

Fate of Carbon Skeleton

The carbon skeleton is the α -keto acids remaining after removal of ammonia from amino acids.

It has the following fates:

- 1- Biosynthesis of nonessential amino acids by transamination with glutamic acid.
- 2- Amino acids which give acetyl CoA are **Ketogenic** amino acids. Leucine is the only pure ketogenic amino acid.
- 3- Amino acids which give rise to pyruvic acid or one of the intermediates of Krebs cycle are **glucogenic** e.g. glycine, alanine and cysteine
- 4- Amino acids which give rise to acetyl CoA and pyruvic acid or one of the intermediates of Krebs cycle are **both glucogenic and ketogenic** e.g. isoleucine, phenyl alanine, tyrosine, tryptophan and lysine
- 5- Oxidation via krebs cycle to give carbon dioxide, water and energy

N.B.

- Amino acid that gives acetyl CoA only (ketogenic)
Leucine
- Amino acids that give pyruvic acid (glucogenic)
Glycine
Alanine
Serine
Cysteine
- Amino acids that give oxalacetic acid (glucogenic)
Aspartic
Asparagine
- Amino acids that give α - ketoglutaric acid (glucogenic)
Glutamic
Glutamine
Arginine
Histidine
Proline
Hydroxy proline
- Amino acids that give succinyl CoA (glucogenic)
Valine
Methionine
Threonine

N.B. Threonine also can give pyruvic acid

- Amino acids that give acetyl CoA and fumarate (both glucogenic and ketogenic)
Phenyl alanine
Tyrosine
- Amino acid that gives acetyl CoA and pyruvic acid (both glucogenic and ketogenic)
Tryptophan
- Amino acid that gives acetyl CoA and succinyl CoA (both glucogenic and ketogenic)
Isoleucine
- Amino acid that gives acetyl CoA and α -ketoglutarate (both glucogenic and ketogenic)
Lysine

AMMONIA

Blood ammonia level is 10- 60 $\mu\text{g/dl}$

Ammonia is toxic to the central nervous system and its accumulation in the body is fatal.

Once formed in the body, ammonia must be removed from blood

It is removed by the liver that converts it to urea, which is less toxic, water soluble and easily excreted in the urine.

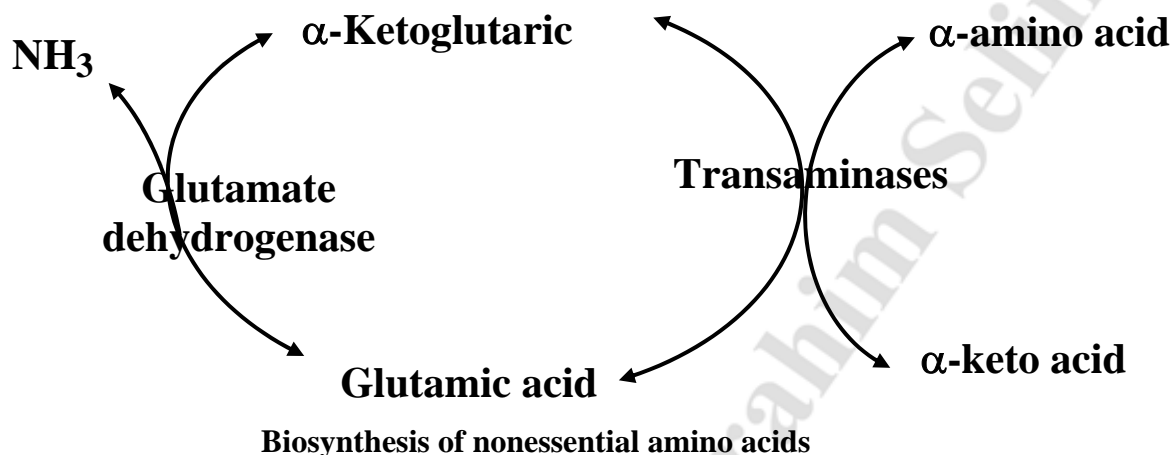
Sources of ammonia

- 1- Deamination of amino acids with formation of α -keto acids and ammonia
- 2- Transamination of most amino acids with α -ketoglutaric acid to form glutamic acid, which in turn is deaminated by glutamate dehydrogenase to form α -ketoglutarate and ammonia.
- 3- Glutamine in the kidney by glutaminase enzyme gives glutamic acid and ammonia which is used by the kidney to regulate the acid base balance
- 4- Ammonia produced by the action of intestinal bacteria on the non-absorbed dietary amino acids.
- 5- Ammonia is released from monoamines (e.g. epinephrine, norepinephrine and dopamine) by the action of monoamine oxidase enzyme
- 6- Ammonia is released during purine and pyrimidine catabolism.

Fate of ammonia

- 1- Biosynthesis of glutamic acid from ammonia and α -ketoglutaric acid by the action of glutamate dehydrogenase enzyme.

2-Biosynthesis of nonessential amino acids through transdeamination reaction (transamination with ketoglutaric acid by transaminases followed by deamination of the produced glutamic acid by glutamate dehydrogenase enzyme).



3-Biosynthesis of glutamine by glutamine synthetase enzyme

4-Biosynthesis of urea is the main fate of ammonia

5- Small amounts of ammonia are excreted in urine.

Urea Biosynthesis

Ammonia is highly toxic to the central nervous system

It is converted to urea, which is much less toxic, water soluble and easily excreted in urine.

The liver is the site of Urea biosynthesis.

Urea biosynthesis occurs by urea cycle (Krebs Hensleit cycle)

It occurs in five steps

The first 2 steps occur in mitochondria

The last 3 steps occur in cytoplasm

It utilizes 3 ATP and 4 high energy bonds

It is catalyzed by five enzymes

Any defect in one of these enzymes leads to ammonia intoxication

Steps of urea biosynthesis

1- Biosynthesis of carbamoyl phosphate

This step occurs in mitochondria and needs CO_2 , ammonia and phosphate and energy

CO_2 is a product of citric acid cycle

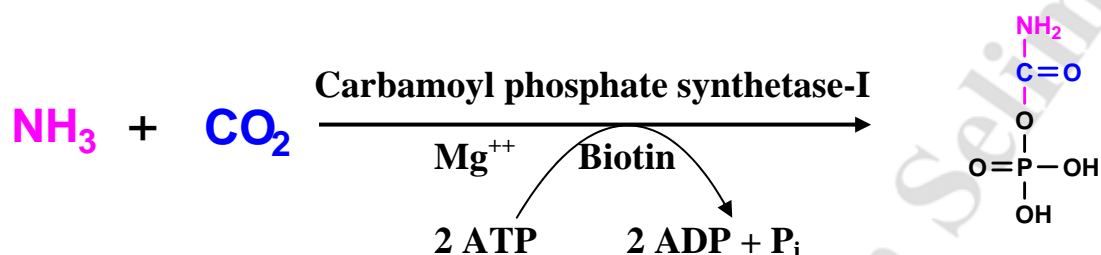
Ammonia is derived from glutamate by deamination

The phosphate and energy are derived from ATP

It is catalyzed by **carbamoyl phosphate synthetase-I**

It needs biotin as a coenzyme. It needs magnesium ions also

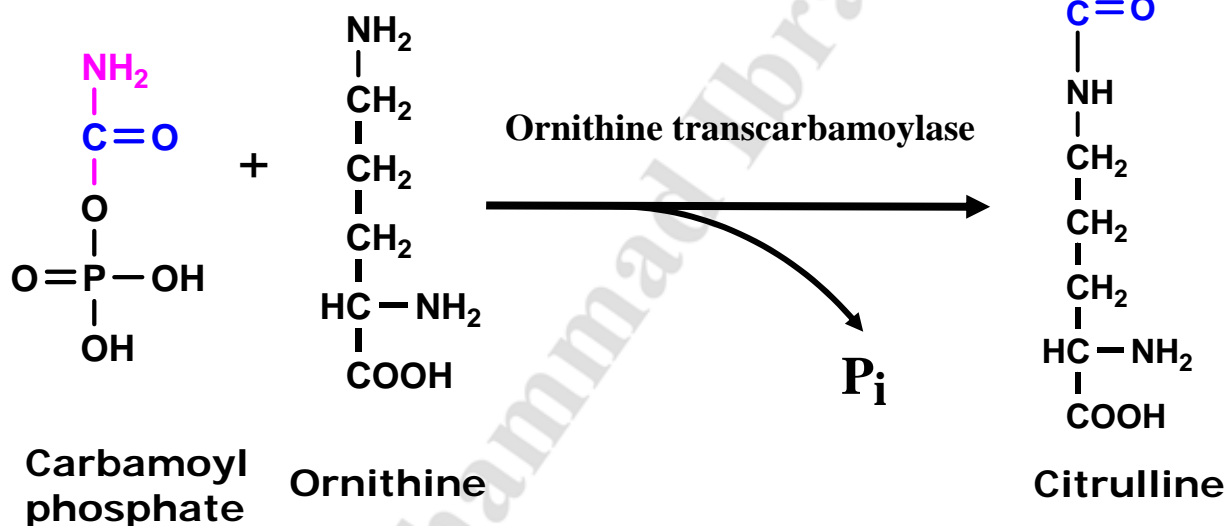
N-acetyl glutamate acts as allosteric activator for carbamoyl phosphate synthetase-I



2- Formation of citrulline

This step occurs in mitochondria

It is catalyzed by ornithine transcarbamoylase

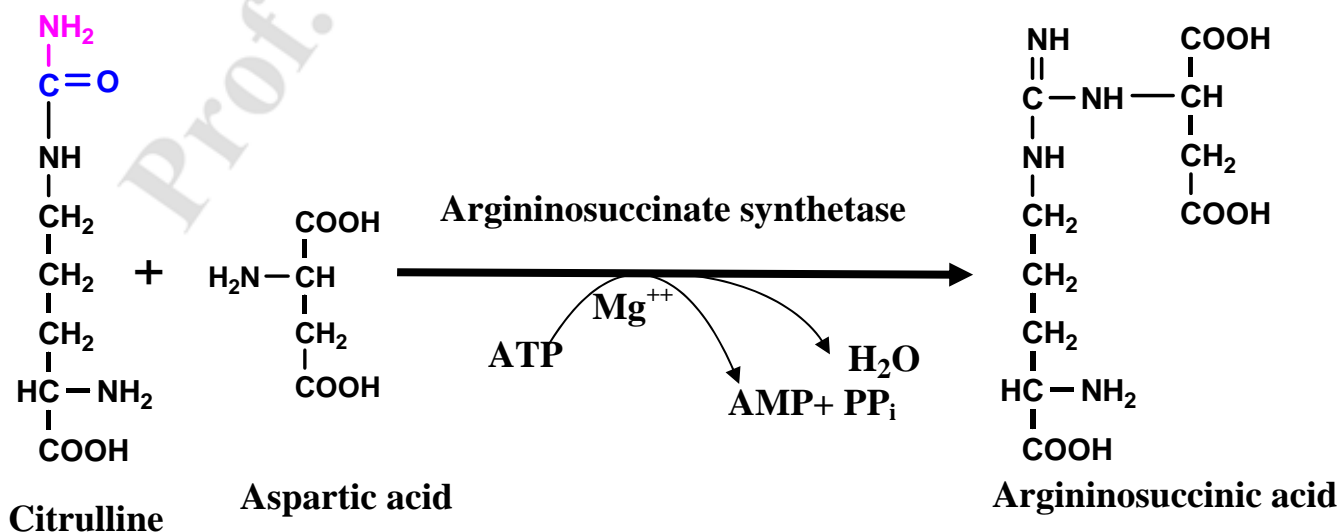


3- Formation of argininosuccinate

This step occurs in cytoplasm

It is catalyzed by argininosuccinate synthetase

It utilizes one ATP and 2 high energy bonds



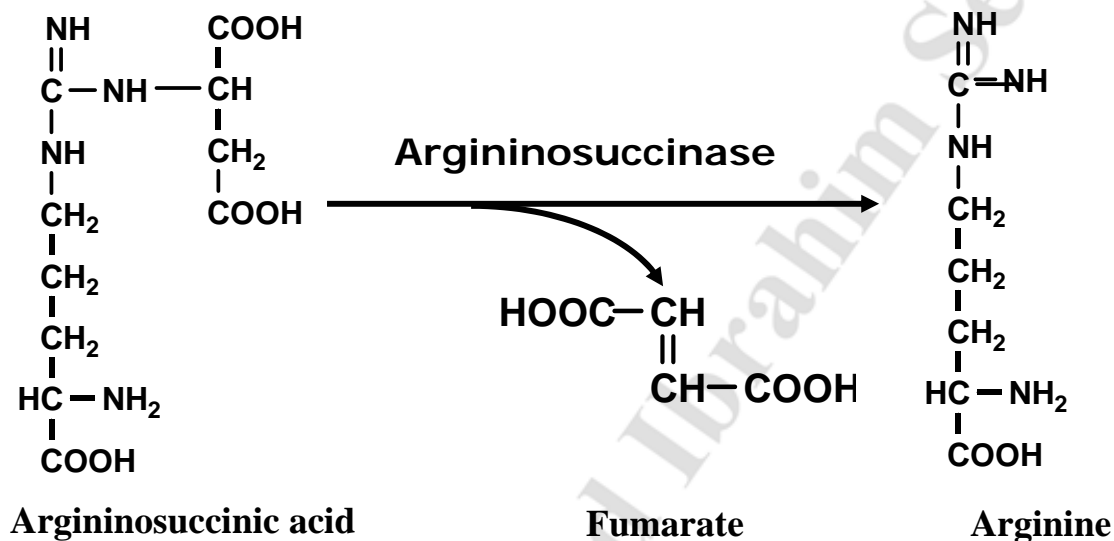
4- Cleavage of argininosuccinate

This step occurs in cytoplasm

It is catalyzed by argininosuccinase enzyme

Argininosuccinate is cleaved into arginine and fumarate

Fumarate produced is used to regenerate aspartic acid again

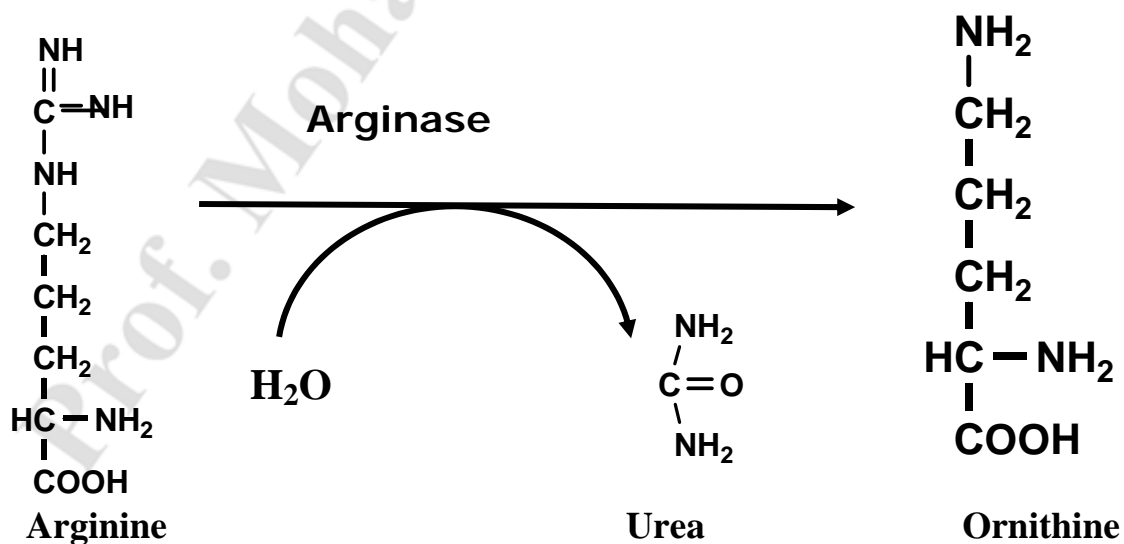


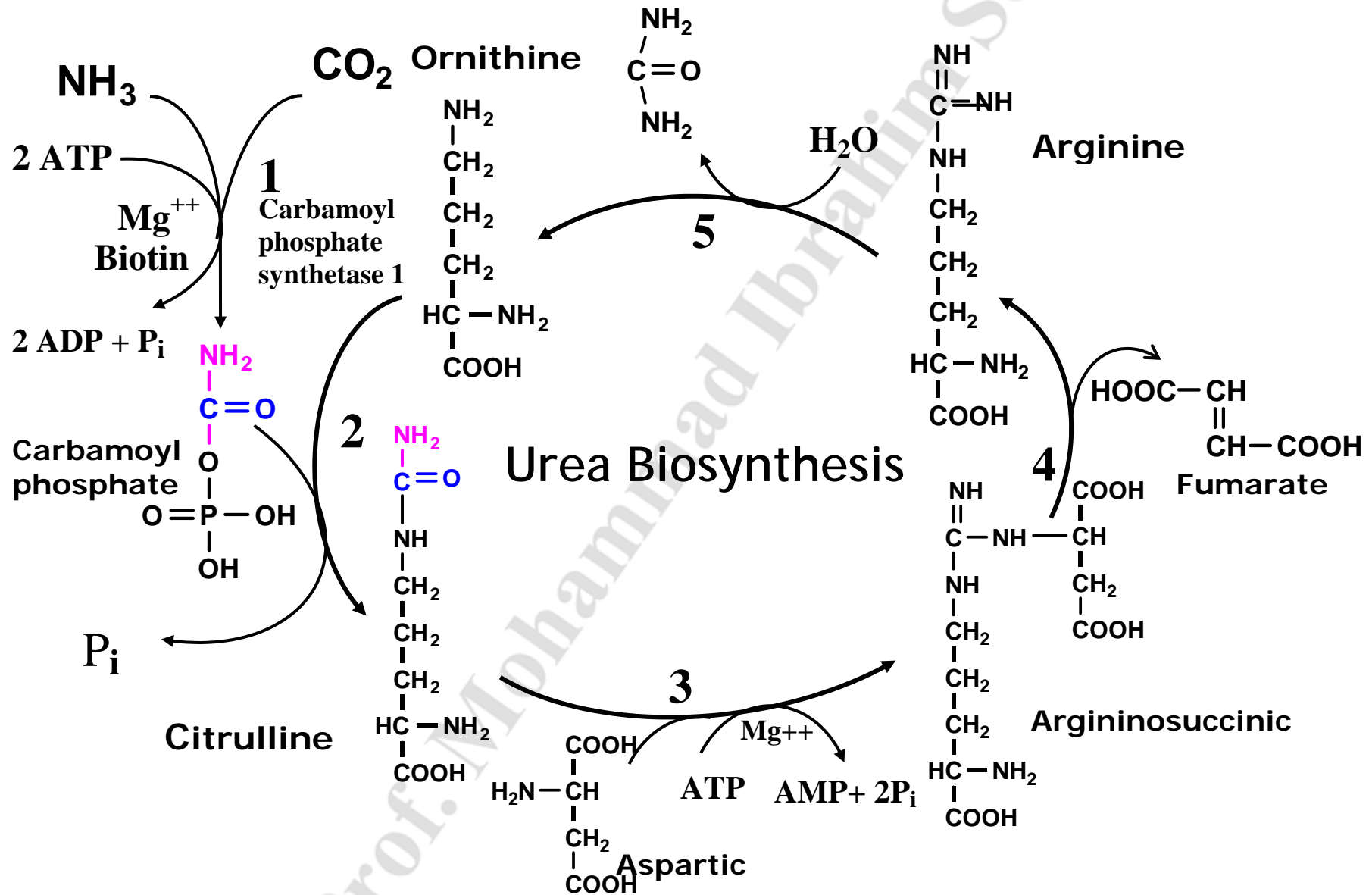
5- Cleavage of arginine

This step occurs in cytoplasm

It is catalyzed by arginase enzyme

Arginine is cleaved to urea and ornithine





In one turn of urea cycle:

- 2 molecules of ammonia are consumed
- 1 molecule of carbon dioxide is consumed
- 1 molecule of urea is formed
- A molecule of ornithine is regenerated for another turn of the cycle.
- 3 ATP are consumed.
- 4 high-energy bonds are consumed.

Regulation of urea cycle

1-Short term regulation

Short-term regulation of urea cycle occurs principally at carbamoyl phosphate synthetase-I.

N-acetylglutamate is allosteric activator of carbamoyl phosphate synthetase-I.

N-acetylglutamate is synthesized from acetyl CoA and glutamate by N-acetylglutamate synthetase enzyme which is allosterically activated by arginine.

2-Long term regulation

Enzymes of the urea cycle are controlled at the gene level with long-term changes in the quantity of dietary protein. Long-term increase in the quantity of dietary proteins leads to a significant increase in the concentration of the enzymes of urea cycle.

On return to a balanced diet, urea cycle enzymes return to normal levels

N.B. Differences between carbamoyl phosphate synthetase-I and carbamoyl phosphate synthetase-II

	CPS-I	CPS-II
Intracellular location	Mitochondria	Cytoplasm
Tissue location	Liver cells	Cells of most tissues
Function	Urea biosynthesis	Pyrimidine biosynthesis
Activation	N-acetyl glutamate	Phosphoribosyl-pyrophosphate (PRPP)
Source of nitrogen	Ammonia	Amide nitrogen of glutamine

Relationship between urea cycle and citric acid cycle

1- CO₂ needed for urea synthesis is mostly produced from citric acid cycle

2- Ammonia used for carbamoyl phosphate synthesis (in mitochondria) is derived from glutamic acid by glutamate dehydrogenase enzyme

3- Fumarate produced by urea cycle can be converted into oxalacetic acid by citric acid cycle

4-Aspartic acid used in urea cycle is formed from oxalacetic by transamination with glutamic acid by AST (GOT) enzyme

5-ATP needed for urea cycle is derived from citric acid cycle

Ammonia Intoxication

Ammonia is highly toxic to the central nervous system

Blood ammonia level 10 – 60 ug/dl

Accumulation of ammonia in the body leads to nervous manifestations and may be fatal.

Causes of hyperammonemia

1-Acquired hyperammonemia

- Liver cell failure
- Shunt operations between portal and systemic circulation

2-Congenital hyperammonemia

Defect in any one of the five enzymes of urea cycle leads to ammonia intoxication. e.g.

- Hyperammonemia type-I due to defect in carbamoyl phosphate synthetase-I
- Hyperammonemia type-II due to defect in ornithine transcarbamoylase enzyme

Mechanism of ammonia intoxication

Ammonia depletes α -ketoglutaric acid from the brain. This leads to inhibition of Krebs cycle, which is the main source of energy in the brain

So, the brain is deprived from its main source of energy leading to neurological manifestations.

Manifestations of ammonia intoxication

Flapping tremors

Slurred speech

Blurred vision

Vomiting

Coma