Urine formation

- Three major processes are essential for urine formation: ***filtration, tubular reabsorption and tubular secretion***

1. Filtration

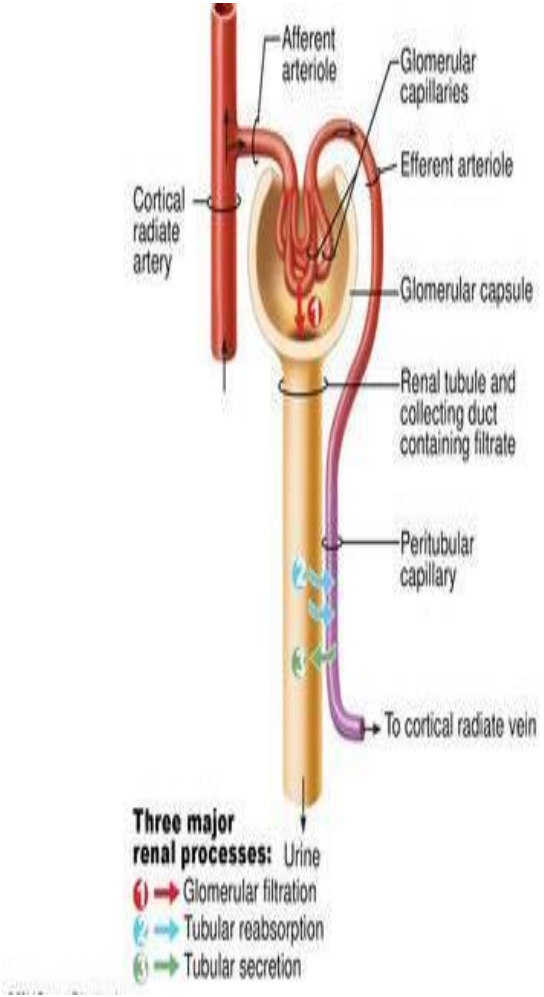
- Filtration is the movement of water and small solutes from blood flowing through the glomerulus across the filtration membrane as a result of pressure differences into the Bowman's capsule forming the **filtrate** .
- Most substances in plasma (except for proteins) are freely filtrated, so their concentrations in the glomerular filtrate in the Bowman's capsule are the same in the plasma.

Glomerular blood flow

- The part of the total cardiac output that passes through the kidney is called **renal fraction .**
- The normal cardiac output is 5600ml\min , which the renal fraction is 1200ml\min which represents 21% and varies from 12-30%.

Glomerular filtrate

- ✓ Glomerular filtrate is the fluid filtrated through the glomerular membrane into Bowman's capsule.
- ✓ Filtration membrane is composed of three layer each of these layer is several hundred times as permeable as the capillary .



- ❑ The reasons for the high selectivity of the glomerular membrane are:

1. **Size of the pores** in the glomerular membrane is large enough to pass molecules with diameter 3 nm.
2. **Electrical charges** of the molecules. The pores are lined by glycosylated proteins which have strong negative electrical charges.

- ❑ Glomerular filtrate has the same components of the plasma except it has no significant amount of proteins.

The glomerular filtration rate (GFR)

- The glomerular filtration rate (GFR) is the quantity of glomerular filtrate form each minute in all nephrons of both kidneys. It is 125ml\min in normal person.
- Glomerular filtrate is reabsorbed in the tubules, while remaining is passing into urine.
- Normal plasma flow through the kidney is 650ml\min and GFR of both kidneys is 125ml\min, so the average filtration fraction is 19%

Factors that affect the GFR

- The factors that determine the filtration pressure (glomerular pressure, plasma colloid osmotic pressure and Bowman's capsule pressure) will determine the GFR.
- The conditions that affect these pressures and therefore affect the GFR are:

1. **Renal blood flow**: an increase in the rate of blood flow through the nephrons increases the GFR by increasing the glomerular pressure which enhances the filtration process.
2. **Afferent arteriolar constriction** decreases the rate of blood flow into the glomerular and also decreases the glomerular pressure causing a decrease in the filtration rate.
3. **Efferent arterioles constriction** causes an increase in the resistance to outflow from the glomeruli. This increases the glomerular pressure and increase in efferent resistance causes slight increase in the GFR.
4. **Sympathetic stimulation of the kidneys** causes the afferent arterioles to constrict, thereby decreasing the GFR .

- With strong sympathetic stimulation, glomerular blood flow and glomerular pressure are reduced so that glomerular filtration decreases to only a few percent of normal and the urinary output can fall to zero for as long as 5 to 10 minutes.

5. Arterial pressure

- When the arterial pressure rises , afferent arteriolar constriction occurs automatically. This prevents a significant rise in glomerular pressure despite the rise in the arterial pressure. Therefore, the GFR increases only few percent even when the mean arterial pressure rises to 150 mmHg. This phenomenon is called **auto regulation**.
- Glomerular nephritis results from inflammation of the filtration membrane within the renal corpuscle. The inflammation leads to increased membrane permeability and accumulation of WBCs in the area resulting in high concentration of plasma proteins that enter the filtrate along with WBCs. glomerular nephritis may be acute when occurs within 1-3 weeks after bacterial infection, or chronic which is long. The filtration membrane becomes thick and replaced by connective tissues.

Reabsorption and secretion in the tubule

- The filtrate entering the nephrons flows through the following tubules:

1. The proximal tubule
2. The loop of Henele
3. The distal tubule
4. The collecting tubule
5. The collecting duct

- Substances are selectively reabsorbed or secreted by the tubular epithelium.
- Reabsorption plays greater role than does secretion in the formation of urine, but secretion is an important in the determining the amount of K^+ and H^+.
- The resulting fluid entering the pelvis is urine.
- Water in the glomerular filtrate is reabsorbed in about 99% as it passes through the tubules.
- Glucose and amino acids are entirely reabsorbed.

Renal transport mechanism

- Substances are reabsorbed or secreted by:

1. **Trancellular transport:** transport across tubular epithelial cells from the tubular lumen into tubular epithelial cells across the luminal membrane, and from inside the epithelial cell into the interstitium and peritubular capillaries across the **basolateral membrane**.

- It involves **active transport** and **passive transport**.
- Active transport is responsible for transport of Na^+ .
- Secondary active transport utilizing Na^+ gradient (sodium symport). It is used for transporting glucose, amino acid ,ions, metabolites

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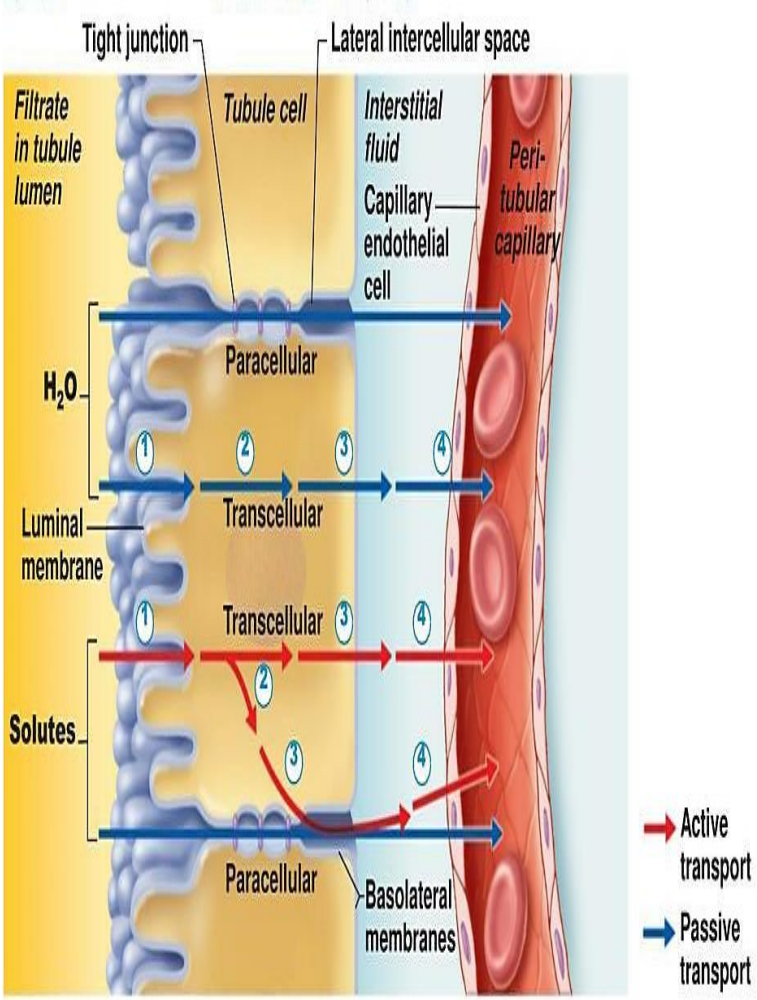
2. **Paracellular transport** done via tight junction and lateral intercellular space.

- It is important for electrolytes K^+ , Ca^{+2} and differs in permeability in different tubules.
- It allows to leak amount of solute and fluid in the proximal tubule, while in collecting tubule is more limited.

Tubular transport maximum

- Transport maximum (T_m) is a limit for the amount of transported substances per unit time.
- It exists for substances that are actively reabsorbed, because the carriers responsible for transport become saturated.
- When the carries are saturated, excess of substances is excreted.
- The renal threshold for substance is the plasma concentration at which this substance first occurs in the urine.
- When the transporters are saturated that is all bound to the substance they transport the excess is excreted in urine as in uncontrolled diabetes mellitus . As plasma levels of glucose exceed 180mg/dl (hyperglycemia) , the glucose T_m is exceeded and large amounts of glucose may be lost in the urine even though the renal tubules are still functioning normally.



1. The proximal tubule

- A bout 2/3 of the glomerular filtrate is reabsorbed from the proximal tubule.
- About 60-70 % of Na^+ ,water and urea is reabsorbed.
- Complete reabsorption of Cl^-, HCO_3^-, HPO_3^-, K^+, glucose, amino acids and proteins.
- H^+, ammonia and organic acids are secreted into the tubule

3. Water reabsorption

- Transport of Na^+ and Cl^- into the lateral intercellular space causes osmotic flow of water from the lumen into the same space.
- Water and solutes transport from the lateral intercellular space into the peritubular capillaries by osmotic and hydrostatic pressure gradients.
- Some water and solutes may leak back into the tubular lumen.
- The volume of reabsorbed water depends partly on the filtration fraction:

- If the filtration fraction increases then more water will be filtrated at the glomerulus leaving high protein concentration in the glomerular capillaries and raising the oncotic pressure in the peritubular capillaries causing an increase in reabsorption from the lateral space.
- If the filtration fraction decreases, the opposite happens.

4. Glucose reabsorption

- All glucose in the filtrate is reabsorbed in the proximal tubule at the a normal level of plasma glucose.
- Glucose is cotransport with Na+ at the luminal membrane . When Na+ moves down its electrochemical gradient , glucose diffuses from the cell into intestinal fluid and then to peritubular capillaries.

- The normal plasma concentration of glucose is (0.6-1 mg/ ml).
- The transport maximum for glucose is about 375mg/ml in man , 350 mg/ml in woman). The renal threshold for glucose (the plasma concentration at which glucose first appears in urine is 375 mg/ml divided by GFR (125ml/min),which is 0.3 mg/ml for man).
- When plasma glucose is high, in diabetes mellitus, glucose appears in urea (**glycosuria**).

5. Bicarbonate reabsorption

- Hydrogen ions enter the lumen in exchange with Na^+ or they are secreted by **H^+ ATPase.**
- Hydrogen ions combine with HCO^+ filtrate at the glomerulus to form $H2CO_3^-$.
- H_2CO_3 dissociate to H_2 and CO_2 raising the luminal PCO_2 . This reaction is catalyze by carbonic anhydrase .
- Carbone dioxide diffuse into the cell ,by reverse reaction H^+ and HCO_3^- are formed. H^+ replace those that enter the lumen. HCO_3^- diffused across the basolateral cell membrane with Na^+ into the interstitial space, then absorbed into peritubular capillaries.

6. Amino acid

- Amino acids are freely filtrated at the glomerulus, so they occur in the filtrate at the same concentration in plasma (**3 mmol/L**).
- They are reabsorbed by cotransport with Na^+ at the luminal membrane .

7. Phosphate

- Phosphate is breakdown product of protein metabolism. Its concentration in plasma is 1 mmol/L.
- It is freely filtrate at the glomerulus and cotransport with Na+ at luminal border of the proximal tubule.
- An increase in phosphate concentration in plasma cause an increase in phosphate excretion.
- Its reabsorption is regulated by hormone PTH and increased by calcitrol.

8. Potassium

- Potassium is filtrated freely at the glomerulus and present in the filtrate at the concentration equal to that in the plasma (4-5 mmol/L).
- It is reabsorbed passively into the cells of proximal tubule through the paracellular pathway and active transport at the luminal border.

9. Calcium

- Plasma Ca^{+2} level is 2.5 mmol/L. about 40-50% of calcium is bound to protein and cannot be filtrate by the glomerulus.
- The ionized form Ca^{+2} is freely filtrated by glomerulus.
- Calcium is reabsorbed from the proximal tubule in parallel with Na^{+} and water, so Ca^{+2} enter the cells passively down its electrochemical gradient and leaves the cells by Ca^{+2}/Na^{+} counter transport or by Ca^{+2} ATPase mechanism.

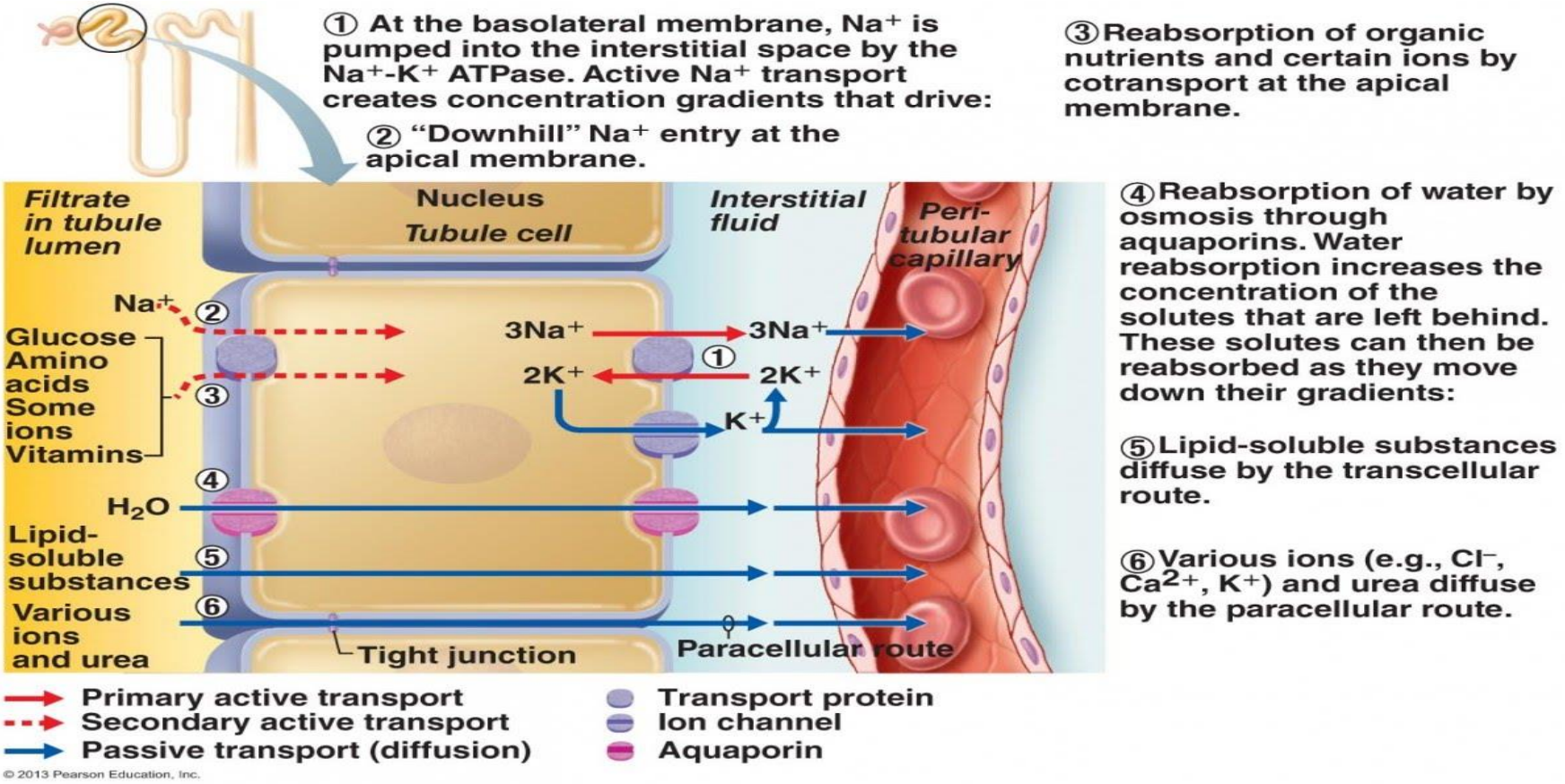
10. Urea

- Urea is the product of protein metabolism. Its concentration in plasma is **2.5-7 mmol/L**.
- It is freely filtrated . About 50% of it is reabsorbed by the end of proximal tubule and ions reabsorption increases urea concentration in the lumen of tubule; therefore it diffuses out of the tubule down its concentration gradient.

11. Organic cations and anions

- Proximal tubule secrets organic cations and anions , some of which are the end products of metabolism that circulate in plasma, e.g. **bile salt, oxalate, urate, prostaglandins and creatinine.**
- The proximal tubule secrets **exogenous organic compounds** e.g. **polycyclic aromatic hydrocarbon (PAH),** which is used to determine renal plasma flow and drugs such as penicillin , aspirin, morphine and quinine.
- Most of them are bound to plasma protein and cannot be filtrated so eliminated by secretion into the lumen.

Reabsorption by PCT cells



Loop of Henle, distal tubule and collecting duct

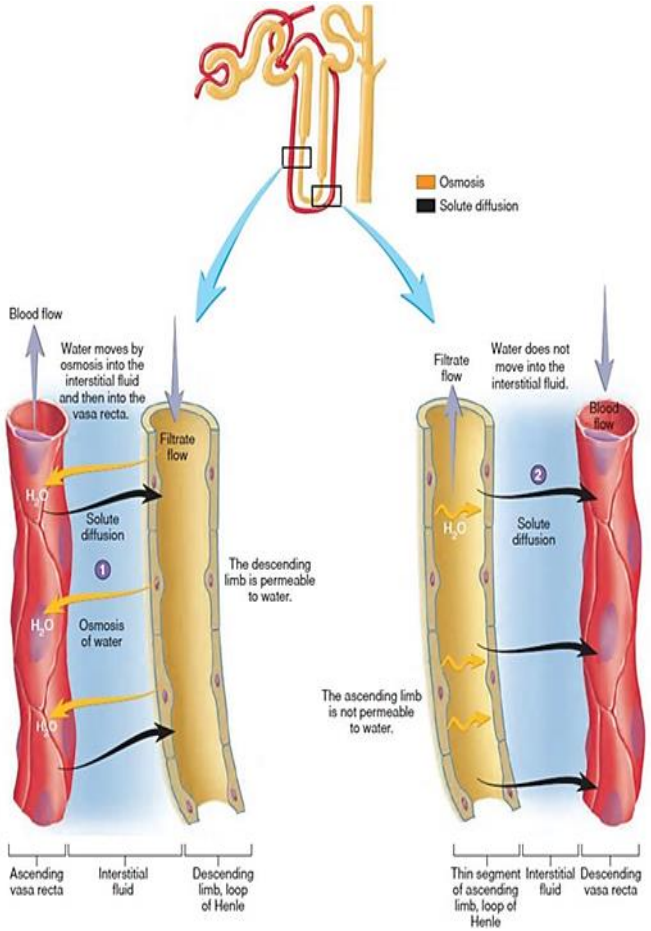
- The part of the nephron after the proximal tubule can be divided into : ***the thin descending and ascending limbs of loop of Henle***, ***the thick ascending limb, the early and later part of distal lobule and the collecting duct***.
- These tubules have different functional characteristics but they have a common role (**concentrating the urine**).
- The descending limb has a high permeability to water and low solute permeability (water moves across the descending limb into the interstitium until osmotic equilibrium).
- The thin and the thick ascending limbs have low permeability to water. The thick ascending limb reabsorbs Na^+ from the tubular fluid .it plays a major role in the diluting the tubular fluid .
- The distal tubule and collecting duct reabsorb Na+ :

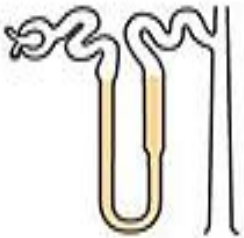
- **In the presence of ADH** , the late part of distal tubule and collecting duct become very permeable to water. This allows water to move out until reaching to the osmotic equilibrium.
- The highest urea permeability is found in the inner medullary part of the collecting duct.
- The thick ascending limb, distal tubule and cortical parts of collecting duct have no permeability to urea but the thin limb of ascending and descending of the loop of Henle are permeable to urea.
- Urea moves passively down its concentration gradients .

- The distal tubule and the collecting duct are important in the secreting K^+, H^+ and in reabsorption of Cl^- and HCO_3^- .

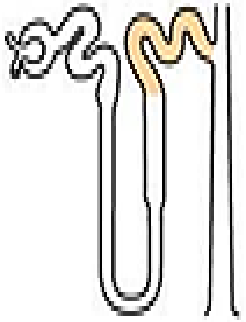
Loop of Henle

- The descending loop has a high permeability to water and low permeability to solutes.
- As the filtrate descends, the higher osmotic pressure causes the water to suck out but small quantities of NaCl can diffuse in.
- By the **bottom** of the loop the osmotic pressure of filtrate increases to **1200 mOsm**.15% of the water is reabsorbed in the descending loop of Henle .
- In the **thin segment** of the ascending loop, the walls are not permeable to water, so as it moves up through lower salt concentrations, some **salt will diffuse out** , to reduce its osmotic pressure.
- In the **thick segment** of the ascending loop, there are Na+ pumps (like in the proximal tubule). **Na^+ is pumped out**, **while Cl^- follows passively**; **K^+ also moves out by cotransport.** This dilutes the filtrate .



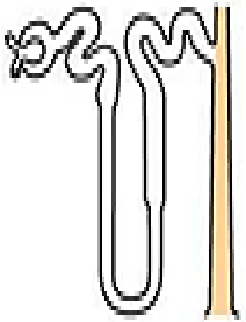
TUBULE SEGMENT	SUBSTANCE REABSORBED	MECHANISM
Proximal Convoluted Tubule (PCT)		
	Sodium ions (Na^+)	Primary active transport via basolateral Na^+-K^+ pump; crosses apical membrane through channels, symporters, or antiporters
	Virtually all nutrients (glucose, amino acids, vitamins, some ions)	Secondary active transport with Na^+
	Cl^-, K^+, Mg^{2+}, Ca^{2+}, and other ions	Passive paracellular diffusion driven by electrochemical gradient
	HCO_3^-	Secondary active transport linked to H^+ secretion and Na^+ reabsorption *(see Chapter 26)*
	Water	Osmosis; driven by solute reabsorption (obligatory water reabsorption)
	Lipid-soluble solutes	Passive diffusion driven by the concentration gradient created by reabsorption of water
	Urea	Primarily passive paracellular diffusion driven by chemical gradient
Nephron Loop		
Descending limb	Water	Osmosis
Ascending limb	Na^+, Cl^-, K^+	Secondary active transport of Cl^-, Na^+, and K^+ via Na^+-K^+-$2Cl^-$ cotransporter in thick portion; paracellular diffusion; Na^+-H^+ antiport
	Ca^{2+}, Mg^{2+}	Passive paracellular diffusion driven by electrochemical gradient

Distal Convoluted Tubule (DCT)



Na^+, Cl^-	Primary active Na^+ transport at basolateral membrane; secondary active transport at apical membrane via Na^+-Cl^- symporter and channels; aldosterone-regulated at distal portion
Ca^{2+}	Passive uptake via PTH-modulated channels in apical membrane; primary and secondary active transport (antiport with Na^+) in basolateral membrane

Collecting Duct



Na^+, K^+, HCO_3^-, Cl^-	Primary active transport of Na^+ (requires aldosterone); passive paracellular diffusion of some Cl^-; cotransport of Cl^- and HCO_3^-; K^+ is both reabsorbed and secreted (aldosterone dependent), usually resulting in net K^+ secretion
Water	Osmosis; controlled (facultative) water reabsorption; ADH required to insert aquaporins
Urea	Facilitated diffusion in response to concentration gradient in the deep medulla region; recycles and contributes to medullary osmotic gradient