Renal handling of substances

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GENERAL PRINCIPLES OF RENAL TUBULAR TRANSPORT

- Transport mechanisms across cell membrane

1) Passive transport

i. Diffusion

ii. Facilitated diffusion (channels, uniport, coupled transport,uniport or symport)

iii. Solvent drag.

2) Active transport

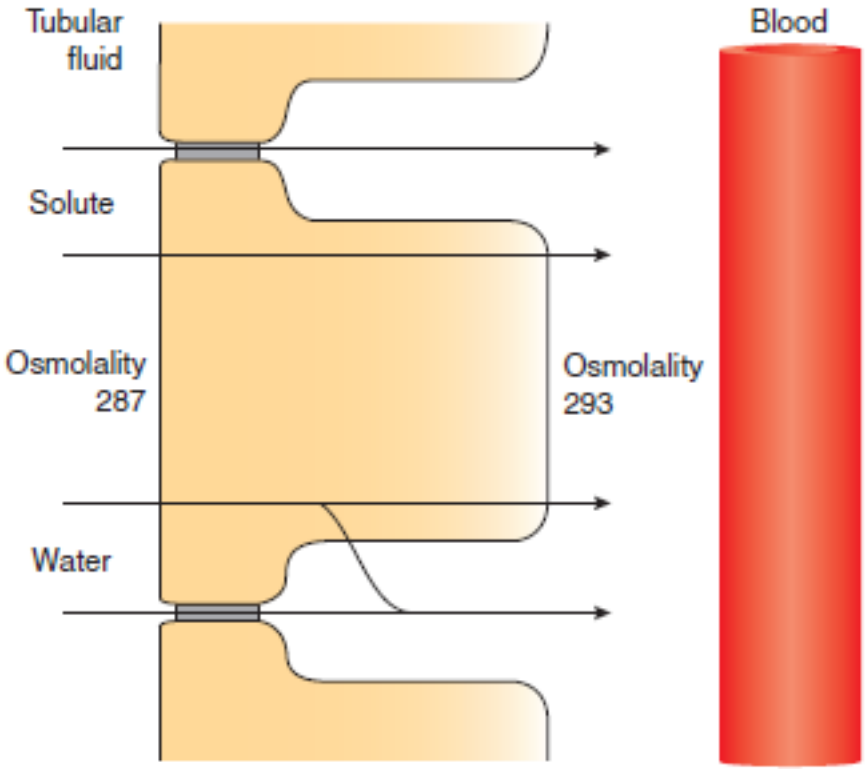
I. Transepithelial transport pathways

A. Transcellular pathway

- Transport through cells.
- Example : Na+ reabsorption by PT in two-step

1. Movement of Na+ into cell across apical membrane occurs down an electrochemical gradient established by Na+−K+−ATPase.

2. Movement of Na+ into extracellular fluid across basolateral membrane occurs against an electrochemical gradient via Na+−K+−ATPase.


Tubular fluid
Blood
Solute
Osmolality 287
Osmolality 293
Water

II. Paracellular pathway

- Transport between cells.
- Examples

1. Reabsorption of Ca^{2+} and K^{+} across PT
2. water reabsorbed across PT
3. Some solutes dissolved in this water (Ca^{2+}, K^{+}) by solvent drag

Tubular reabsorption

- Active transport of solutes & passive movement of water from tubular lumen into peritubular capillaries.
- Removal of substances of nutritive value, such as glucose,amino acids, electrolytes (Na^+, K^+, Cl^-, HCO_3^-) and vitamins from the glomerular filtrate.
- Small proteins ,peptide hormones are reabsorbed in PT by endocytosis.

Tubular secretion

- Transport of solutes from peritubular capillaries into tubular lumen
- It is addition of a substance to glomerular filtrate.
- Take help of certain non-selective carriers.
- Carrier which secretes PAH can also secrete uric acid, bile acids, oxalic acid, penicillin, probenecid, cephalothin and furosemide.

Renal clearance

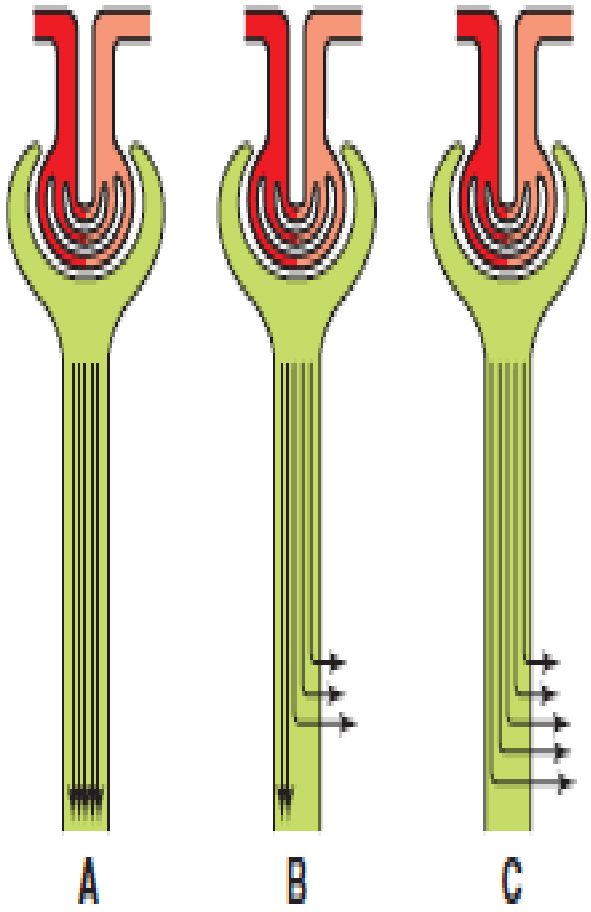
- Volume of plasma that is cleared of a substance in 1min by excretion of substance in the urine.
- PAH > K+ (high K+ diet) > Inulin> Urea > Na+ > Glucose, amino acids and HCO_3^-

Patterns of renal handling of a substance

1. Glomerular filtration only (e.g. inulin)
- Glomerular markers
- Renal clearance equal to GFR.

2. Glomerular filtration f/b partial reabsorption
- Substances have renal clearance less than GFR.

3. Glomerular filtration followed by complete tubular reabsorption
- Substances have lowest renal clearance, e.g. Na+, glucose, amino acids, HCO_3^- ,Cl^-.
- Substances that are not filtered at all (e.g. protein)



4. Glomerular filtration f/b tubular secretion

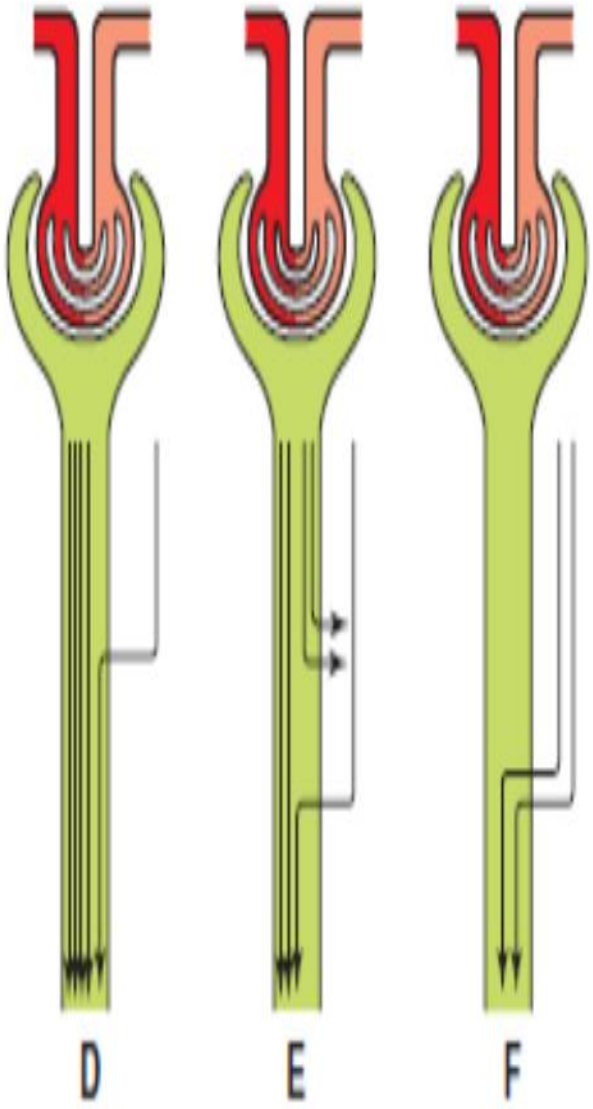
- Substances that are both filtered & secreted have highest renal clearances (e.g. PAH).

5. Glomerular filtration f/b partial reabsorption & secretion

- Which processes is dominant
- Net absorption = substance excreted is less than GFR
- Net secretion = substance excreted is more than GFR

6. No glomerular filtration, no absorption, only secretion

- Many organic compounds are bound to plasma proteins therefore unavailable for ultrafiltration.
- Secretion is thus their major route of excretion in urine.



Renal tubular transport maximum (Tm)

- Maximal amount of a solute that can be actively transported (reabsorbed or secreted) per min by renal tubules.

- Tm = solutes that are actively transported

  E.g. Phosphate Ion, Sulphate, Glucose, Amino Acids, Uric Acid, Albumin, Acetoacetate,β-hydroxybutyrate, B-ketoglutarate

- No Tm =Substances that are passively transported

  E.g. Urea, Reabsorption of Na^+ & HCO_3^-

- Threshold conc. = plasma conc. at which substance first appears in urine.

Tubular fluid concentration (TF)/plasma concentration (Px) ratio

- Compares conc. of substance in tubular fluid at any point along nephron with its conc. in plasma.
- Micropuncture technique.

1. Micropipette inserted into Bowman's space & different portions of tubules of living kidney in experimental animals
2. Composition of aspirated tubular fluid is determined by microchemical techniques.

Significance of TF/Px ratio

TF/Px ratio of 1.0
- No reabsorption or
- Reabsorption of substance = Reabsorption of water.

TF/Px ratio < 1.0
- Reabsorption of a Substance > Reabsorption of water
- Its Conc. in tubular fluid < plasma conc.

- **TF/Px ratio of > 1.0**
- Reabsorption of substance < Reabsorption of water
- Secretion of substance.

TRANSPORT ACROSS DIFFERENT SEGMENTS OF RENAL TUBULE

Reabsorption		Non-reabsorption	Secretion
Active	**Passive**		
Proximal tubule			
Na^+	Cl^-	Inulin	H^+
K^+	HCO_3^-	Creatinine	Water
Ca^{2+}	HPO_4^-	Sucrose	Penicillin
Mg^{2+}	Water	Mannitol	Sulphonamide
HPO_4^{2-}	Urea		Creatinine
SO_4^{2-}			Urate
NO_3^-			Water
Glucose			
Amino acids			
Protein			
Urate			
Vitamins			
Acetoacetate			
β-hydroxybutyrate			
Henle's loop			
Na^+	Cl^-		
K^+	HCO_3^-		
Ca^{2+}	Water		
Distal tubule and collecting duct			
Na^+	Cl^-		K^+
Ca^{2+}	HCO_3^-		H^+
Mg^{2+}	Water		
Water			

Transport across PT

PT reabsorbs:

1. 67% of filtered water, Na+, Cl−, K+ & other solutes.
2. All glucose & amino acids filtered by glomerulus.
3. PT does not reabsorb inulin, creatinine,sucrose & mannitol.
4. PT secretes H+, PAH, urate, penicillin, sulphonamides & creatinine.

Transport across LOH

1. 20% of filtered Na+ and Cl−,
2. 15% of filtered water & cations,such as K+, Ca2+ and Mg2+ reabsorbed in LOH

Transport across DT & CD

1. 7% of filtered NaCl and about 8–17% of water is reabsorbed
2. K+ & H+ are secreted

1.RENAL HANDLING OF SODIUM AND WATER

1. PT : 67%
2. LOH (mainly thick : 20% ascending limb)
3. DT : 7%
4. Cortical CD : 5%

1.Reabsorption in proximal tubule

Isosmotic

Mechanisms of Na+ reabsorption

a) In early PT

- Co transport with H+/organic solutes (glucose, amino acids, phosphate and lactate)
- Two-step process

i. Across basolateral membrane-

- Na+ moves against electrochemical gradient via Na+–K+–ATPase pump, which pumps Na+ into paracellular spaces & lowers intracellular Na+ conc.

ii. Across apical membrane

- Sodium moves down electrochemical gradient
- antiporter & symporter

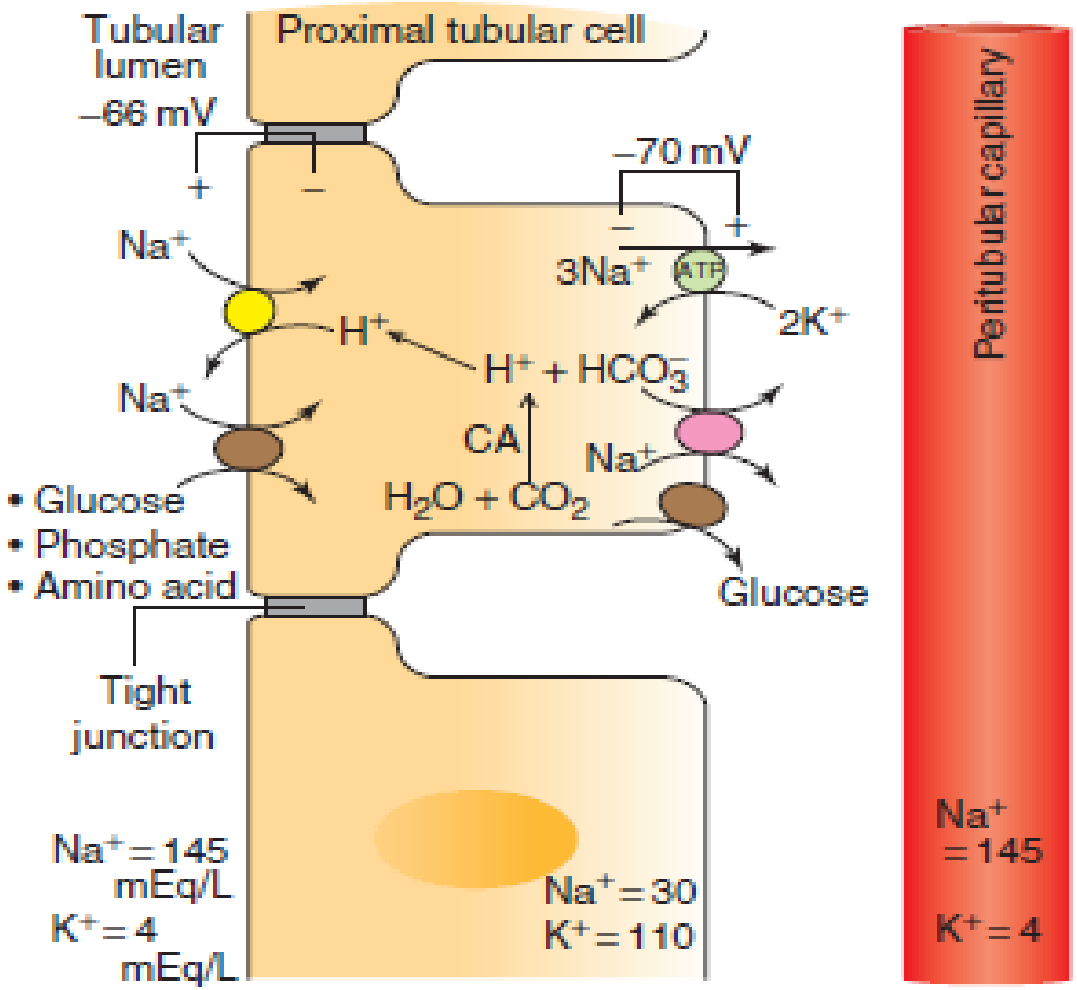


Fig. 6.2-7 Mechanism of reabsorption of sodium and other solutes across early proximal tubule.

Na+−H+ antiporter

- Main determinant of Na+ & H2O reabsorption in PT.
- Na+−H+ exchange is linked directly to reabsorption of HCO3−.
- Carbonic anhydrase inhibitors (e.g. acetazolamide)
- Early PT by inhibiting reabsorption of filtered HCO3−.

Na+−glucose (and other organic solutes) symporter

- Establishes transtubular osmotic gradient that provides driving force for passive absorption of water by osmosis.
- Because more water than Cl− is reabsorbed in early segment of PT, Cl− conc. in tubular fluid rises along length of the early PT

b) In late PT

1. Chloride-driven sodium transport both transcellular & paracellular pathways

- Reabsorption via paracellular pathway.

Fluid entering late PT contains very low glucose, a.a. & HCO_3^- but contains a high conc. of Cl^- (140 mEq/L) (In early PT 105 mEq/L).

↓

Creates conc. gradient which favours diffusion of Cl^- from lumen into lateral intercellular space across tight junctions

↓

Tubular fluid to become positively charged relative to blood.

↓

Diffusion of Na^+ across tight junctions into blood.

- Luminal membrane of late PT –

1. Na+–H+ & one or more Cl– anion (formate) antiporters

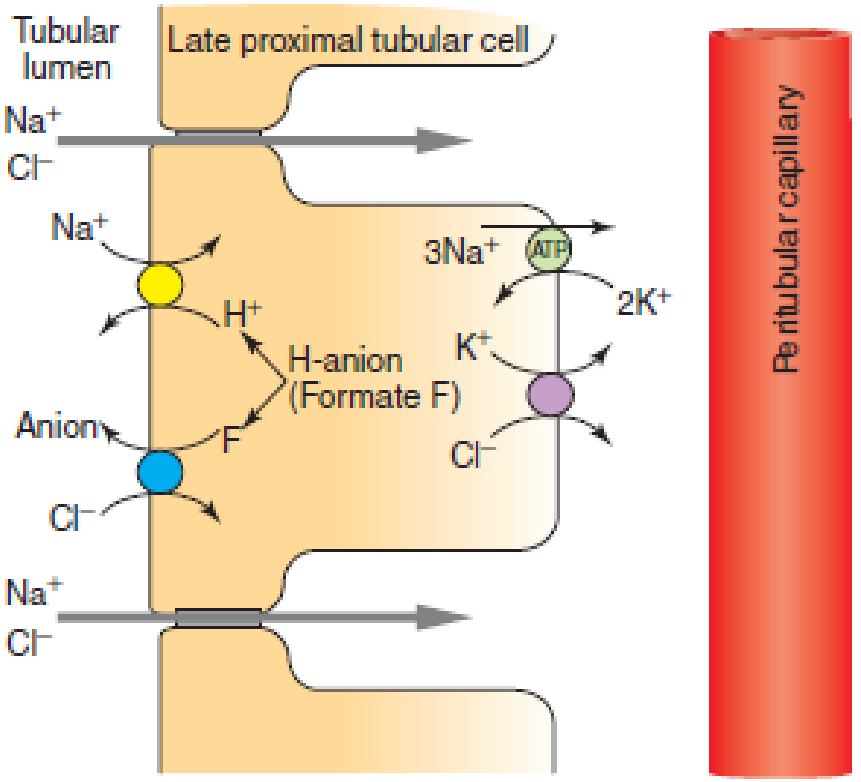
- Across basolateral membrane

1. Na+ leaves cell –

by Na+–K+–ATPase pump

2. Cl– leaves –

by K+–Cl– co-transporter



2.Reabsorption in LOH

Thin descending limb of LOH

- Water absorption occurs passively (because of hypertonic interstitial fluid)
- Diffusion of sodium ions from interstitial fluid into tubular lumen.

Thin ascending limb of LOH

- Water-impermeable limb.
- Because of this , fluid leaving this limb is hypotonic

Thick ascending limb of LOH

- Impermeable to water
- Reabsorption of 20% of the filtered Na^+, Cl^- and other cations.
- Half Na^+ is reabsorbed actively and transcellularly
- Other half of Na^+ is reabsorbed passively by paracellular pathway along with other cations.

Basolateral membrane

Na+, K+−2Cl− symporter-mediated active transport of Na

1. Na+−K+−ATPase in basolateral membrane

   (extrudes Na+ & lead to low intracellular Na+ conc.)

Chemical gradient is created which favours movement of Na+ from lumen into cell.

2. Due to presence of ‘tight’ , Na+ is unable to leak back into tubule to produce a luminal potential

However, some of K+ which enters cell leaks back across apical membrane into tubular lumen, generating a lumen-positive transepithelial potential difference of +6 to +10 mV.

Apical membrane

- $Na^+ – K^+ – 2Cl^–$ symporter
- Downhill movement of Na^+ & $Cl^–$, drives the uphill movement of K^+ influx.
- loop diuretics (e.g. furosemide, ethacrynic acid) inhibit it.

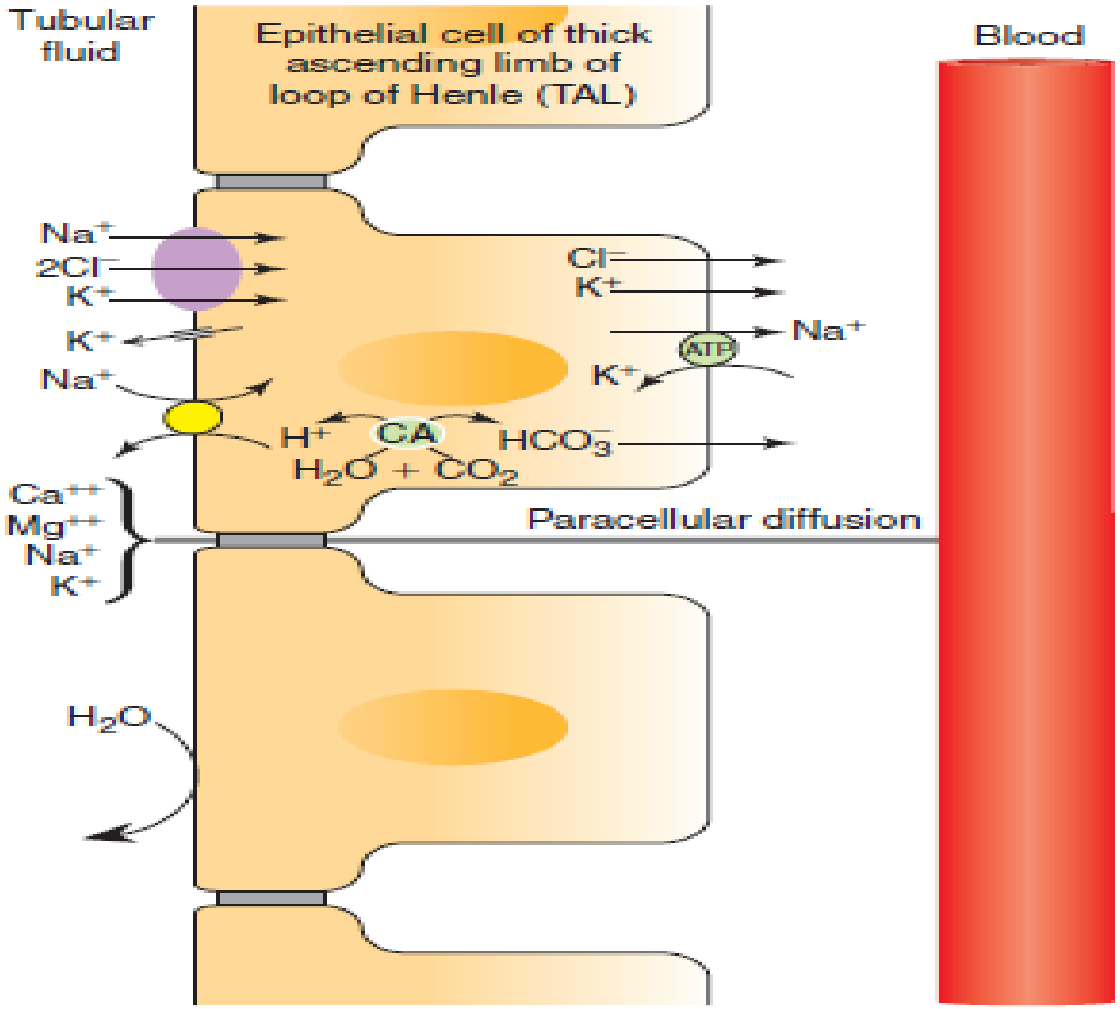


Fig. 6.2-9 The active (transcellular) and passive (paracellular) transport mechanism operating across the tubular cells in thick ascending limb (TAL) of loop of Henle.

- Na+−H+ antiporter-mediated active reabsorption of sodium also occurs transcellularly leading to H+ secretion (HCO_3^- reabsorption)

- Paracellular passive reabsorption of Na^+, K^+, Ca^{2+} and Mg^{2+} is function of voltage across thick ascending limb.

- Because of unique location of transport proteins in apical & basolateral membranes, tubular fluid is positively charged relative to blood.

- Increased salt reabsorption by thick ascending limb increases magnitude of positive charge in lumen, which plays a major role in driving passive paracellular reabsorption of cations

3. Reabsorption across distal tubule

Early distal tubule

- Reabsorbs Na+, Cl−
- Impermeable to water
- Dilution of tubular fluid
- So called cortical diluting segment.

- Apical membrane - Na+−Cl− symporter
- Basolateral membrane –
  Na+ leaves cell via Na+−K+−ATPase
  & Cl− leaves cell by diffusion

- Thiazide diuretics reduce NaCl reabsorption by inhibiting Na+−Cl− co-transport.

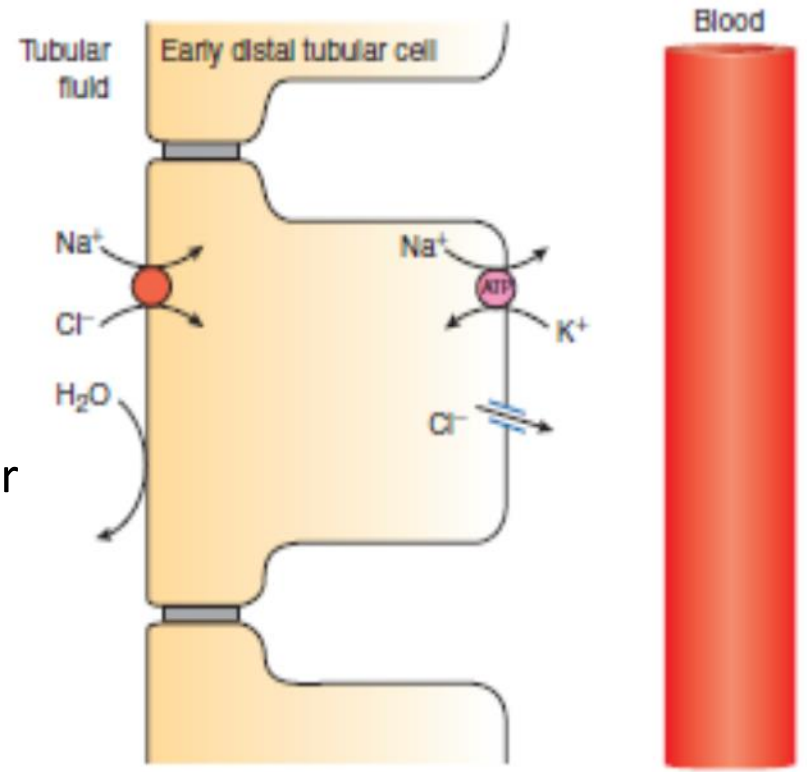


Fig. 6.2-10 Mechanism of reabsorption of Na^+ and Cl^- in the early distal tubule. This segment is impermeable to water (see text for details).

Late distal tubule and collecting duct

- Principal cells & intercalated cells

Principal cells reabsorb Na^+, Cl^- and H_2O and secrete K^+

1. Na^+ reabsorption.

- Na^+–K^+–ATPase across basolateral membrane.
- Apical membrane diffusion due to chemical gradient.

2. Cl^- reabsorption

- Paracellular pathway.
- Cl^- is driven by lumen-negative charge generated by diffusional influx of sodium.

3. H2O absorption

- ADH increases H2O permeability by directing insertion of H2O channels in luminal membrane of principle cell
- In absence of ADH, principal cells are impermeable to water.

4. K+ secretion.

- K+ uptake across basolateral membrane via Na+−K+−ATPase f/b diffusion

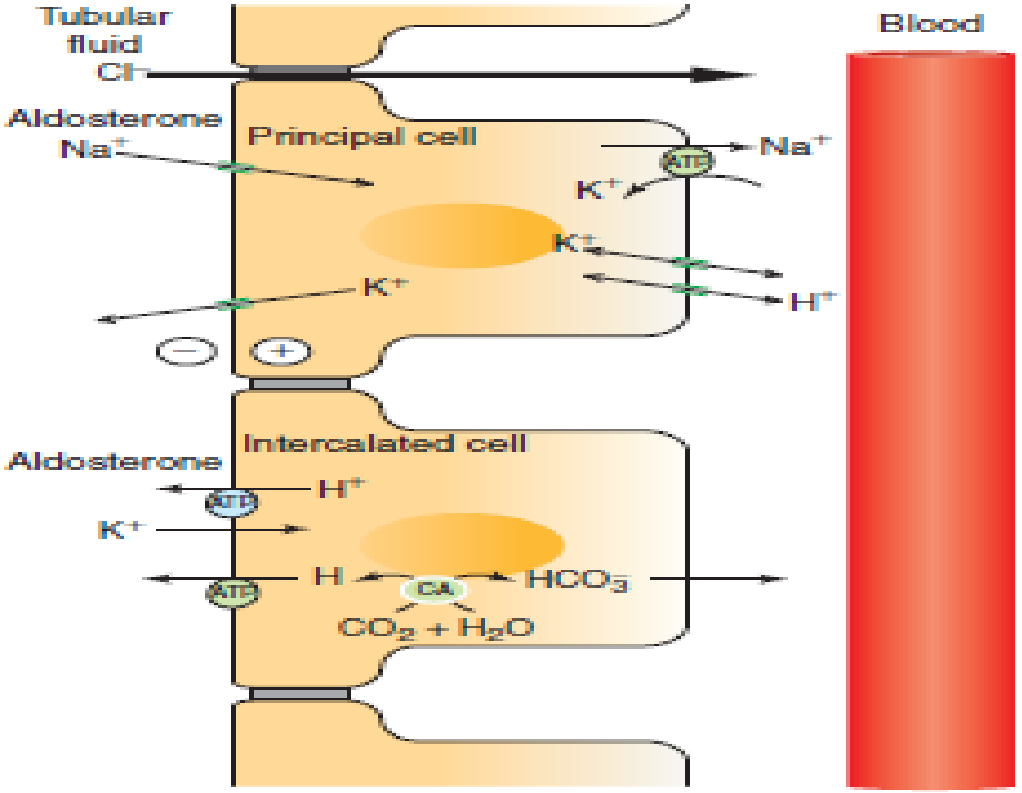


Fig. 6.2-11 Mechanism of transport in principal cells and intercalated cells of the late distal tubule and collecting duct. CA = Carbonic anhydrase.

Role of aldosterone on principal cell

- Aldosterone increases Na+ reabsorption and increases K+ secretion.
- It takes several hours
- About 2% of overall Na+ absorption is affected by it.

Role of aldosterone on Intercalated cells

- Reabsorb K+ and secrete H+.
- Aldosterone increases H+ secretion by intercalated cells by stimulating H+−ATPase

Table 6.2–3 Summary of mechanism of Na^+ absorption across different segments of renal tubule

Segment of the tubule	Absorption active/passive/ Impermeable	Mediated by
Proximal tubule		
• Early proximal tubule	Active	• Na^+, K^+ antiport • Na^+—glucose (and other organic solutes) symport
• Late proximal tubule	Active	• Cl^- driven Na^+ transport
Loop of Henle		
• Descending thin segment (DTS)	Passively secreted in interstitium	
• Ascending thin segment (ATS)	Passive	
• Thick ascending limb (TAL)	Active (Transcellular)	• Na^+—K^+—$2Cl^-$ symporter • Na^+, H^+—antiporter
Distal tubule and collecting duct		
• Early distal tubule	Active	• Na^+, Cl^- symport
• Late distal tubule and collecting duct (Principal cell)	Active	• Regulated by aldosterone

II. Water reabsorption

- Osmosis
- Aquaporins
- Aquaporin-1, 2, 5, 9- present in the kidney.

PT-

- Passively reabsorbed (67%).

LOH –

✓ Descending thin segment : Passively reabsorbed (15%)

✓ Ascending thin segment : Impermeable

✓ Thick ascending limb : Impermeable

DT & CD - (8–17%)

✓ Distal convoluted tubule : Impermeable

✓ Connecting tubule (CNT) : Impermeable

✓ Cortical CD : Reabsorbed (ADH)

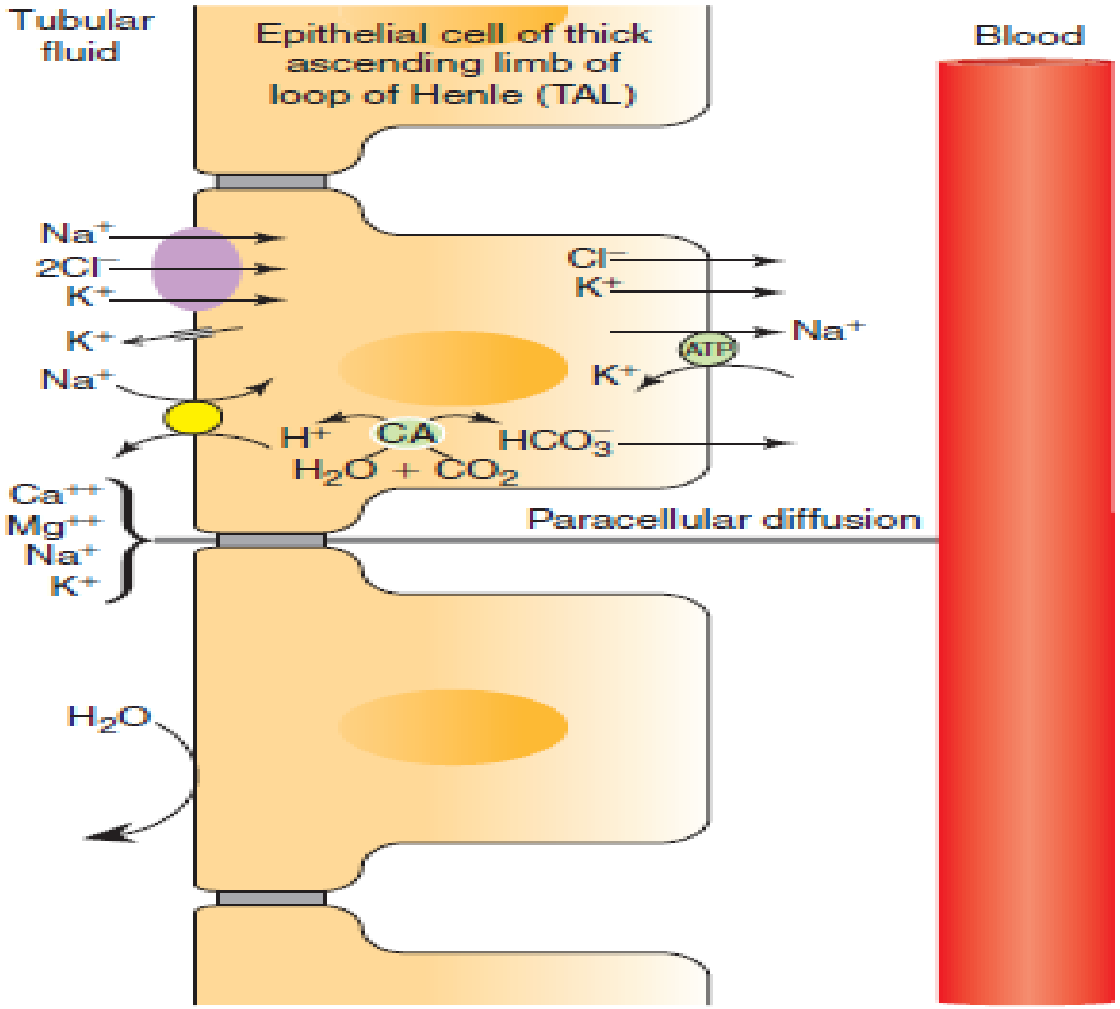
✓ Outer & inner medullary CD : Reabsorbed (ADH)

Obligatory reabsorption. (MUST)

- About 85% of filtered water is always reabsorbed, irrespective of body water balance.
- This reabsorption occurs by osmosis in response to a transtubular osmotic gradient
- 67% of obligatory reabsorption occurs in PT and 15−18% of obligatory in descending thin segment of LOH.

Facultative reabsorption. (OPTIONAL)

- Remaining 15−18% of water may or may not be absorbed depending upon body water balance.
- Occurs in CD (under control of ADH)



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Regulation of K+ tubular secretion

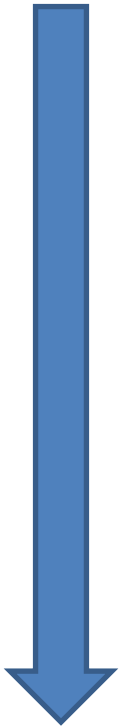
1. Plasma K+ level

- Hyperkalaemia -High K+ diet or rhabdomyolysis stimulates K+ secretion within minutes.
- Hypokalaemia- low K+ diet or diarrhoea, decreases K+ secretion

2. Aldosterone.

- Hyperkalaemia & angiotensin II - Aldosterone secretion increased
- Hypokalaemia & ANP- Aldosterone secretion is decreased

Chronic rise in aldosterone level



Increases K+ secretion by principal cells

Mechanisms

1. By increasing Na+–K+–ATPase activity.

leads to increased pumping of Na+ out of cell at basolateral membrane &

Increased Na+ entry into cells across luminal membrane.

2. By making transepithelial potential difference (TEPD) more lumen negative.

3. By increasing permeability of apical membrane to K+

3. Glucocorticoids

- Indirectly work
- Increase K+ excretion by increasing GFR which increases tubular flow which increases K+ secretion.

4. ADH

- Increases Na+ & water reabsorption

➢ ADH-induced increased Na+ uptake across luminal membrane creates an electrochemical gradient which increases K+ secretion into lumen

- Decreases tubular flow which in turn decreases K+ secretion

- Inhibitory effect + stimulatory effect = maintained constant level despite wide fluctuations in water excretion.

5. Flow of tubular fluid.

- Increase flow –

Increases K+ secretion rapidly,

- Decrease flow –

Decreases secretion of K+ by DT & CD

6. Acid–base balance

K+ secretion affect by DT & CD

Acute acidosis reduces K+ secretion by

1. By decreasing Na+–K+–ATPase activity across basolateral membrane

   It reduces intracellular K+ Conc.

- Reduces electrochemical driving force for K+ exit across apical membrane.

2. By reducing permeability of apical membrane

- It decreases K+ secretion & tends to increase intracellular K+ Conc.

Net result = K+ constant

Acute alkalosis : opposite effects