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Semester: 5th

Assignment No: 03

Assignment Topic: Nitrogen Metabolism

Subject: Biochemistry

Submitted To: Dr. Raziya Allahyaar

Date: 17-01-2021

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Introduction:

Nitrogen is essential for all organisms (in amino acids and nucleic acids). Most of the conversions between organic and inorganic nitrogen are catalyzed by bacterial and archaeal enzymes. Liver is main site of nitrogen metabolism site in humans.

What is Metabolism?

Definition:

The entire spectrum of living chemical reactions, occurring in living systems is known as metabolism. Metabolism is broadly classified into two categories of reaction such as:

- Catabolism which is degradative processes concerned with the breakdown of complex molecules to simpler ones with release of energy.
- Anabolism which is biosynthetic reactions involving in the formation of complex molecules from simple precursors.

Nitrogen Metabolism:

Amino acids are not stored in the body, that is, no protein exists whose function is to maintain a supply of amino acids for future use. Amino acid catabolism is a part of the large process of the metabolism of nitrogen-containing molecules. Nitrogen enters the body in a variety of compounds found in the 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

Importance of Amino Acids:

Amino acid is really important in several processes. It plays an important role throughout the body:

- Assisting in the creation and growth of muscles, connective tissue, and skin
- Assisting in maintaining muscle tone and tissue strength
- Healing and repair
- Normal digestion
- Providing energy for your body
- Regulating moods by helping produce hormones
- Producing neurotransmitters

- Maintaining healthy skin, hair, and nails

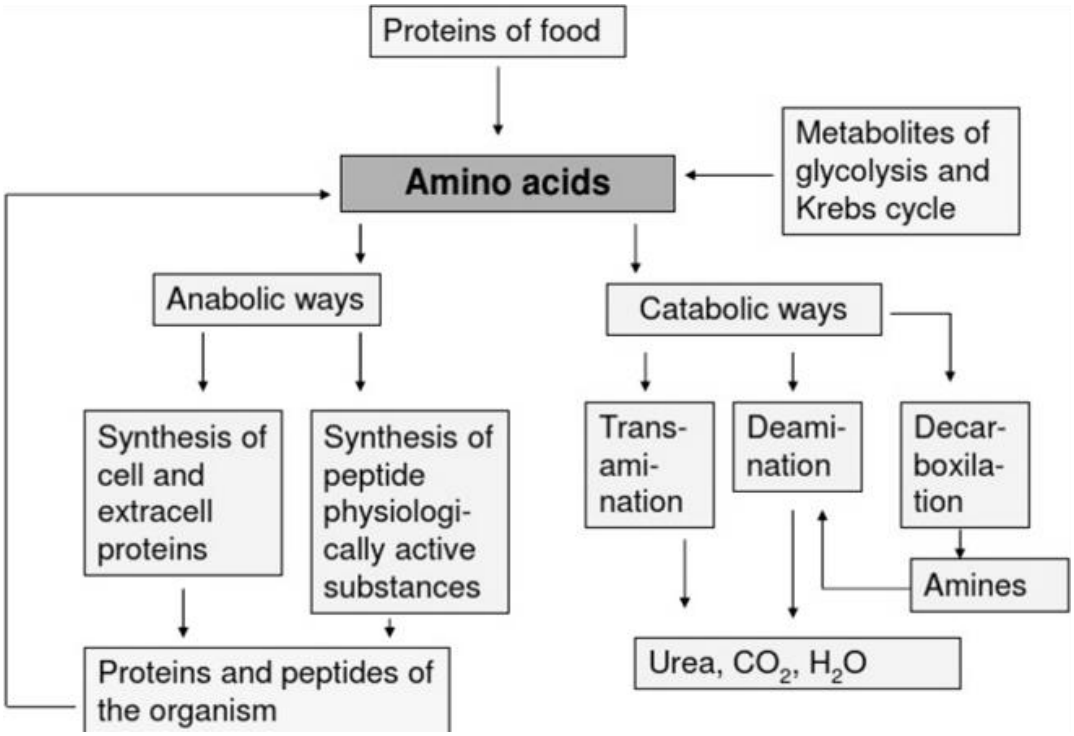
Metabolic Fates of Amino Acids:

Here are the following future reactions that can be displayed by the amino acids for several processes:

- All tissues of our body have ability to synthesize non- essential amino acids and remodeling of amino acids.
- In case of dietary surplus nitrogen in amino acids is eliminated through transamination, deamination and urea formation.
- The carbon skeletons act as metabolic fuel during starvation or diabetes mellitus.

Amino acids assimilated by our body cells face two possible fates:

- Protein synthesis: either directly, in the form in which they have been assimilated into the cell, Or after being restructured by transamination to non-essential amino acids, needed by the cell to assemble particular proteins.



Classification of Amino Acid according to Metabolic Fate:

Amino acids can be classified according to the metabolic fate of the carbon skeleton such as:

1. Ketogenic
2. Glucogenic
3. Ketogenic and glucogenic

Explanation:

1. Ketogenic:

Ketogenic are those amino acids that yields acetyl CoA or acetoacetyl CoA which is the precursor of ketone bodies and myelin (e.g. they don't produce metabolites that can be converted into glucose).

For Example:

Leucine and lysine are ketogenic.

2. Glucogenic:

Glucogenic amino acids are those amino acids whose catabolism yields to the formation of pyruvates or Krebs cycle metabolites that can be converted in glucose through glucogenesis.

For Example:

Alanine, arginine and asparagine etc.

3. Glucogenic and Ketogenic:

These are the amino acids that yield some products that can become glucose and others that can yield ketone bodies as Acetyl CoA or acetoacetyl CoA.

For Example:

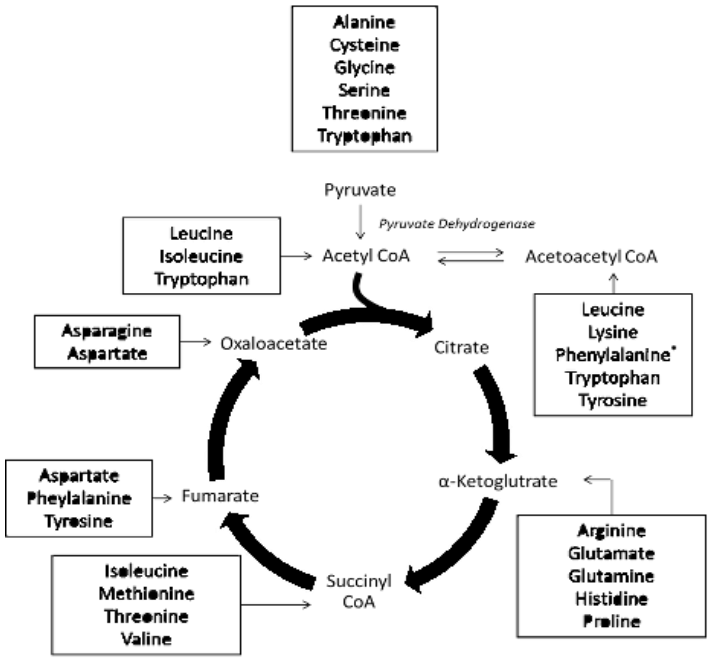
Phenylalanine, tryptophan and tyrosine and some others are example of ketogenic and glucogenic amino acids.

Fates of Carbon Skeleton of Amino acids:

Here the amino acids with reference to carbon atom play its role in ketogenic and glucogenic reaction.

- Proteins constantly undergo turnover. Amino acids are also used to synthesize non-proteins metabolites such as TCA cycle.

- If there is no protein stored so it must come through your diet.



Catabolism of Amino Acid in Humans:

Catabolism of amino acids increases for use in gluconeogenesis when glucose is unavailable (e.g., starvation/diabetes or when protein content of diet exceeds need for building blocks during times of stress)

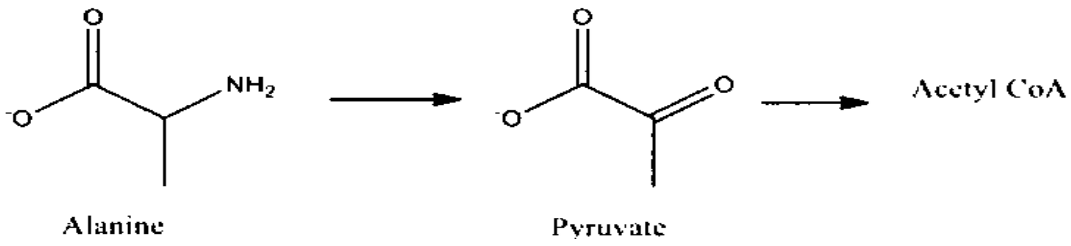
Digestive events are triggered of the hormone gastrin, released when food enters the stomach. The Low pH activates digestive enzymes; e.g., pepsin that helps in breakdown of proteins in stomach. In small intestine trypsin acts to absorb amino acids results from break down proteins. Resulting amino acids are absorbed by the intestinal mucosa, enter the capillaries, and travel to the liver.

Metabolic Fates of Amino acid By Degradation and Catabolism:

Amino acid Degradation:

The splitting of amino group from the carbon skeleton, with the amino group either disposed of through the urea cycle, or used for nucleotide synthesis is known as amino acid degradation. The carbon skeleton is converted to metabolites feeding catabolic energy producing pathways such as glycolysis and Krebs cycle.

For Example:



Nitrogen processing is the first step in degradation and then carbon chain is metabolized. There are two reaction of amino acids takes place which are as follows:

1. Transamination
2. Deamination

Explanation:

1. Transamination:

Transamination is the chemical reaction that transfers an amino group or keto acids as to form new amino acids. This pathway is responsible for the deamination of most amino acids. This is one of the major degradation pathways which convert essential amino acids to non-essential amino acids. Amino groups can be removed by transamination. This reaction is catalyzed by aminotransferase and co-factor is pyridoxal phosphate. It is a reversible reaction. Not all amino acids undergo transamination. The amino acids can vary such as aspartate transaminase.

For Example:

Lysine. Threonine and proline.

2. Deamination:

Deamination is the removal of an amine group from a molecule. Enzymes which catalyze this reaction are called deaminases. In the human body, deamination takes place primarily in the liver; however glutamate is also deaminated in the kidneys. Deamination is the process by which amino acids are broken down if there is an excess of protein intake. The amino group is removed from the amino acid and converted to ammonia. Deamination - elimination of amino group from amino acid with ammonia formation.

Four types of deamination:

- Oxidative (the most important for higher animals)
- Reduction
- Hydrolytic
- Intermolecular

Reactions of Deamination:

Reduction deamination:

$$\text{R-CH(NH}_2\text{)-COOH} + 2\text{H}^+ \rightarrow \text{R-CH}_2\text{-COOH} + \text{NH}_3$$

amino acid *fatty acid*

Hydrolytic deamination:

$$\text{R-CH(NH}_2\text{)-COOH} + \text{H}_2\text{O} \rightarrow \text{R-CH(OH)-COOH} + \text{NH}_3$$

amino acid *hydroxyacid*

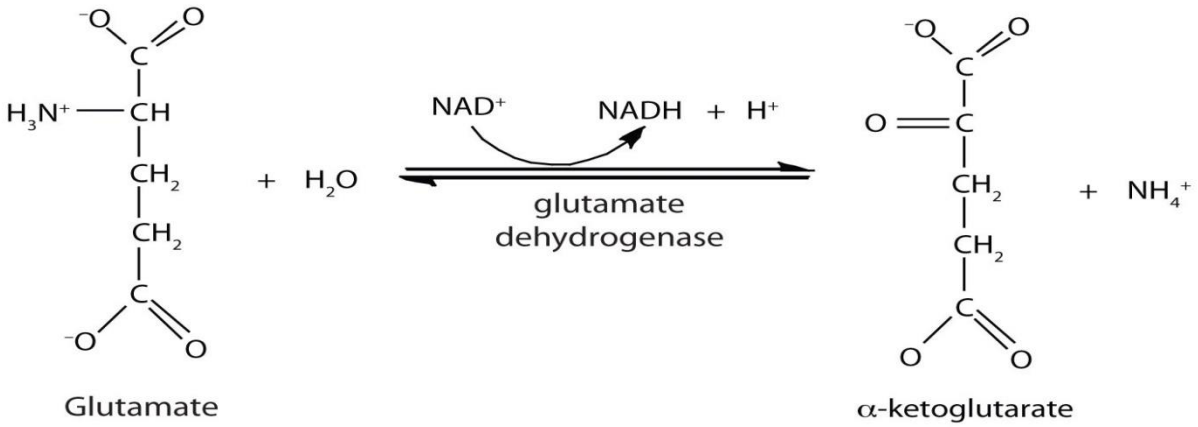
Intramolecular deamination:

$$\text{R-CH(NH}_2\text{)-COOH} \rightarrow \text{R-CH-CH-COOH} + \text{NH}_3$$

amino acid *unsaturated fatty acid*

Oxidative Deamination:

During oxidative deamination, an amino acid is converted into the corresponding keto acid by the removal of the amine functional group as ammonia. The amine functional group is replaced by the ketone group. The ammonia eventually goes into the urea cycle. Oxidative deamination occurs primarily on glutamic acid because glutamic acid was the end product of many transamination reactions. The glutamate dehydrogenase is controlled by NAD+ and NADH.



Nitrogen Excretion:

Animals excrete three main nitrogen products:

Ammonia, urea and uric acid as well as some minor nitrogen excretory products such as trimethylamine oxide, guanine, creatine, creatinine and amino acids.

The term ammonia will be used to indicate the total ammonia, whereas NH3 and NH4+ will refer to non-ionic ammonia and ammonium ion, respectively. Whether an animal excretes predominantly ammonia, urea or uric acid depends upon a number of factors in the animal's environment.

For Example:

Aquatic animals excrete mostly ammonia, whereas terrestrial animals excrete either urea or uric acid. Ammonia, urea and uric acid are transported across cell membranes by different mechanisms corresponding to their different chemical properties in solution. Ammonia metabolism and excretion are linked to acid–base regulation in the kidney.

Urea Cycle:

Definition:

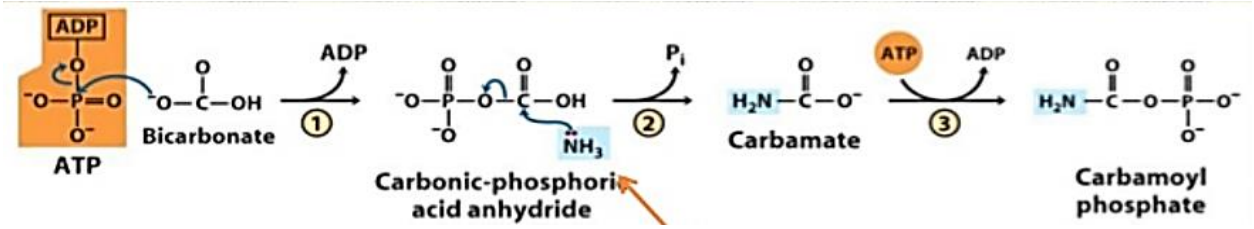
The urea cycle is a cycle of biochemical reactions that produces urea $(NH_2)_2CO$ from ammonia. This cycle occurs in ureotelic organisms. The urea cycle converts highly toxic ammonia to urea for excretion. This cycle was the first metabolic cycle to be discovered, five years before the discovery of the TCA cycle. Urea cycle is also known as Ornithine cycle and Kreb- Hensley cycle as well.

This reaction occurs in the liver in two cellular compartments:

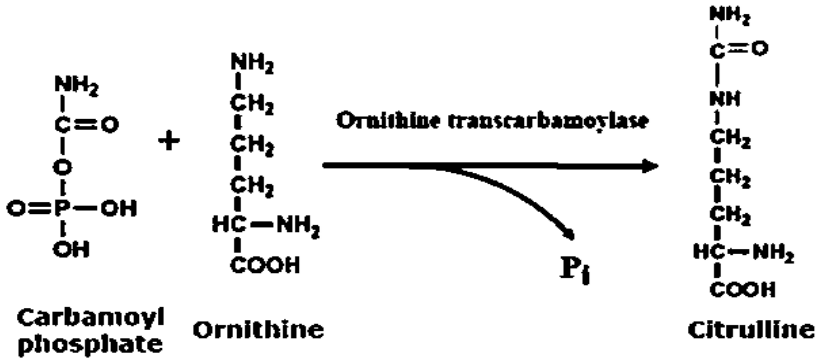
- Mitochondrial Matrix
- Cytosol

Steps for Urea Cycle:

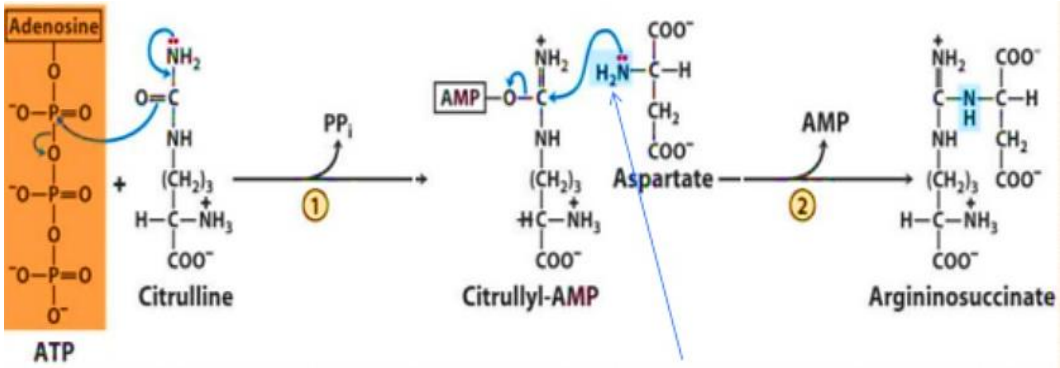
1. **Preparatory phase Step 1**: This step includes condensation of ammonium ion with bicarbonate ion resulting in the formation of carbamoyl phosphate by the help of the enzyme carbamoyl phos-phate synthase-I present in the liver mitochondria. It requires Mg2+ and a carboxylic acid i.e. N-acetyl glutamate. This step requires 2 ATPs. This step occurs in the matrix of mitochondria.



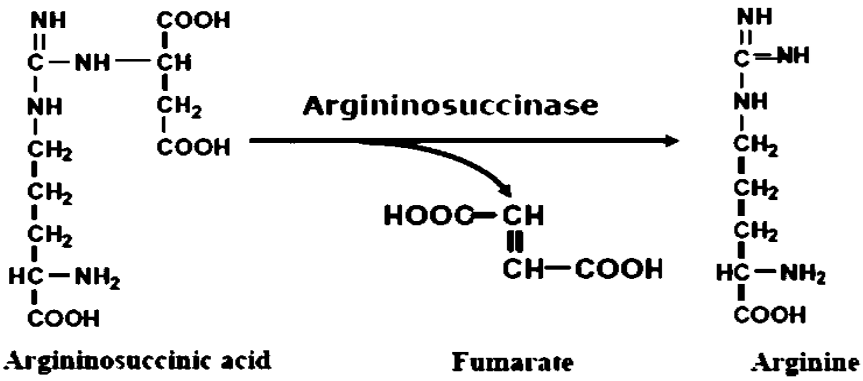
2. **Synthesis of Citrulline:** The carbamoyl phosphate formed in the first step combines with ornithine resulting in the synthesis of citrulline aided by the enzyme citrulline synthase or ornithine transcarbamoylase. Citrulline is easily permeable to the mitochondrial membrane and hence it diffuses into the cytosol. This step also occurs in the matrix, but citrulline is transported to cytosol



3. **Synthesis of Argininosuccinate**: In the cytosol, citrulline combines with the amino acid aspartate forming Argininosuccinate catalysed by the enzyme argininosuccinate synthase. It requires ATP which is hydrolyzed to AMP resulting in utilization of two high energy bonds. Mg2+ acts as cofactor.

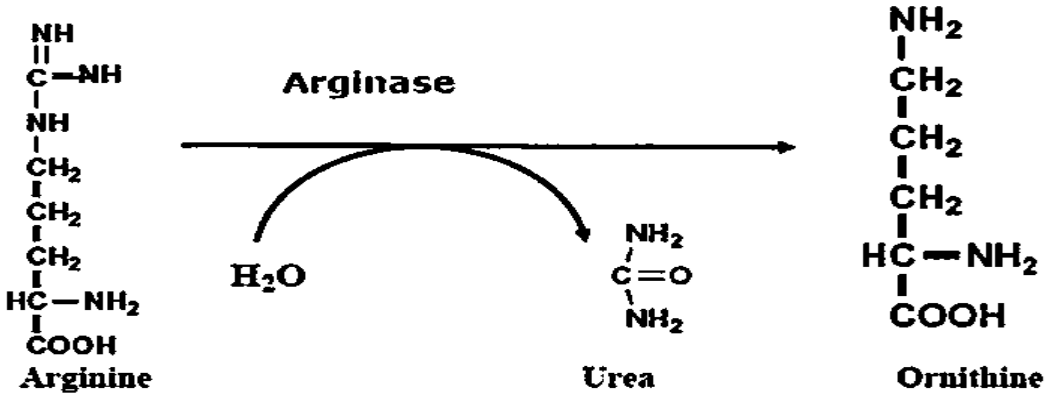


4. **Cleavage of Argininosuccinate:** The enzyme argininosuccinate acts reversibly to cleave arginino-succinate into Arginine and fumarate. Fumarate enters the TCA cycle (the linkage between TCA and urea cycle is known as Krebs bi-cycle).



5. **Cleavage of Arginine:** Arginine is lysed into ornithine and urea under the influence of the enzyme arginase. Hence arginine is known as semi-essential amino acid i.e. though it is synthesized in the body it is not available for protein synthesis. Ornithine is regenerated in this step and the urea cycle completes by the formation of urea. Ornithine and lysine are potent inhibitors of the enzyme arginase. Ornithine is transported back to matrix

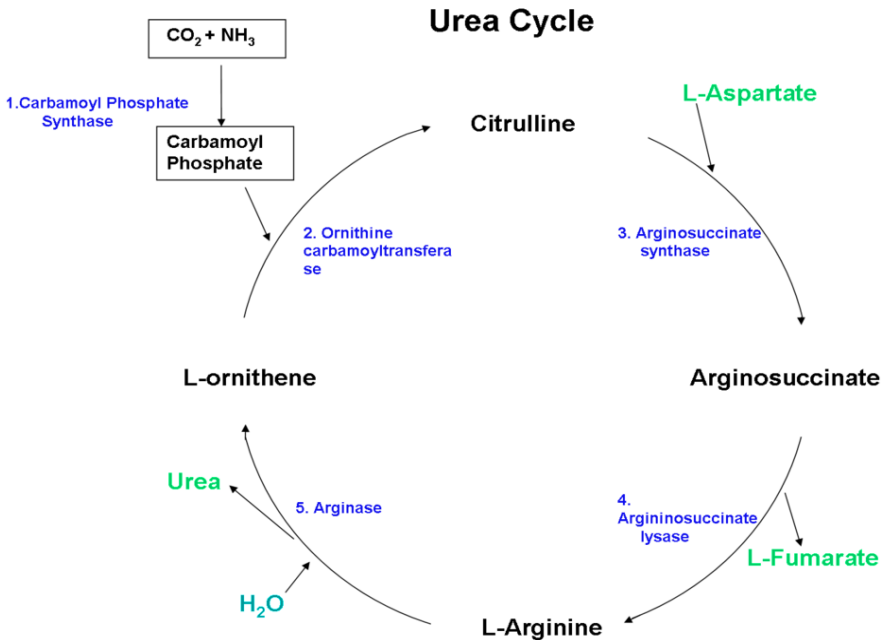
   Arginase is also present in testis, renal tubules, mammary gland and skin in minute quantities. The intermediate amino acids formed in the urea cycle i.e. ornithine, citrulline and argininosuccinate are known as non-protein amino acids.



Over all Equation of Urea Cycle:

The overall equation of urea formation is:

$NH4 + CO2 + Aspartate + 3ATP \rightarrow Urea + Fumarate + 2ADP + 2Pi + AMP + PPi$



Regulation of Urea Cycle:

- Here are the following factors that regulate the urea cycle:
- Carbamoyl phosphate synthase (CPS-I) is rate limiting enzyme in urea cycle.
- CPS-I is allosteric ally activated by N- acetyl glutamate (NAG). It is synthesized from glutamate & acetyl CoA by synthase & degraded by a hydrolase.
- The rate of urea synthesis in liver is correlated with the concentration of N-acetyl glutamate.
- High concentrations of arginine increase NAG.
- The consumption of a protein-rich meal increases the level of NAG in liver, leading to enhanced urea synthesis. CPS-I & GDH are present in mitochondria.
- They coordinate with each other in the formation of NH3 & its utilization for carbamoyl phosphate synthesis.
- Glucagon, insulin, and glucocorticoids are major regulators of the expression of urea cycle enzymes in liver.

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