UREA CYCLE

- The urea cycle (also known as the ornithine cycle) is a cycle of biochemical reaction occurs in many animals that produce urea from ammonia .

- When the nitrogen of the amino acids is converted to urea in the liver , their carbon skeletons are converted either to glucose (in the fasting state) or to fatty acid (in the fed state) .

- Ammonia travels to the liver from other tissues in the form of alanine and glutamine . It is released from amino acids in the liver by a series of transamination and deamination reactions .

Urea Cycle

1. Ammonium is toxic (N = 15 – 40 μM , max 70 μM) .
2. Excretion NH_4^+ by kidneys important for acid - base balance ***but*** normally 80-90% N → urine as urea.
3. Hyperammonium > **500 μM** plasma $[NH_4^+]$ = **TOXIC** related to inborn errors of metabolism (genetic defects) as well as induced (liver failure) .

4 . Urea is measured in the blood as blood urea nitrogen (BUN) . BUN may be elevated in :

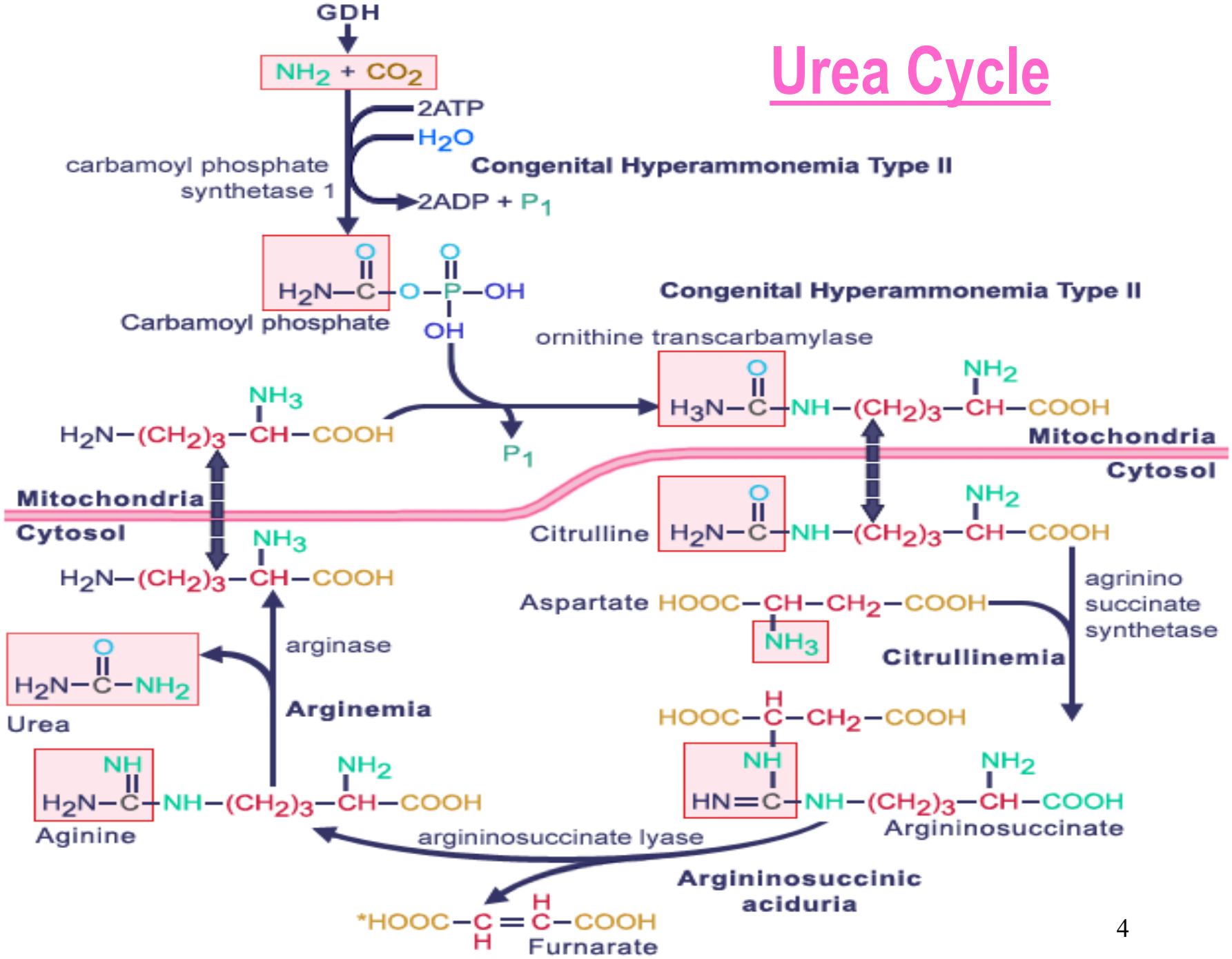
- Both acute and chronic renal (kidney) failure .
- Congestive heart failure lead to a low blood pressure and consequent reduced filteration rates through the kidneys .
- urinary tract obstruction . In, these hemodialysis is used to remove the soluble urea and other waste products from the blood .

5 . Ammonia is very toxic , particularly to the CNS .

Nitrogen-containing components of normal urine

End Product	Excreted %
Urea	86.0
Creatinine	4.5
Ammonium	2.8
Uric acid	1.7
Other compounds	5.0

Urea Cycle


GDH
NH2 + CO2
2ATP
H2O
carbamoyl phosphate synthetase 1
2ADP + P1
Congenital Hyperammonemia Type II
Carbamoyl phosphate
Congenital Hyperammonemia Type II
ornithine transcarbamylase
Mitochondria
Cytosol
Citrulline
agrinino succinate synthetase
Citrullinemia
Aspartate
Mitochondria
Cytosol
arginase
Arginemia
Urea
Aginine
Argininosuccinate
argininosuccinate lyase
Argininosuccinic aciduria
Furnarate

Notes

1. In human , uric acid is not produced from ammonia , but is synthesized from adenine and guanine found in various nucleotide . Uric acid concentration may become elevated in kidney diseases and leukemia .

   A painful articular disorder called gout results from deposition of uric acid salts in cartilage in the joints. (Gout can be controlled by diet or by a drug called allopurinol which inhibit the enzyme that produce uric acid) .

2. Role of Urea cycle : rid the body of toxic NH_4^+ therefore permitting the use of AA as an energy source.

3. Liver major site of urea synthesis , major source of arginase , (small amounts in small intestine) and is the only tissue with the complete set of all 5 enzymes required .

4 . Carbamoyl phosphate synthetase is the rate limiting enzyme of the urea cycle .

5. Symptoms of hyperammonemia with in 1–3 days include : feeding intolerance , vomiting , irritability , seizures and coma .

6 . Synthesis of one mole of carbamoyl phosphate requires 2 mole of ATP . One ATP serves as the phosphoryl donor for formation of the mixed acid anhydride bond of carbamoyl phosphate . The second ATP provides the driving force for synthesis of the amide bond of carbamoyl phosphate .

7 . Normal value of the blood urea is 3.3 – 7.5 mmole/l while the normal value of serum uric acid is 180 – 420 mmole / l .

8 . Defects in each enzyme of the urea cycle have been described . (see diagram)