Tishk International University
Faculty of Applied Science
Nutrition and Dietetics Department
2nd Grade
Nutritional Biochemistry I

Protein Metabolism Disorders

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Outline

- Regulation of the Urea Cycle
- Disorders of the urea cycle
- Glucose- Alanine Cycle
- Amino acid metabolism disorders

Regulation of the Urea Cycle

- The urea cycle is comprised of five enzymes but also requires other enzymes and mitochondrial amino acid transporters to function fully.
- The complete urea cycle is expressed in liver and to a small degree also in enterocytes, also in many other tissues.
- CPS-I is allosterically activated by N-acetylglutamate (NAG).
- The rate of urea synthesis in the liver is correlated with the concentration of N-acetylglutamate.

Cont.

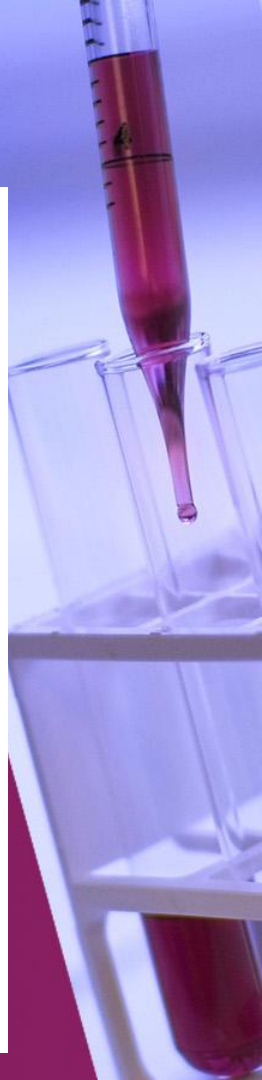
- **On high-protein diets** the carbon skeletons of the amino acids are oxidized for energy or stored as fat and glycogen, but the amino nitrogen must be excreted. ***To facilitate this process, enzymes of the urea cycle are controlled at the gene level.***

- Under conditions of starvation, enzyme levels rise as proteins are degraded and amino acid carbon skeletons are used to provide energy, thus increasing the quantity of nitrogen that must be excreted.

Short-term regulation of the cycle occurs principally at Carbamoyl-phosphate synthetase (CPS-I)

acetyl-CoA + glutamate ----> N-acetylglutamate + CoA

CPS-I is stimulated by **N-acetylglutamine**, which signals the presence of high amounts of nitrogen in the body.



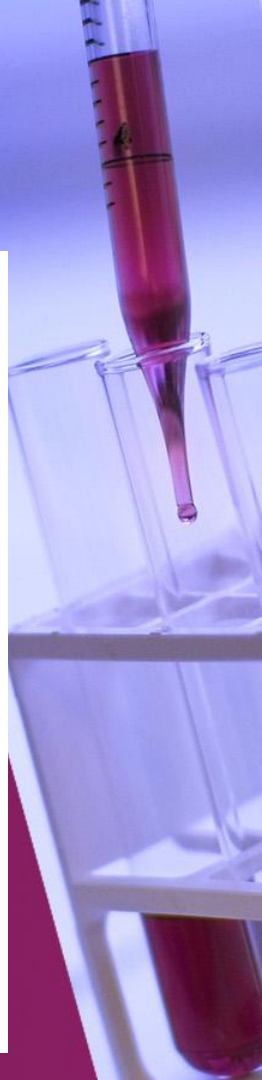
Disorders of the Urea cycle

- The main function of urea cycle is to remove toxic ammonia from blood as urea.
- Defects in the metabolism of conversion of ammonia to urea, i.e., Urea cycle leads to Hyperammonemia or NH3 intoxication.

❖ ***Ammonia Toxicity (Encephalopathy)***

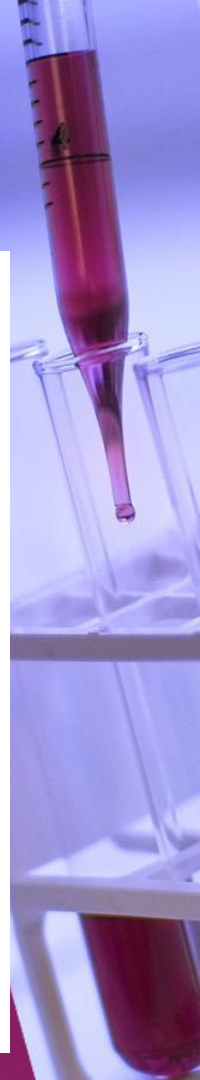
Ammonia is the main participant in amino acid synthesis and degradation but it's accumulation >25-100 µg/dl becomes toxic mainly to central nervous system (CNS).

HMW: What are the causes for toxicity of ammonia to CNS?



Inherited defects in the Urea cycle

- Ammonia intoxication can be caused by inherited defects in *ammonia trapping* or in urea cycle.
- Most of the inhabited defects occur at a rate of 1 in every 30 000 births.
- All inherited defects in the urea cycle enzymes result in *mental retardation.*
- Ammonia intoxication after argininosuccinate synthase can be treated by a diet low in protein and amino acid and supplemented by Arginine and citrulline.
- Another mechanism for the treatment of defects in the urea cycle is the *administration of ketoacids*.



Acquired defects in Urea Cycle

Any disease or condition that adversely affects liver mitochondria can also produce an increased level of ammonia in the blood such condition include;

- Liver cirrhosis,
- Alcoholism,
- Hepatitis and
- Reye's syndromes.

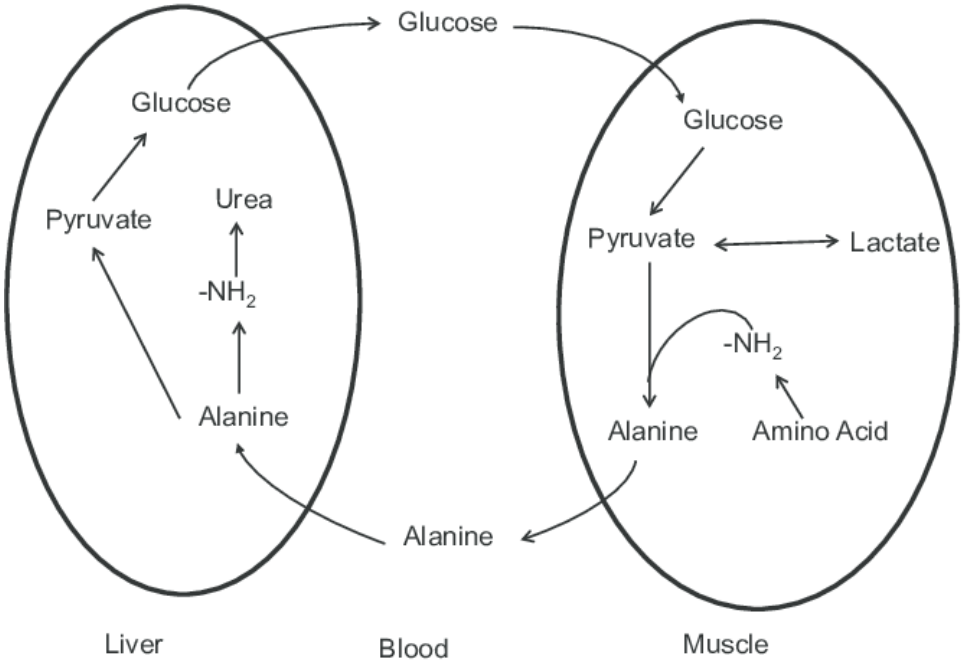
Glucose- Alanine Cycle

- The glucose-alanine (Cahill cycle)—involves muscle protein being degraded to provide more glucose to generate additional ATP for muscle contraction.
- It allows pyruvate and glutamate to be transported out of muscle tissue to the liver where gluconeogenesis takes place to supply the muscle tissue with more glucose as mentioned previously.
- To initiate the cycle, muscle and tissues that catabolize amino acids for fuel generate amino groups—most commonly in the form of glutamate—through the process of transamination.

Cont.

- These amino groups are transferred via alanine aminotransferase to pyruvate (a product of glycolysis) to form alanine and alpha-ketoglutarate.
- Alanine subsequently moves through the circulatory system to the liver where the reaction previously catalyzed by alanine aminotransferase is reversed to produce pyruvate.
- This pyruvate is converted into glucose through the process of gluconeogenesis which subsequently is transported back to the muscle tissue.
- Meanwhile, glutamate dehydrogenase in the mitochondria catabolizes glutamate into ammonium.
- Ammonium moves on to form urea in the urea cycle.

Glucose –Alanine cycle



Amino acid metabolism disorders

Phenylketonuria(PKU) :

- Deficiency of phenylalanine hydroxylase is responsible for PKU, an autosomal recessive disease that results in accumulation of too much phenylalanine, because the synthesis of tyrosine is blocked.

- When untreated, this metabolic defect leads to excessive urinary excretion of phenyl pyruvate and phenyl lactate, followed by severe mental retardation, seizure, psychosis and eczema.

- Can be diagnosed by measurement of plasma phenylalanine which may be raised above (300mg/dl), in which the normal value must be (30mg/dl).

Tyrosinemia

- Also called Richner-Hanhrt Syndrome, caused due to the failure of tyrosine transaminase giving a raised level of tyrosine in blood and urine.

Clinical symptoms:

- Moderate mental retardation
- Eye and skin lesions
- Disturbance in fine coordination.

Alkaptonuria

- A second inherited defect in the phenylalanine-tyrosine pathway.

- Involves a deficiency in the enzyme that catalyzes the oxidation of homogentisic acid (an intermediate in the metabolic breakdown of tyrosine and phenylalanine).

Maple Syrup Urine disease

- The normal metabolism of the branched chain amino acids Leucine, Isoleucine and Valine involves loss of the α-amino acid by transamination followed by oxidative decarboxylation of the respective ketoacids.

- Approximately 1 in 300 000 live birth in US population are affected by this enzyme defect leading to *ketoaciduria*.

- If this condition remains untreated it may lead to both physical and mental retardation of the newborn and distinct maple syrup odor of the urine.

- This can be partially managed with a low protein or modified diet. In some instances, supplementation with high doses of thiamine pyrophosphate is recommended.

Hyperproteinaemia

Increased amount of total proteins which is above normal is called hyperproteinaemia.

Causes of hyperproteinaemia:

1. Haemoconcentration: Increased albumin and globulin.

a. Dehydration (loss of protein-free fluid).

b. Venous stasis (excessive stasis during venipuncture).

2. Hypergammaglobulinaemia: Increased immunoglobulin.

a. Polyclonal (chronic disease).

- Chronic liver disease.
- Chronic infections.

b. Monoclonal (carcinoma).

- myeloma.

Hypoproteinaemia

Decreased amount of total proteins which is below normal is called hypoproteinaemia.

Causes of hypoproteinaemia:

1. Haemodilution.

- Inappropriate IV therapy.
- Syndrome of inappropriate secretion of ADH.
- Sample taken from above IV drip needle.

↑ADH release ⟶ renal water reabsorption to dilute ECF ⟶ urine is concentrated.

2. Hypoalbunaemia.
3. Hypogammaglobulinaemia.

Increase blood urea levels

May occur in a number of diseases in addition to those in which the kidney are primarily involved.

The causes can be classified as:

1. Pre- renal:

Conditions in which plasma volume/ body fluid are reduced. e.g.:

- Salt and water depletion (urea concentrated).
- Severe vomiting.
- Severe and prolonged diarrhea.
- Haemorrhage and shock.
- In burns.

2. Renal:

- In acute glomerulonephritis (↓filtration of urea).
- In type II nephritis- in later stage.
- Chronic pyelonephritis.
- Malignant nephrosclerosis.

3. post-renal:

When there is obstruction to urine flow, this causes retention of urine so reduces the effective filtration so produce irreversible kidney damage.

- Enlargement of prostate-benign and malignant.
- Tumors of the bladder affecting urinary flow.
- Stricture of urethra.

Decrease blood urea level

It is rare, it may be seen in:

- Some cases of severe liver damage.
- Physiological conditions. e.g. in pregnancy < non-pregnant women.

questions?

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OR

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