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.

<table>
<thead>
<tr>
<th>tubular epithelial cell</th>
<th>tubular lumen</th>
</tr>
</thead>
<tbody>
<tr>
<td>low intracellular [Na⁺]</td>
<td>high luminal [Na⁺]</td>
</tr>
<tr>
<td>-70mV</td>
<td>-3mV</td>
</tr>
</tbody>
</table>
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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} x 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 \([\text{glucose}]_{\text{plasma}}\) → reach transport maximum → 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 → different transport capacities → 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 → fluid reaching loop of Henle isosmotic with plasma.

<table>
<thead>
<tr>
<th>Substances</th>
<th>Reabsorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>glucose, amino acids</td>
<td>~100%</td>
</tr>
<tr>
<td>creatinine</td>
<td>~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 → Na⁺, Cl⁻ cotransport in later parts of tubule.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substances</th>
<th>Secretion</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 → aids in water reabsorption.
- Increasing concentration from base to apex.

<table>
<thead>
<tr>
<th>Segment</th>
<th>Thin descending limb</th>
<th>Thin ascending limb</th>
<th>Thick ascending limb</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>Na⁺/H⁺ exchanger secretes H⁺.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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| Reabsorption | Most of water reabsorption in loop of Henle occurs here. | Most of Na⁺, Cl⁻ and K⁺ reabsorption in loop of Henle occurs here. Significant reabsorption of Ca²⁺, HCO₃⁻ and Mg²⁺. Paracellular reabsorption of cations due to +8mV luminal potential. |
| Change in tubular fluid | Osmolality of fluid greatly increases here. | Dilution of fluid. Fluid entering distal tubule very dilute. |
| Others | Loop diuretics block Na⁺,2Cl⁻,K⁺ cotransporter. Cotransporter complements primary active transport of Na⁺. |

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### Distal tubules

| First part | Part of juxtaglomerular apparatus. | Controls RBF and GFR. |
| First half | Diluting segment. Behaves like thick ascending limb. | Reabsorbs Na⁺, Cl⁻ and K⁺. Impermeable to water. Impermeable to urea. |
| Second half | Functionally and anatomically similar to cortical collecting tubule. | Comprises principal cells and intercalated cells. Impermeable to urea. Variably permeable to water. |

Na⁺,Cl⁻ cotransport in first half inhibited by thiazide diuretics.
- Treatment for hypertension and heart failure.

**Principal cells**
- Late distal tubule and cortical collecting duct.
- Secrete K⁺, reabsorb Na⁺.
  - Luminal Na⁺ channels and K⁺ channels.
  - Basolateral Na⁺,K⁺-ATPase.
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- K⁺ sparing diuretics act here.
  - Block Na⁺ channel (e.g. amiloride).
  - Inhibit action of aldosterone in stimulating Na⁺,K⁺-ATPase (e.g. spironolactone).

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 regulation.
- 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>Angiotensin II</td>
<td>Body’s most powerful Na⁺ retaining hormone. Formed in response to low blood pressure and/or low ECF volume.</td>
<td>Stimulates aldosterone secretion. Constriction of efferent arterioles → ↓peritubular capillary pressure → ↑proximal tubular reabsorption. Constriction of efferent arterioles → ↓RBF → ↑filtra-</td>
</tr>
<tr>
<td>hormone (ADH)</td>
<td></td>
<td>↓Na⁺ and water reabsorption → ↓blood volume.</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⁺ reabsorption.</td>
</tr>
<tr>
<td>Parathyroid</td>
<td>Acts on distal tubule</td>
<td>↓phosphate reabsorption.</td>
</tr>
<tr>
<td>hormone</td>
<td>Acts on proximal tubule</td>
<td></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.