Tubular Reabsorption & Secretion

1. Explain the process of renal tubular secretion and reabsorption, giving examples of the major ion transport mechanisms in the kidney.

Tubular reabsorption is selective.

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>glucose, amino acids</th>
<th>usually 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolytes</td>
<td>Na⁺</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td></td>
<td>K⁺</td>
<td>&gt; 87%</td>
</tr>
<tr>
<td>Waste products</td>
<td>creatinine</td>
<td>zero</td>
</tr>
<tr>
<td></td>
<td>urea</td>
<td>50%</td>
</tr>
</tbody>
</table>

Bulk flow (ultrafiltration)
- Transport of water and solutes across peritubular capillary wall.
- Mediated by hydrostatic and colloid osmotic forces.

Active transport
- Transport a species against its concentration gradient.
- Primary active transport – requires breakdown of ATP.
  - Primary transport ATPases:
    → Na⁺,K⁺-ATPase (electrogenic sodium pump)
    → H⁺-ATPase
    → H⁺,K⁺-ATPase
    → Ca²⁺-ATPase (calcium pump)
  - Secondary active transport – requires coupling to a secondary energy source.

Osmosis: Movement of solvent down a solvent concentration.

2. Describe the two barriers across which renal tubular reabsorption occurs.

Reabsorption involves transport across two barriers: tubular cells and peritubular capillary walls.

Paracellular transport
- Transport through junctional spaces between cells of tubular epithelium.
- Purely passive diffusion.

Transcellular transport
- Transport across luminal membrane and basolateral membrane of epithelium.
- Active transport or simple diffusion.

3. Describe the 3-step mechanism of renal sodium reabsorption.

(1) Electrogenic Na⁺ pump (Na⁺,K⁺-ATPase) → generates large electrochemical gradient across luminal membrane.
- Na⁺ diffuses across luminal membrane.
- Occurs in most parts of tubule.
- Brush border in proximal tubule → 20x surface area of membrane richly embedded with Na⁺ channels.
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(2) Electrogenic Na⁺ pump (Na⁺,K⁺-ATPase) → actively transports Na⁺ across basolateral membrane against electrochemical gradient.
   - Generate high intracellular [K⁺] and low intracellular [Na⁺].

(3) Ultrafiltration – Na⁺, water and other substances reabsorbed from ISF into peritubular capillaries.


Primary active transport → produces inwardly directed electrochemical gradient for Na⁺ → energy from gradient stoichiometrically coupled to:
   - Secondary reabsorption of glucose and amino acids through protein co-transporters.
     - Passive facilitated diffusion of glucose and amino acids by bulk flow into peritubular capillaries.
   - Secondary secretion of H⁺ by Na⁺/H⁺ antiporter.

5. Define the terms ‘gradient-time transport’, ‘transport maximum’ and ‘renal threshold’.

Gradient-time transport
   - Occurs for passive transport.
   - Rate of transport depends on:
     - Electrochemical gradient.
     - Time that the substance is in the tubule, which in turn depends on tubular flow rate.
     - Membrane permeability.

Na⁺ reabsorption in proximal tubules obeys mainly gradient-time transport principles rather than maximum transport characteristics.
   - Maximum transport capacity of basolateral Na⁺,K⁺-ATPase far exceeds actual rate of net Na⁺ reabsorption → no saturation of carriers.
   - Reabsorption rate depends on [Na⁺] in proximal tubules and tubular flow rate.

Transport maximum
   - Occurs for most actively reabsorbed or secreted substances.
   - Amount of solute delivered to tubule (filtered load) > capacity of carrier proteins and enzymes → saturation of transport system involved
   - Example: glucose transport system in proximal tubule.

Filtered load = [X]_plasma × GFR
   - Constant GFR → simple linear function of FL vs. [X]_plasma.
   - Normal [glucose] → all FL reabsorbed → no excretion of glucose.
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- High $[\text{glucose}]_{\text{plasma}} \rightarrow$ reach transport maximum $\rightarrow$ excretion of glucose in urine.

Renal threshold: Plasma concentration beyond which a normally totally reabsorbed substance begins to appear in urine.
- Different nephrons have different tubular lengths $\rightarrow$ different transport capacities $\rightarrow$ excretion curve rises curvilinearly.

6. **Summarise the functions of the proximal tubules, the loops of Henle, the distal tubules and the collecting ducts.**

**Proximal tubules**

- 65% of filtered load reabsorbed by end of proximal tubules.
- High water permeability $\rightarrow$ fluid reaching loop of Henle isosmotic with plasma.

<table>
<thead>
<tr>
<th><strong>Substances</strong></th>
<th><strong>Reabsorption</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>glucose, amino acids</td>
<td>$\sim 100%$</td>
</tr>
<tr>
<td>creatinine</td>
<td>$\sim$ zero</td>
</tr>
<tr>
<td>$Na^+$</td>
<td>Cotransport with glucose and amino acids. Na$^{+}$/H$^{+}$ exchange. Cotransport with Cl$^-$.</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>Less reabsorption than $Na^+$. Little glucose or amino acids in later parts of tubule for cotransport $\rightarrow$ Na$^{+}$,Cl$^-$ cotransport in later parts of tubule.</td>
</tr>
</tbody>
</table>

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<tr>
<th><strong>Substances</strong></th>
<th><strong>Secretion</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>H$^+$</td>
<td>Na$^{+}$/H$^{+}$ exchange.</td>
</tr>
<tr>
<td>organic acids and bases</td>
<td>Including bile salts and metabolic end products.</td>
</tr>
<tr>
<td>toxins</td>
<td>Including potentially harmful drugs.</td>
</tr>
</tbody>
</table>

**Loops of Henle**

Renal medullar is hypertonic to filtrate $\rightarrow$ aids in water reabsorption.
- Increasing concentration from base to apex.

<table>
<thead>
<tr>
<th><strong>Segment</strong></th>
<th><strong>Thin descending limb</strong></th>
<th><strong>Thin ascending limb</strong></th>
<th><strong>Thick ascending limb</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular wall</td>
<td>Thin epithelial membrane, no brush borders.</td>
<td>Thick epithelial membrane, no brush borders.</td>
<td></td>
</tr>
<tr>
<td>Metabolic activity</td>
<td>Few mitochondria, minimal metabolic activity.</td>
<td>Many mitochondria, high metabolic activity.</td>
<td></td>
</tr>
<tr>
<td>Permeability to water</td>
<td>Highly permeable to water.</td>
<td>Impermeable to water (even in presence of ADH).</td>
<td></td>
</tr>
<tr>
<td>Permeability to solutes</td>
<td>Moderately permeable to most solutes.</td>
<td>Little solute reabsorptive capacity.</td>
<td></td>
</tr>
<tr>
<td>Secretion</td>
<td></td>
<td></td>
<td>Na$^{+}$/H$^{+}$ exchanger secretes H$^+$.</td>
</tr>
</tbody>
</table>
Tubular Reabsorption & Secretion

<table>
<thead>
<tr>
<th>Reabsorption</th>
<th>Most of water reabsorption in loop of Henle occurs here.</th>
<th>Most of Na(^+), Cl(^-) and K(^+) reabsorption in loop of Henle occurs here. Significant reabsorption of Ca(^{2+}), HCO(_3)(^-) and Mg(^{2+}). Paracellular reabsorption of cations due to +8mV luminal potential.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in tubular fluid</td>
<td>Osmolality of fluid greatly increases here.</td>
<td>Dilution of fluid. Fluid entering distal tubule very dilute.</td>
</tr>
<tr>
<td>Others</td>
<td>Loop diuretics block Na(^+),2Cl(^-),K(^+) cotransporter. Cotransporter complements primary active transport of Na(^+).</td>
<td></td>
</tr>
</tbody>
</table>

 Distal tubules

<table>
<thead>
<tr>
<th>First part</th>
<th>Part of juxtaglomerular apparatus.</th>
<th>Controls RBF and GFR.</th>
</tr>
</thead>
<tbody>
<tr>
<td>First half</td>
<td>Diluting segment. Behaves like thick ascending limb.</td>
<td>Reabsorbs Na(^+), Cl(^-) and K(^+). Impermeable to water. Impermeable to urea.</td>
</tr>
<tr>
<td>Second half</td>
<td>Functionally and anatomically similar to cortical collecting tubule.</td>
<td>Comprises principal cells and intercalated cells. Impermeable to urea. Variably permeable to water.</td>
</tr>
</tbody>
</table>
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Na⁺,Cl⁻ cotransport in first half inhibited by thiazide diuretics.
- Treatment for hypertension and heart failure.

Intercalated cells
- Late distal tubules and cortical collecting duct.
- H₂CO₃ formed intracellularly → dissociation catalysed by carbonic anhydrase → H⁺ → secreted via H⁺-ATPase.
  - Intracellular HCO₃⁻ available for reabsorption → key role in acid-base refulation.
- Reabsorb K⁺ via H⁺,K⁺-ATPase (antiporter).

Urea
- Almost all urea that enters late distal tubule and cortical collecting tubule is excreted.
- Some urea reabsorption in medullary collecting ducts.

Water
- No ADH → late distal tubule and cortical collecting duct impermeable to water.
- ADH controls water reabsorption here.

Medullary collecting duct
- Reabsorb final few percent of filtered load of water and Na⁺ → important role in determining final composition of urine.
- Smooth surfaced cells with few mitochondria.
- ADH controls water and urea permeability.
- Significant urea permeability → reabsorption → high medullary interstitial osmolarity.
- H⁺ secretion → acid-base regulation.

7. Describe the regulation of renal tubular reabsorption by local, hormonal and neural mechanisms.

Local control of tubular reabsorption – depend on physical factors.
- Glomerulotubular balance – intrinsic ability of tubules to match rates of reabsorption to filtered tubular load.
  - ↑GFR → ↑proximal tubular reabsorption → remain at ~65% of GFR.
  - Prevents overloading of distal portions of nephron.
  - Works synergistically with autoregulatory mechanisms.
  - Tubular reabsorption and filtration depend on hydrostatic and colloid osmotic forces.
    → Tubular reabsorption in turn influences same physical forces.
- Arterial pressure → pressure natriuresis and pressure diuresis.
  - Incomplete autoregulation → ↑arterial pressure → ↑GFR.
  - ↑arterial pressure → ↑peritubular capillary hydrostatic pressure → ↓Na⁺ and water reabsorption.
  - ↑arterial pressure → ↓angiotensin II → ↓Na⁺ reabsorption.
## Tubular Reabsorption & Secretion

### Hormonal control of tubular reabsorption

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Sites of secretion/action</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone</td>
<td>Acts on principal cells of cortical collecting tubules</td>
<td>Stimulates basolateral Na⁺,K⁺-ATPase → ↑luminal Na⁺ permeability.</td>
</tr>
<tr>
<td>Antidiuretic hormone (ADH)</td>
<td>Secreted from posterior pituitary gland. Acts on late distal collecting tubule and collecting duct.</td>
<td>Movement of AQP-2 protein molecules → form water channels in luminal membrane → ↑water permeability. Chronic high levels of ADH → stimulate AQP-2 gene transcription.</td>
</tr>
<tr>
<td>Atrial natriuretic peptide (ANP)</td>
<td>↑blood volume → distended cardiac atrial cells → secrete ANP. Acts on collecting duct.</td>
<td>↓Na⁺ and water reabsorption → ↓blood volume.</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>Acts on distal tubule</td>
<td>↑Ca²⁺ reabsorption.</td>
</tr>
<tr>
<td></td>
<td>Acts on proximal tubule</td>
<td>↓phosphate reabsorption.</td>
</tr>
<tr>
<td></td>
<td>Acts on loop of Henle</td>
<td>↑Mg²⁺ reabsorption.</td>
</tr>
</tbody>
</table>

### Neural control of tubular reabsorption – sympathetic activation → ↓Na⁺ and water excretion.

- Arteriolar constriction → ↓GFR.
- ↑tubular Na⁺ reabsorption.
- ↑renin release → ↑angiotensin II → ↑aldosterone release → ↑Na⁺ reabsorption.
- ↑ADH secretion → ↑renal water retention.