Describe ammonia metabolism and excretion (70% of marks). Outline the pharmacology of lactulose (30% of marks). (37.5%)

**Formation of Urea from Ammonia**
- Liberation of ammonia from AAs
- Formation of carbamoyl phosphate from NH3
- Reactions of the urea cycle

**Urea Cycle**
- Ammonia carried in blood from tissues to liver mitochondria by glutamate as amino groups.
- Hepatocyte Mitochondria
  - $2\text{ATP} + \text{CO}_2 + \text{NH}_3 + \text{Carbamoyl Phosphate} \rightarrow \text{citrulline}$ using enzyme Carbamoyl phosphate synthetase I
- Hepatocyte Cytosol
  - Citrulline + ATP + H$_2$O $\rightarrow$ ornithine + urea
- Urea Fate:
  - Enterohepatic circulation (25%)
  - Excreted by kidneys (75%).
- Ornithine reenters the mitochondria and is combined with new carbamoyl phosphate to form citrulline

**Excretion of ammonia by Kidney**
1. Ammoniagenesis:
   - Glutamine enters the peritubular cells of the PCT
     - 80% from the peritubular capillaries
     - 20% from the filtrate, reabsorbed by PCT
   - Deaminated via Glutaminase (increased activity in acidosis)
   - HCO$_3$ reabsorbed into peritubular capillary blood
   - NH$_4$ excreted via Na/NH$_4$ antiporter
2. Ammonium cycling:
   - 80% reabsorbed TAL of LoH via replacing K on Na/K/2Cl cotransporter
   - Increased conc in medullary intersitium
   - Diffuses down conc grad into CD
   - Buffer ability can be utilised to excrete H.

**Pharmacology of Lactulose:**

<table>
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<tr>
<th>PC</th>
<th>Non-absorbable synthetic, non-digestible disaccharide. osmotic laxative</th>
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<tbody>
<tr>
<td>PD</td>
<td>MOA: ↑ intraluminal osmotic pressure $\rightarrow$ retention of water in stool Abdminal cramping and flatulence</td>
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| PK | A: Not absorbed (PO BA 0%  
D: Not applicable  
M: fermented by gut flora producing metabolites (such as acetate) which have osmotic and peristalsis-stimulating effects  
E: Faecal |
Examiner Comments

It was expected candidates would identify sources of ammonia (colon from metabolism of proteins, kidney, small amounts from breakdown of red blood cells and metabolism in muscles). The liver converts all circulating ammonia to urea (the urea cycle) \(2\text{NH}_3+\text{CO}_2 = \text{urea} +\text{H}_2\text{O}\). Urea then undergoes enterohepatic circulation (25%) or is excreted by kidneys (75%). Ammonia (NH3) is lipid soluble and diffuses into the interstitial cell and tubular fluid by non-ionic diffusion where it buffers H+ to become non diffusible NH4+. No candidate mentioned enterohepatic circulation and most answers had very little detail on the metabolism and excretion and lacked depth.

Lactulose is a non absorbable synthetic, non-digestible disaccharide. It is an osmotic laxative fermented by gut flora producing metabolites (such as acetate) which have osmotic and peristalsis-stimulating effects, and methane causing in flatulence. Few could describe how lactulose decrease absorption of ammonia and a surprising number of people did not even state that lactulose was an osmotic laxative.