Formation and transport of Ammonia and its associated disorders

Department of Biochemistry

Specific Learning Objectives

- Outline formation and transport of ammonia
- Describe importance of reactions catalyzed by glutamine synthetase, glutaminase, and glutamate dehydrogenase
- Role of Glutamine in Nitrogen metabolism
- Ammonia Intoxication
- List causes for hyperammonemia, its consequences, and treatments to reduce blood ammonia levels

Sources of Ammonia

1. From glutamine
2. From bacterial action in intestine
3. From amines
4. From purines and pyrimidines

Role of Glutamine in Nitrogen Metabolism

1. When muscle degrades branched chain aa, it exports their nitrogen as part of glutamine
2. In liver, hepatocytes use glutamine synthetase catalyzed reaction to remove ammonia from blood
3. In brain, astrocytes use glutamine synthetase reaction to remove neurotransmitter and recycle a precursor of it to neurons as part of a glutamate/GABA cycle

Glutamine Transport Ammonia in Bloodstream

- Free ammonia produced in tissues is combined with glutamate to yield glutamine by glutamine synthetase and it requires ATP

- Glutamate and ATP react to form ADP and γ-glutamyl phosphate intermediate which reacts with ammonia to produce glutamine and inorganic phosphate (Pi)

- Glutamine is a nontoxic transport form of ammonia

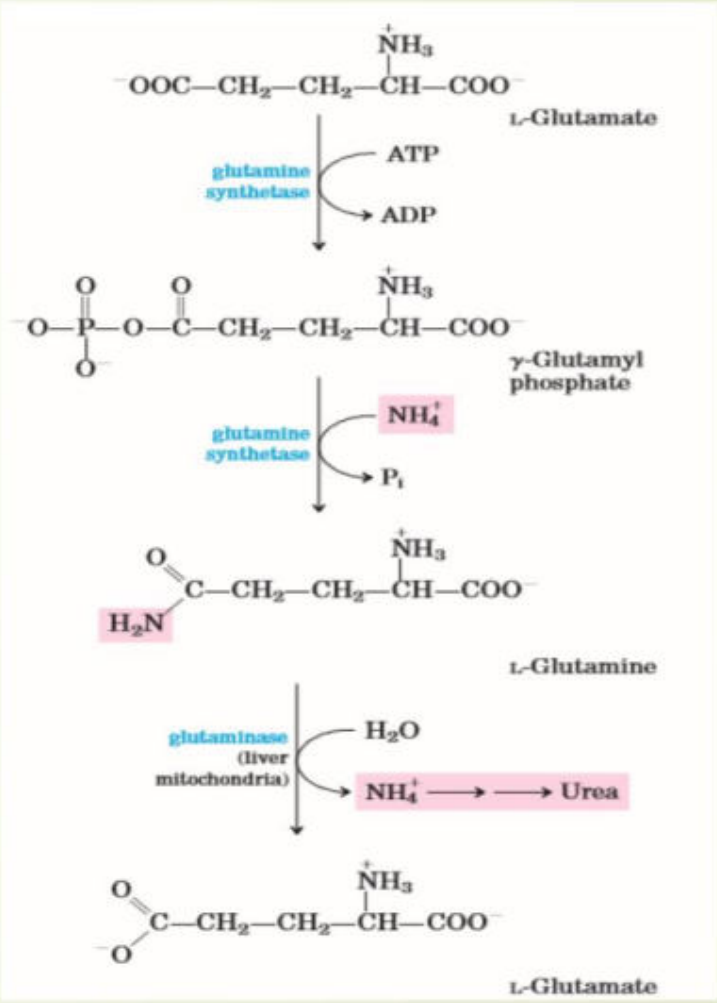

Fig18.8: Lehninger Principles of Biochemistry by David L Nelson, 6th Ed

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- Free ammonia converted to non toxic compounds before export from extrahepatic tissues into blood and transport to liver or kidneys

- For this transport function, glutamate critical to intracellular amino group metabolism, is replaced by glutamine

- Free ammonia produced in tissues combined with glutamate gives glutamine by glutamine synthetase, this requires ATP

Glucose-Alanine Cycle: Alanine transport ammonia from skeletal muscle to liver

Two mechanisms are available in humans for transport of ammonia from peripheral tissues to liver for its ultimate conversion to urea

1) Combine ammonia with glutamate to form glutamine (nontoxic transport form of ammonia) by glutamine synthetase

- Glutamine is transported into blood and then to liver where it is cleaved by glutaminase to produce glutamate and free ammonia which is converted to urea

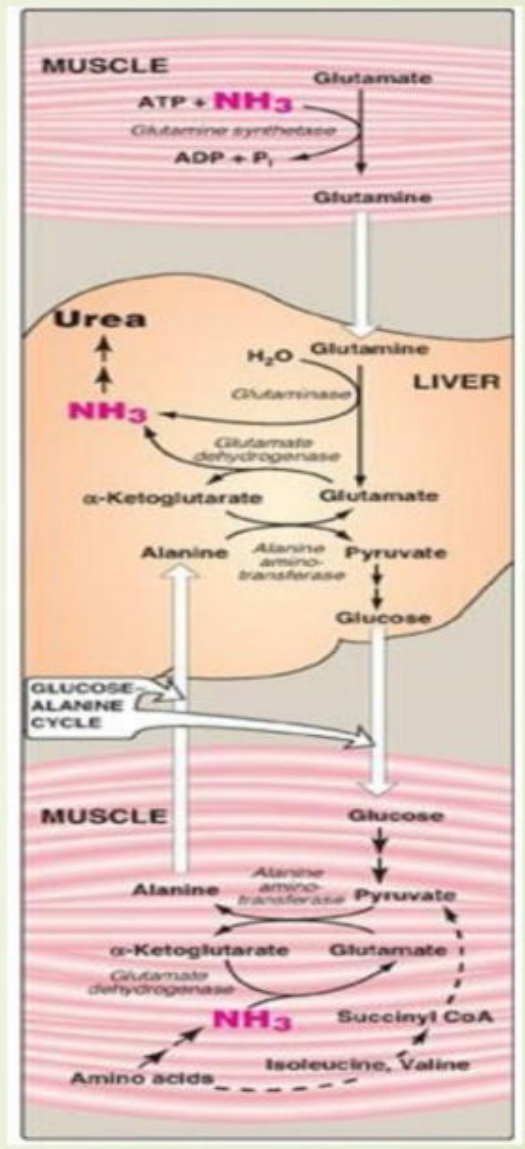

Fig 19.13. Alanine serves as a carrier of ammonia and of the carbon skeleton of pyruvate from skeletal muscle to liver. The ammonia is excreted and the pyruvate is used to produce glucose, which is returned to the muscle.
Lippincott's Illustrated Reviews, Biochemistry, 6th Ed

2) Formation of alanine by transamination of pyruvate produced from both aerobic glycolysis and metabolism of succinyl CoA generated by catabolism of branched-chain aa

- Alanine is transported by blood and then to liver, where it is converted to pyruvate by transamination

- Pyruvate is used to synthesize glucose by gluconeogenesis, which can enter blood and be used by muscle

Ammonia Toxicity

- Emptying cytosol of excess ammonia require reductive amination of α-ketoglutarate to glutamate by glutamate dehydrogenase and conversion of glutamate to glutamine by glutamine synthetase

- Both enzymes present at high levels in brain, although glutamine synthetase reaction pathway imp for removal of ammonia

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- High level of ammonium ions leads to increased level of glutamine, which acts as osmotically active solute in brain astrocytes of CNS provides nutrients, support to neurons

- This triggers uptake of water into astrocytes to maintain osmotic balance leads to swelling of cells and brain, which lead to coma

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- Hyperammonemia: Blood ammonia level must be low because even slight elevation leads hyperammonemia (toxic to CNS)

- Normal blood ammonia is 30-60µM

Elevated levels of ammonia in blood cause symptoms of ammonia intoxication, which include tremor, slurring of speech, and blurring of vision

- There are two types of conditions: Acquired and Hereditary

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Acquired: Cirrhosis of liver may result in formation of collateral circulation around liver

- As a result, portal blood is shunted directly into systemic circulation and does not have access to liver

- Therefore, conversion of ammonia to urea is severely impaired, leading to elevated levels of ammonia.

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Hereditary: Genetic deficiency of each of five enzymes in urea cycle pathway

- X-linked ornithine transcarbamoylase/ornithine carbomyl transferase deficiency is common of these disorders

- In each case, failure to synthesize urea leads to hyperammonemia during first weeks of birth

- Treatment included restriction of dietary protein in presence of sufficient calories to prevent catabolism

Two Clinical-cases discussed

Reference Books

1) Biochemistry, Lippincott's Illustrated Reviews, 6th Ed
2) Harper's Illustrated Biochemistry-30th Ed
3) Lehninger Principles of Biochemistry-6th Ed

Thank you