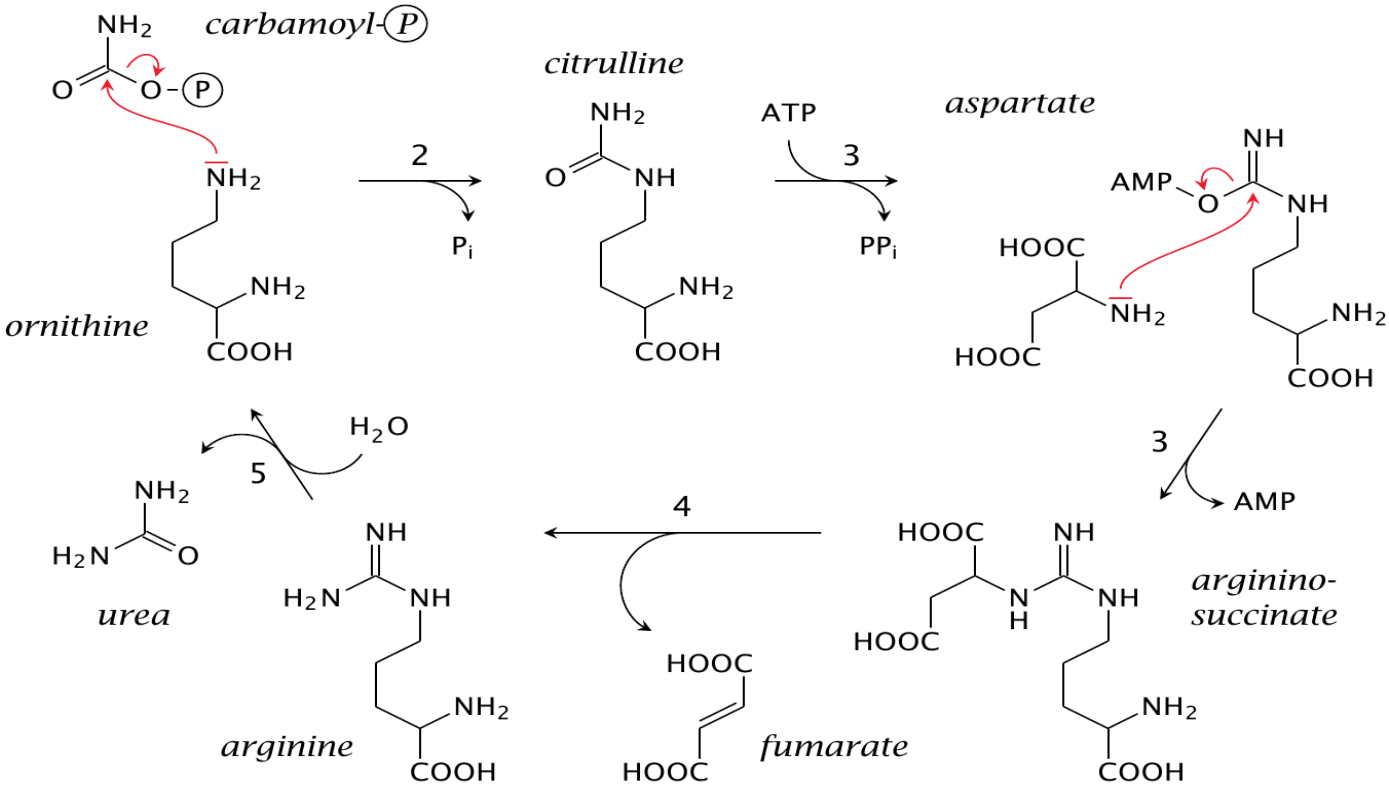
UREA CYCLE

INTRODUCTION

All tissues have some capability for synthesis of the non- essential amino acids, amino acid by remodeling, and the conversion of non-amino acid carbon skeletons into amino acids and other derivatives that contain nitrogen. However, the liver is the major site of nitrogen metabolism in the body. In times of dietary surplus, the potentially toxic nitrogen of amino acids is eliminated via transaminations, deamination, and urea formation; the carbon skeletons are generally conserved as carbohydrate, via gluconeogenesis, or as fatty acid via fatty acid synthesis pathways. In this respect amino acids fall into three categories: glucogenic, ketogenic, or glucogenic and ketogenic.




8 Tissues in addition to the liver use this pathway to make arginine.
CYTOSOL
MITOCHONDRIAL MATRIX
Malate
Fumarate
L-Arginine
Urea
Arginase
Arginino-succinate lyase
Argininosuccinate
6 Ornithine is regenerated and transported into the mitochondrion.
L-Ornithine
L-Ornithine
Ornithine trans-carbamoylase
Carbamoyl phosphate
4 Citrulline is transported out of the mitochondrion.
Argininosuccinate synthase
AMP + PPi
ATP
L-Citrulline
L-Citrulline
Pi
3H+ + 2ADP + Pi
Carbamoyl phosphate synthetase I
5 The amino group of aspartate provides one of the nitrogen atoms of urea.
L-Aspartate
1 Carbon dioxide provides the carbon atom of urea.
CO2 + NH3 + 2 ATP
Oxaloacetate
2 Free ammonia provides one of the nitrogen atoms of urea.
Glutamate
α-Ketoglutarate
3 The enzyme has an absolute requirement for N-acetyl-glutamate, which acts as an allosteric activator.
7 Fumarate is hydrated to malate, which is oxidized to oxaloacetate, which is transaminated to aspartate.



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 NH3, and the other nitrogen by aspartate.

[Note: Glutamate is the immediate precursor of both ammonia (through oxidative deamination by glutamate dehydrogenase) and aspartate nitrogen (through transamination of oxaloacetate by AST).] 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.

Reactions of the cycle

The first two reactions leading to the synthesis of urea occur in the mitochondria, whereas the remaining cycle enzymes are located in the cytosol

Formationof 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

Carbamoyl phosphate synthetase I requires N- acetylglutamate as a positive allosteric activator

Formation of citrulline

Ornithine and citrulline are basic amino acids that participate in the urea cycle.

(They are not incorporated into cellularproteins, because there are no codons for these amino acids)

Ornithine is regenerated with each turn of the urea cycle, much in the same way that oxaloacetate is regenerated by the reactions of the citric acid cycle

Synthesis of argininosuccinate

Citrulline condenses with aspartate to form argininosuccinate. The α-amino group of aspartate provides the second nitrogen that is ultimately incorporated into urea. ATP to adenosine monophosphate (AMP) and pyrophosphate. This is the third and final molecule of ATP consumed in the formation of urea

Cleavage of argininosuccinate

Argininosuccinate is cleaved to yield arginine and fumarate. The arginine formed by this reaction serves as the immediate precursor of urea.

Fumarate produced in the urea cycle ishydrated to malate, providing a link with several metabolic pathways.

For example, the malate can be transported into the mitochondria via the malate shuttle and reenter the tricarboxylic acid cycle. Alternatively, cytosolic malate can be oxidized to oxaloacetate, which can be converted to aspartate

Cleavage of arginine to ornithine and urea

Arginase cleaves arginine to ornithine and urea,and occurs almost exclusively in the liver.

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 neomycin1 reduces the number of intestinal bacteria responsible for this NH3 production.

Regulation of the urea cycle

N-Acetylglutamate is an essential activator for carbamoyl phosphate synthetase I—the rate- limiting step in the urea cycle N-Acetylglutamate is synthesized from acetyl coenzyme A and glutamate by N-acetylglutamate synthase in a reaction for which arginine is an activator.

Therefore, the intra hepatic concentration of N-acetylglutamate increases after ingestion of a protein-rich meal, which provides both the substrate (glutamate) and the regulator of N-acetylglutamate synthesis. This leads to an increased rate of urea synthesis.

Metabolism of Ammonia

Transport of ammonia to liver(glucose-alanine cycle)

Sources of ammonia: Liver(Trans deamination) Renal/Intestinal (glutaminase) Bacterial urease

Amines (hormones/neurotransmittors) Purines/Pyrimidines

Transport of ammonia in circulation (urea)(glutamine)

BIOENERGETICS

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

DISORDER OF UREA CYCLE

Deficient of any urea cycle's enzyme result in HYPERAMMONEMIA

Generally disorder of urea cycle described as hyperammonemia, encephalopathy, respiratory alkalosis

Symptoms include vomitting, irritability, lethargy, severe mental retard

Deficiency	Disorder	Clinical Feature
N-Acetylglutamate synthase	Hyperammonemia that may be accompanied by high plasma concentrations of alanine and glutamine	Lethargy; persistent vomiting; poor feeding; hyperventilation; enlarged liver; seizures
Carbamoyl phosphate synthetase	Hyperammonemia; citrullinemia; respiratory alkalosis	Lethargy; coma; seizures; vomiting; poor feeding; hyperventilation; hepatomegaly
Ornithine transcarbamylase	Hyperammonemia; respiratory alkalosis; elevated orotic acid in urine	Seizures; vomiting; poor feeding; hyperventilation; hepatomegaly
Arginosuccinate synthetase	Citrullinemia	Lethargy; coma; seizures; vomiting; poor feeding; hepatomegaly
Arginosuccinate lyase	Elevated arginosuccinic acid in urine	Lethargy; seizures; vomiting; poor feeding; hyperventilation; hepatomegaly
Arginase	Markedly elevated plasma arginine, lactate, and CSF glutamine, and modestly elevated blood ammonia	Delayed development; protein intolerance; spasticity; loss of muscle control; seizures; irritability

CSF indicates cerebrospinal fluid.