University of Fallujah
College of Medicine

Protein metabolism

Lecture : 4 & 5

Stage : 2nd Stage

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الرؤية والرسالة والاهداف لكلية طب الفلوجة

الرؤية :

تحقيق الريادة في التعليم الطبي وأن نكون شريكاً فعالاً في الإرتقاء بالمستوى الأكاديمي والصحي على مستوى القطر.

الرسالة :

تعليم وتدريب الطلبة في بيئة تعليمية هادفة لتهيئة الخريجين لممارسة طبية متميزة وآمنة مع ترسيخ القيم الانسانية والعلمية والمبادئ الاجتماعية ومعايير الجودة.

تخريج اطباء قادرين على الاستجابة للاحتياجات والتحديات الصحية وتوجيه البحث العلمي لحل المشكلات الصحية في المجتمع.

تجنيد وتطوير هيئة تدريسية بمواصفات عالية لتصبح الأفضل في مجال التعليم والبحوث العلمية

الاهداف :

تخريج أطباء لديهم المعرفة والإرادة والمهارة التي تمكنهم من ممارسة الطب بشكل آمن مع تجسيد القيم الإنسانية والأخلاقية.

التحسين المستمر للعملية التعليمية وتطوير مهارات الهيئة التدريسية وفق معايير الجودة بواسطة التعليم والتدريب الطبي المستمر من خلال الورش والمؤتمرات العلمية.

تعزيز علاقات التعاون مع المؤسسات العلمية والطبية داخل وخارج العراق لتطوير المستوى الأكاديمي للهيئة التدريسية ولتعليم الممارسة الطبية الآمنة للطلبة الخريجين.

السعي في أن تكون الكلية مركزاً بحثياً علمياً رائداً في البحوث الصحية التطبيقية مع الاستغلال الأمثل لنتائج تلك البحوث في خدمة المجتمع وبالتعاون مع مختلف الجهات المستفيدة.

المساهمة في تحسين صحة المجتمع من خلال دعم وتطوير نظام الرعاية الصحية عبر علاقات تكامل وتعاون فعال.

Learn objectives:

-Know the urea cycle and it’s role
-Know , what are protein metabolic disorders
-know , how occur relation between urea and krebs cycles

Conversion of ammonia to urea: Urea cycle (Krebs-Henseleit cycle)

The first two steps occur in mitochondrial matrix and the remaining three take place in cytosol of hepatic cells.

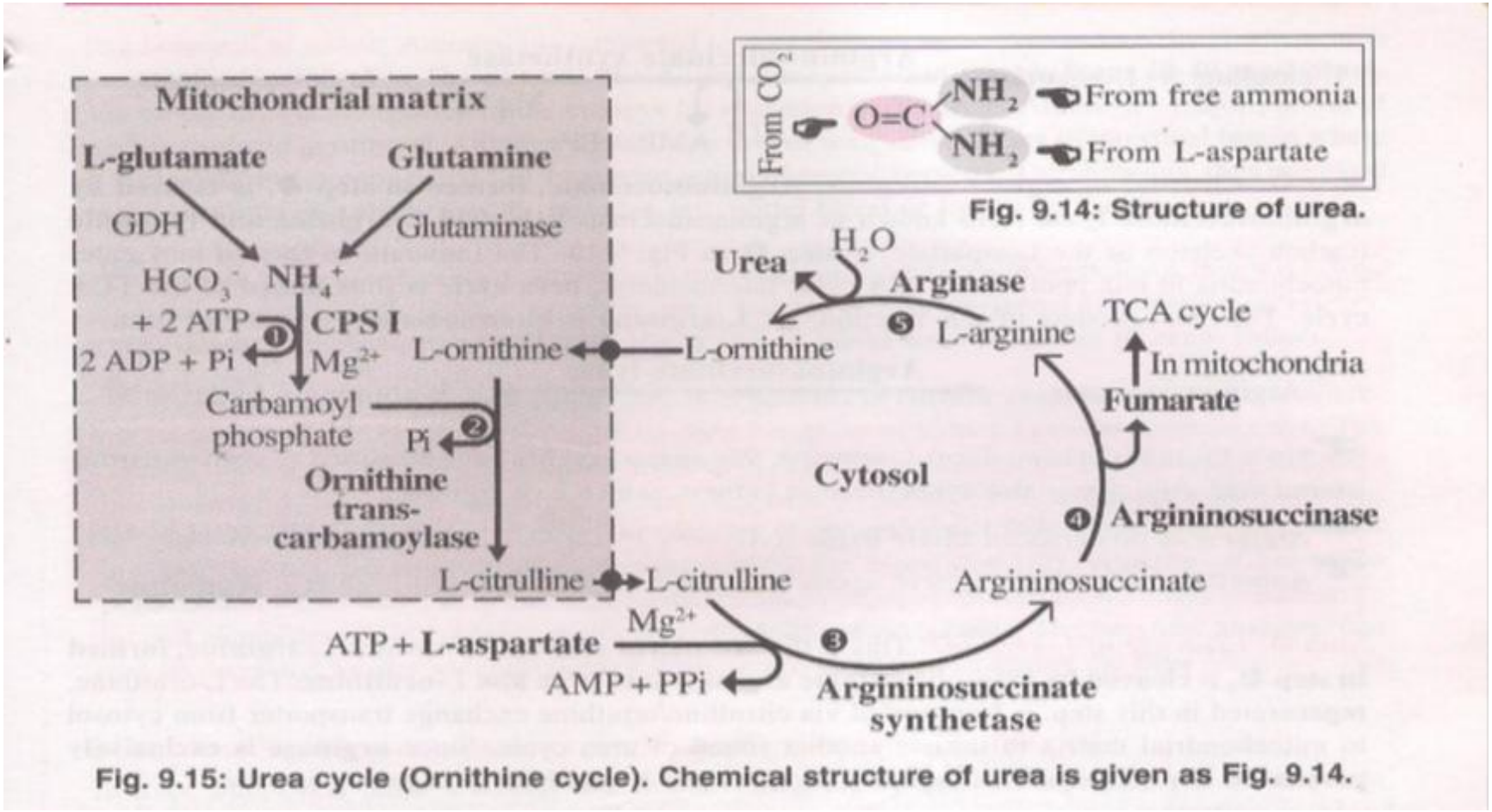


Fig. 9.15: Urea cycle (Ornithine cycle). Chemical structure of urea is given as Fig. 9.14.

Step 1: synthesis of carbamoyl phosphat

Another enzyme carbamoyl phosphate synthetase II (CPS II) is present in cytosol of hepatic cells. CPS II catalyzes the synthesis of carbamoyl phosphate using amide group of L-glutamine and takes part in biosynthesis of the pyrimidine nucleotide

Step2 synthesis of L-citrulline

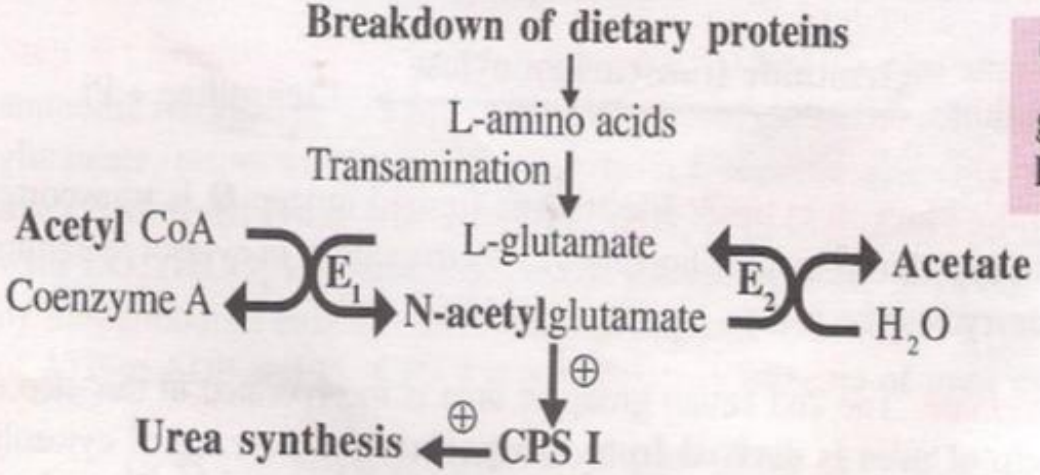
L-ornithine that reacts with carbamoyl phosphate to form L-citrulline, is regenerated with each turn of the urea cycle (step 5) and plays a role similar to that of oxaloacetate in TCA cycle. Therefore, urea cycle is also known as ornithine cycle.

**L-citrulline formed in step 2 is transport via citrulline/ ornithine cycle exchange transporter from mitochondrial matrix to cytosol

Step 3: Synthesis of argininosuccinate
Step 4: cleavage of argininosuccinate
Step 5: cleavage of L-arginine

Regulation of urea cycle:

Carbamoyl phosphate synthetase I (CPS I) is an allosteric regulatory enzyme of urea cycle. Activity of CPS I is absolutely dependent on concentration N-acetylglutamate (NAG) for activity. CPS I is allosterically activated by NAG. *After* ingestion of meal rich in protein, an increase in intrahepatic concentration of L-glutamate accelerates the synthesis of NAG; which in turn activates CPS I and enhances the rate of urea synthesis (Fig. 9.16). NAG is synthesized from acetyl CoA and glutamate in presence of enzyme N-acetylglutamate synthase (Fig. 9.16). Thus, a protein rich diet accelerates the urea cycle.



Deficiency of N-acetyl-glutamate synthase causes **hyperammonemia**.

E_1 = N-acetylglutamate synthase
E_2 = N-acetylglutamate hydrolase
⊕ = Stimulation

Fig. 9.16: Synthesis and hydrolysis of N-acetylglutamate.

Disposable of urea: Ammonia is converted to urea a major portion of urea is excreted in urine via kidneys, a small fraction of urea also diffuses in intestinal lumen where it is cleaved into ammonia and CO2 by urease action of enteric bacteria. The ammonia, thus produced in gut, is either absorbed from the large intestine into portal blood or lost in the faeces.

A rise in blood urea level occurs due to
-pre-renal cause (high protein diet, increased tissue protein breakdown, thyrotoxicosis, prolonged high fever, intestinal obstruction, leukemia, GI bleeding disorders, etc.),
-renal cause (chronic nephritis, renal tuberculosis, renal carcinoma, acute glomerulonephritis, etc.)
-post-renal cause (bilateral obstruction in urinary tract, tumours of urinary bladder, enlargement of prostate, etc.).
The term 'uremia' is used to indicate rise in blood urea level due to renal failure (renal cause), whereas the term 'azotemia' indicates increase in blood urea level due to any cause other than renal disorder .

A decrease in blood urea level is seen in advanced liver diseases (liver cirrhosis, chronic hepatitis, hepatocellular carcinoma, etc.), inherited disorders of urea cycle and low protein diet.

Biomedical significant of urea cycle (metabolic disorder of urea cycle):

known as hyperammonemia) is observed in patients with liver dysfunction, renal dysfunction or inherited disorders of urea cycle.

Hyperammonemia may be classified into two major types-

1. acquired hyperammonemia

2. hereditary hyperammonemia (inherited hyperammonemia or familial hyperammonemia).

Acquired Hyperammonemia

-liver cirrhosis, hepatitis, alcoholic liver disease or biliary obstruction,

The acquired hyperammonemia is also seen in renal failure. Impaired detoxification of ammonia in advanced liver cirrhosis is an important cause of acquired hyperammonemia.

Hereditary hyperammonemia(inherited disorder of urea cycle): it occurs due to inherited defect in any one of the five enzymes of urea cycle.

Table 9.1: Defective enzyme and Inherited metabolic disorder of urea cycle

Inherited metabolic disorder of urea cycle	Defective/deficient enzyme of urea cycle
Hyperammonemia type 1	Carbamoyl phosphate synthetase I
Hyperammonemia type 2	Ornithine transcarbamoylase
Citruliinemia	Argininosuccinate synthetase
Argininosuccinic aciduria	Argininosuccinase
Hyperargininemia	Arginase