Hepatic Encephalopathy

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Outline

- **Overview**
- Normal Physiology
- Pathology
- Symptoms
- Diagnosis
- Treatment

Overview

- Ammonia (NH_3) is a byproduct of amino acid and nitrogenous waste breakdown.
- NH_3 levels in circulation are controlled by hepatic metabolism and renal excretion.
- Liver disease can impair NH_3 metabolism and lead to elevated blood concentrations.
- Excess NH_3 levels in our blood can cross the Blood-brain-barrier (BBB) and cause encephalopathy.

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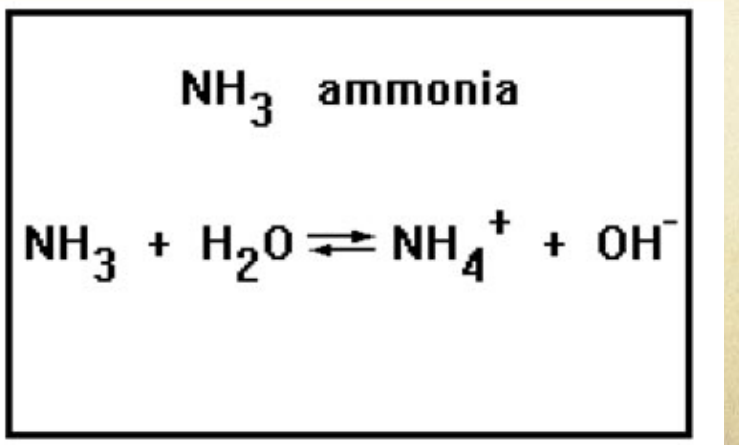
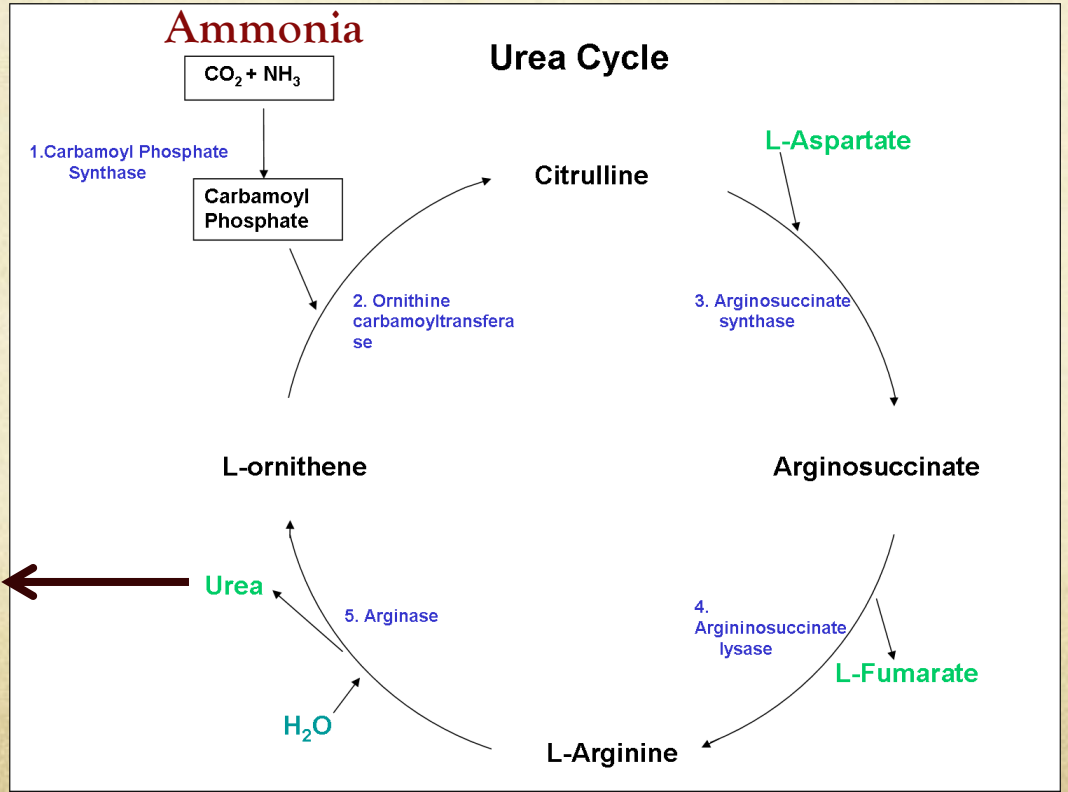
Physiology: NH_3 Production

- Ammonia (NH_3) is a byproduct of amino acid and nitrogenous waste breakdown. Ammonia can be generated from exogenous and endogenous sources including:
  - Degradation of proteins in our diet by colonic bacteria
  - Gluconeogenesis: A byproduct of AA breakdown.
  - GI Bleeding: Protein in our blood is broken down => Increased NH_3 levels
  - Severe Constipation: Reduced excretion of ammonia => Increased absorption
- The NH_3 produced by our gut bacteria is absorbed into the portal system and metabolized by the liver in the urea cycle.
  - Note: Any ammonium (NH_4^+) generated in our colon is not able to be absorbed, it is trapped in the lumen and excreted.



Physiology: NH_3 Metabolism

- Ammonia taken up into the portal system is metabolized in the liver via the urea cycle.
- The urea is put into circulation and excreted by the kidneys.
  - Note: Carbamoyl Phosphate Synthase I is the rate-limiting step of the urea cycle.



To kidneys for excretion

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Pathology: Impaired Metabolism & Increased [NH_3]

- Hepatic Encephalopathy is caused by an acute exacerbation of an already dysfunctional liver.
  - Underlying liver pathology (e.g., due to chronic HCV infection or alcoholic cirrhosis) impairs hepatic processing of ammonia.
  - An acute event (e.g., infection, alcoholic binge, GI bleeding, severe constipation) leads to increased [NH_3] and symptomatic Hepatic Encephalopathy.

Pathology: CNS Effects

- Elevated NH_3 levels in the blood cross the BBB and lead to increased levels of glutamate.
  - NH_3 + α– Ketoglutarate → Glutamate
- Increased levels of glutamate in astrocytes increases their osmotic pressure and draws fluid into the cell.
  - This leads to progressively worsening cerebral edema and associated symptoms.
- In addition to symptoms generated by the cerebral edema, the elevated levels of glutamate may itself directly contribute to altered CNS function.

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Signs & Symptoms

- A patient may present with a number of varied signs and symptoms:
  - CNS symptoms:
    - Disorientation
    - Lethargy
    - Personality Changes
    - Coma and Death: possible if cerebral edema is severe
  - Signs of liver failure may also be present:
    - Jaundice
    - Scleral Icterus
    - Ascites
    - Varices (e.g., esophageal, caput medusae)
    - Peripheral Edema

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Diagnosis

- Liver disease must be confirmed for a diagnosis of Hepatic Encephalopathy as other diseases may cause similar CNS symptoms.
  - E.g., Uremic encephalopathy caused by renal pathology => Decreased excretion of nitrogenous waste products may present with similarly altered cognitive function.
- Confirmation may include:
  - LFTs
  - Imaging (e.g., ultrasound or CT)
  - Liver biopsy
- Would expect elevated levels of NH_3 in circulation.
  - Note: NH_3 levels may not directly correlate with severity of symptoms

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Treatment

- Treatment is focused on reducing NH_3 production and absorption in the colon.
  - **Rifaximin / Neomycin:** These antibiotics kill the colonic bacteria that break down protein in our diet (or from GI bleeding) thereby preventing NH_3 production.
  - **Lactulose**: A mainstay of treatment, lactulose acidifies the colon, trapping NH_3 as NH_4^+ and increasing fecal excretion.
    - Also used as an osmotic laxative, Lactulose can be particularly beneficial in a patient with constipation.