The Nephron

Nephron is the functional unit of the kidney.

Each nephron consists of two parts:

1. Renal Corpuscle: filters the blood plasma. It consists of two components: **glomerular capillaries** and **glomerular (Bowman's) capsule.**

2. Renal Tubules: into which the filtered fluid passes. Consists of **Proximal Convoluted Tubule**, **Loop of Henle**, **Distal Convoluted Tubules**. Loop of Henle has an ascending limb and a descending limb.

80-85% nephrons are **cortical nephrons**. Their corpuscles are in the cortex and they have short loop of Henle that receives blood supply from peritubular capillaries of efferent arterioles.

15-20% nephrons are **juxtamedullary nephrons**, which have corpuscles deep in the cortex and long loop of Henle that extends into the medulla. Long loops of Henle receive blood supply from peritubular capillaries and vasa recta that arise from efferent arterioles.

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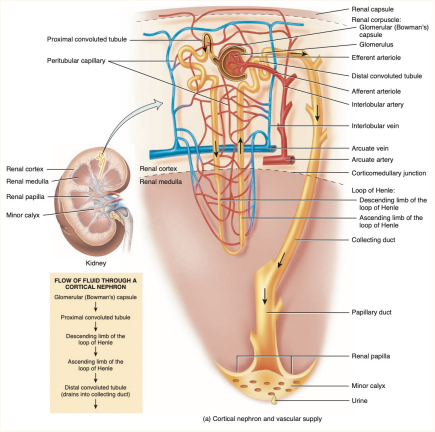

The structure of nephrons and associated blood vessels.

Renal Physiology

Nephrons and collecting ducts perform three basic process for urine formation:

1. Glomerular Filteration: water and most solutes in the blood plasma move across the wall of glomerular capillaries into the glomerular capsule and then into renal tubule.

Renal Physiology (cont)

2. Tubular Reabsorption: As filtered fluid passes down the renal tubule and through the collecting duct, tubule cells reabsorb 99% of the filtered water and many useful solutes. The water and solutes return to the blood as it flows through the peritubular capillaries and vasa recta.

3. Tubular Secretion: As the fluid flows through the renal tubule and collecting ducts, the tubule and ducts secrete other materials, such as wastes, drugs and excess ions, into the fluid.

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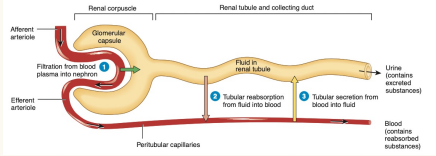
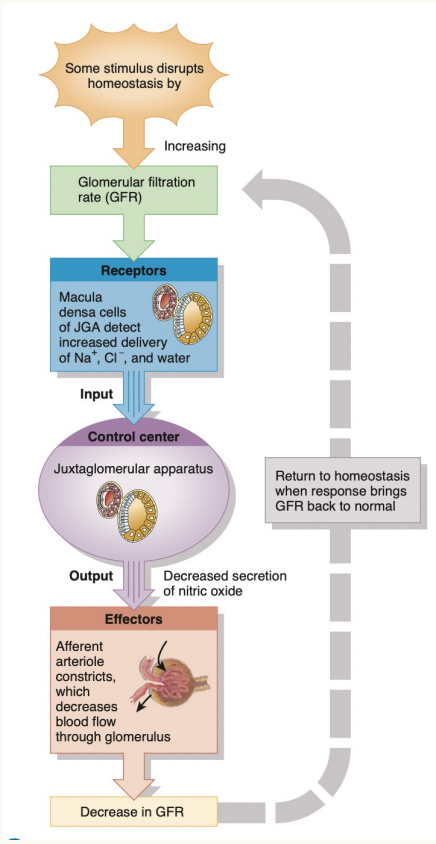


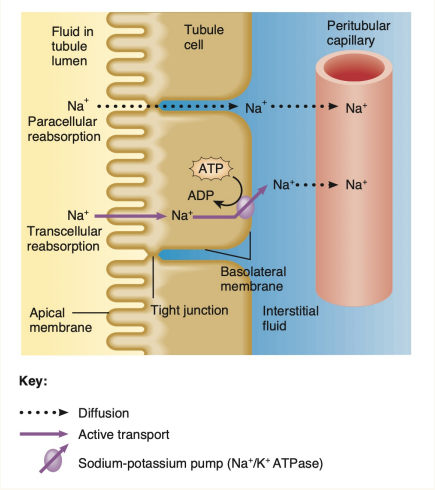
Relation of a nephron's structure to its three basic functions: glomerular filtration, tubular reabsorption, and tubular secretion

Figure:



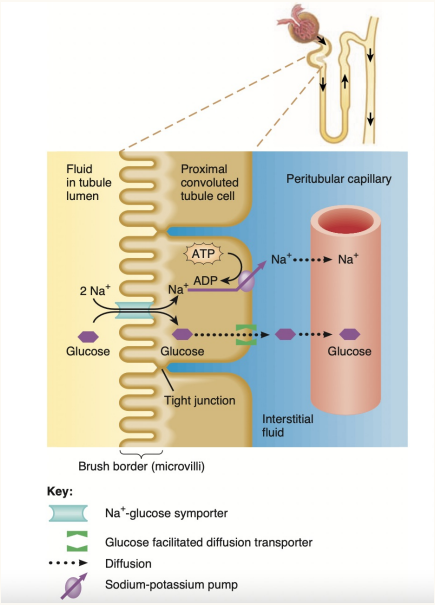
Tubuloglomerular feedback.

Figure:



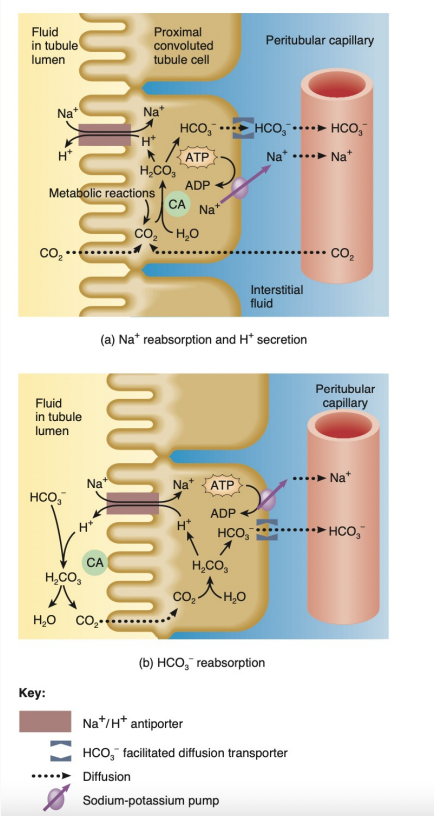
Reabsorption routes: paracellular reabsorption and transcellular reabsorption

Figure:



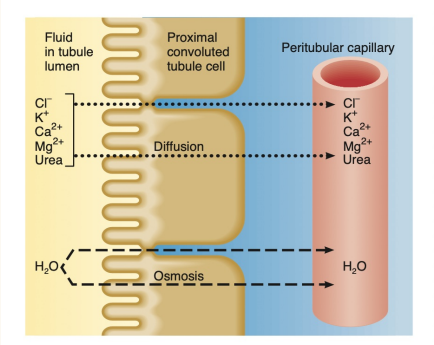
Reabsorption of glucose by Na^+-glucose symporters in cells of the proximal convoluted tubule (PCT).

Figure:



Actions of Na^+/ H^+ antiporters in proximal convoluted tubule cells. (a) Reabsorption of sodium ions (Na^+) and secretion of hydrogen ions (H^+) via secondary active transport through the apical membrane; (b) reabsorption of bicarbonate ions ($HCO3^-$) via facilitated diffusion through the basolateral membrane. CO2 = carbon dioxide; H2CO3 = carbonic acid; CA = carbonic anhydrase.

Figure:



Passive reabsorption of Cl, K^+, $Ca2^+$, $Mg2^+$, urea, and water in the second half of the proximal convoluted tubule.

Hormonal Regulation

Renin-Angiotensin-Aldosterone System

When blood volume and blood pressure decrease, walls of the afferent arterioles are stretched less and Juxtaglomerular apparatus secretes **renin**.

Renin clips of **angiotensin I** (10 amino acid peptide) from **angiotensinogen** (synthesised by hepatocytes). **Angiotensin converting enzyme** clips off two more amino acids from angiotensin I and forms angiotensin II

Angiotensinogen --*renin*--> angiotensin I --*ACE*--> angiotensin II

Angiotensin II decreases GFR, enhances Na^+ and Cl^- reabsorption in PCT and stimulates adrenal cortex to release **aldosterone**. Aldosterone stimulates principal cells in collecting ducts to reabsorb more Na^+ and Cl^-.

Antidiuretic Hormone

Released by pituitary gland, it regulates facultative water reabsorption by increasing the water permeability of the prinicpal cells in the DCT and collecting duct.

Within principal cells are tiny vesicles containing many copies of a water channel protein known as aquaporin-2. ADH stimulates insertion of the aquaporin-2–containing vesicles into the apical membranes via exocytosis.

When the osmolarity or osmotic pressure of plasma and interstitial fluid increases—that is, when water concentration decreases—by as little as 1%, os- moreceptors in the hypothalamus detect the change. Their nerve impulses stimulate secretion of more ADH into the blood, and the principal cells become more permeable to water. As facultative water reabsorption increases, plasma osmolarity decreases to normal.

Atrial Natriuretic Peptide

A large increase in blood volume promotes release of atrial natriuretic peptide (ANP) from the heart. It can inhibit reabsorption of Na^+ and water in the proximal convoluted tubule and collecting duct. ANP also suppresses the secre- tion of aldosterone and ADH.

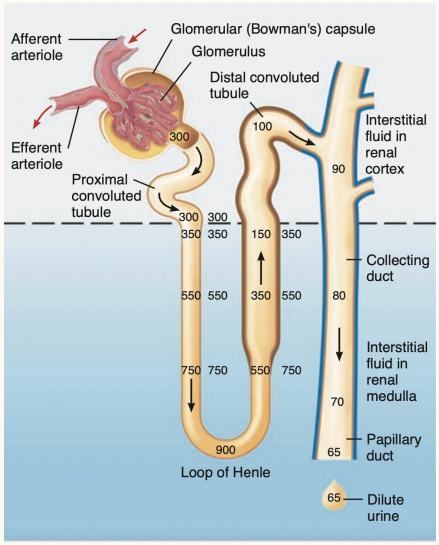
These effects increase the excre- tion of Na☐ in urine (natriuresis) and increase urine output (diuresis), which decreases blood volume and blood pressure.

Parathyroid Hormone

Hormonal Regulation (cont)

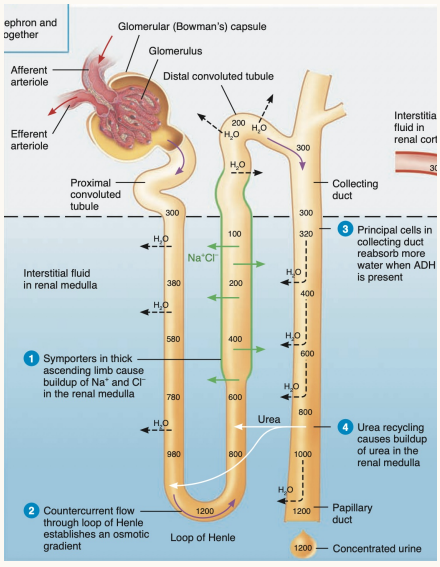
A lower-than-normal level of $Ca2^+$ in the blood stimulates the parathyroid glands to release parathyroid hormone (PTH). PTH in turn stimulates cells in the early distal convoluted tubules to reabsorb more $Ca2^+$ into the blood.

Figure:



Formation of dilute urine.

Figure:



Mechanism of urine concentration in long-loop juxtamedullary nephrons.

Glomerular Filteration

Fluid that enters capsular space- **Glomerular Filtrate**

The fraction of blood plasma in the afferent arterioles of the kidney that becomes glomerular filtrate- **filtration factors**

The Filtration Membrane:

Endothelial cells of the glomerular capillaries and the podocytes (which completely encircle the capillaries) form a leaky barrier know as the **Filtration Membrane**. This assembly permits filtration of water and solutes but prevents filtration of plasma proteins, platelets and blood cells.

Substances filtered from the blood cross three barriers- glomerular endothelial cell, basal lamina and filtration slit formed by podocyte.

1. Glomerular endothelial cells are leaky because they have large fenestrations. Located among the glomerular capillaries and in the cleft between the afferent and efferent arterioles are the **mesangial cells**. These contractile cells help regulate glomerular filtration rate.

2. the **basal lamina** is a layer of acellular material between the endothelium and the podocytes, consisting of collage fibres and proteoglycans in a glycoprotein matrix. It prevents filtration of large plasma proteins.

3. Extending from each podocyte and thousands of footlike projections termed **pedicels** which wrap around glomerular capillaries. The spaces between pedicels are the **filtration slits**. A thin membrane extends across the slits called the **filtration membrane** that permits the passage of smaller molecules such as water, glucose, vitamins, amino acids, ammonia, urea and ions.

Volume of fluid filtered by the glomerular capillaries is much larger than in other capillaries of the body because:

1. Glomerular capillaries present a large surface area for filtration because they are long and extensive. When mesangial cells are relaxed, the surface area is maximal and the glomerular filtration is very high. Contraction of mesangial cells reduces the available surface area, and the glomerular filtration decreases.

2. The filtration membrane is thin and porous. Glomerular capillaries are about 50 times leakier than regular capillaries.

Glomerular Filteration (cont)

3. Glomerular capillary blood pressure is higher than in capillaries elsewhere in the body because the efferent arteriole's diameter is much smaller than the afferent arteriole's diameter. Hence, resistance to outflow of blood from the glomerulus is high.

Net Filtration Pressure:

Glomerular filtration depends of three main pressures:

1. Glomerular Blood Hydrostatic Pressure: blood pressure in the glomerular capillaries. It is about **55mmHg** and *promotes* filtration by forcing water and solutes in the blood plasma through the filtration membrane.

2. Capsular Hydrostatic Pressure: hydrostatic pressure exerted against the filtration membrane by the fluid already in the capsular space and renal tubule. It *opposes* filtration and exerts a pressure of **15mmHg.**

3. Blood Colloid Osmotic Pressure: due to presence of proteins such as albumins, globulins, and fibrinogen in blood plasma *opposes* filtration. It is about **30 mmHg.**

Net filtration pressure: (GBHP-CHP-BCOP) = (55-15-30) =10mmHg.

Glomerular Filtration Rate:

The amount of filtrate formed in all the renal corpuscles of both kidneys in a minute, is the **Glomerular Filtration Rate**. Average GFR of males- 125 ml/min and of females- 105 ml/min.

Any change in net filtration pressure affects GFR. Filtration ceases if the GBHP drop to 45mmHg.

Three mechanisms control GFR:

1. Renal Autoregulation: ability of the kidneys to help maintain a constant blood flow and GFR despite changes in blood pressure. Renal autoregulation consists of two mechanisms: **myogenic mechanism** and **tubuloglomerular feedback**.

~ Myogenic Mechanism occurs when stretching of afferent arteriole due to elevated blood pressure triggers the smooth muscle fibres in the wall to contract, which narrows the arteriole's lumen, thereby decreasing renal blood flow and restoring GFR.

Glomerular Filteration (cont)

~Tubuloglomerular Feedback occurs when the macula densa detect increased density of Na^+ and Cl^- ions as they are not being reabsorbed by the Loop of Henle. The macula densa inhibits release of NO from the Juxtaglomerular apparatus, causing arterioles to contract and restoring GFR.

2. Neural Regulation: blood vessels of kidney are supplied by sympathetic ANS fibres that release norepinephrine. Norepinephrine causes vasoconstriction through activation of alpha 1 receptors, which are plentiful in smooth muscle fibres of afferent arterioles. With great sympathetic stimulation, blood flow into the glomerular capillaries is decreases and GFR drops. This reduces urine output, which helps conserve blood volume and it permits greater blood flow to other body tissues.

3. Hormonal Regulation: Hormonal regulation of GFR is done by **Angiotensin II** and **Atrial Natriuretic Peptide**. Angiotensin II is a vasoconstrictor that narrows both efferent and afferent arterioles and reduces renal blood flow, thereby reducing GFR. Atrial Natriuretic Peptide is secreted by cells in atria of heart when the atria is stretched due to increase in blood volume and causes relaxation of the glomerular mesangial cells, increasing capillary surface area and increasing GFR.

Tubular Secretion and Tubular Reabsorption

Tubular Reabsorption: the return of filtered water and many of the filtered solutes back to the blood stream.

Epithelia cells along renal tubule and duct and PCT cells carry out reabsorption.

Tubular Secretion: transfer of materials from the blood and tubule cells into the tubular fluid.

Reabsorption routes

1. **Paracellular Reabsorption**: Reabsorption of fluid through between the cells in a passive process.

2. **Transcellular Reabsorption**: Reabsorption of fluid through the apical membrane, cytosol ad basolateral membrane of a tubule cell.

Transport Mechanisms

Primary Active Transport: Energy derived from hydrolysis of ATP is used to pump a substance across a membrane. Eg. Na^+/K^+ ATPase.

Tubular Secretion and Tubular Reabsorption (cont)

Secondary Actie Transport: Energy stored in an ion's electrochemical gradient drives another substance across the membrane.

Symporters: membrane proteins that move two or more substances across a membrane in the same direction.

Antiporters: membrane proteins that move two or more substances across a membrane in opposite directions.

Transport Maximum (Tm): maximum rate at which a system is able to transport a solute.

Obligatory Water Reabsorption: Solute reabsorption drives water reabsorption because all water reabsorption occurs via osmosis and water is obliged to follow the solutes when they are reabsorbed. Occurs in PCT and descending loop of Henle

Facultative Water Reabsorption: Reabsorption regulated by antidiuretic hormone. Occurs in the collecting ducts.

Reabsorption and Secretion in PCT

Solute reabsorption in the proximal convoluted tubules involves Na^+. Na^+ transport occurs via symporters and antiporters.

Filtered glucose, amino acids, lactic acid, water soluble vitamins and other nutrients are completely reabsorbed by several types of Na^+ symporters located in the apical membrane.

Na^+/ H^+ antiporters carry filtered Na^+ down its concentration gradient into a PCT cell as H^+ is moved from cytosol into the lumen, causing Na^+ to be reabsorbed into the blood and H^+ to be secreted into the tubular fluid.

PCT cells produce H^+ by dissociation of Carbonic Acid into H^+ and $HCO3^-$.

Solute reabsorption in PCT promotes water reabsorption by osmosis. Reabsorption of solutes creates a concentration gradient that promotes osmosis.

Cells lining the PCT and descending loop of Henle are more permeable to water because they have molecules of *aquaporin-1* (integral protein in plasma membrane that forms a water channel, increasing the rate of water movement across the apical and basolateral membrane).

Tubular Secretion and Tubular Reabsorption (cont)

In the second half of PCT, electrochemical gradients for Cl^-, K^+, Mg^{2+}, Ca^{2+} and urea promote their passive diffusion into peritubular capillaries.

Diffusion of Cl^- ions into interstitial fluid via paracellular route makes the interstitial fluid more negative than the tubular fluid. This negativity promotes movement of positive ions such as K^+, Mg^{2+}, Ca^{2+}.

Ammonia is a poisonous waste product derived from the deamination of various amino acids, a reaction occuring in hepatocytes.

Hepatocytes convert ammonia into urea. Urea and ammonia in blood are both filtered at the glomerulus and secreted by proximal convoluted tubule cells into the tubular fluid.

Reabsorption and Secretion in Loop of Henle

Loop of Henle reabsorbs 15% water, 20-23% sodium and calcium, 35% Chlorine, 10-20% $HCO3^-$

Ascending limb of the Loop of Henle is relatively impermeable to water.

Apical membrane of thick ascending loop of Henle have Na^+-K^+-Cl^- symporters. Na^+ is actovely transported into interstitial fluid and diffuses into vasa recta. Cl^- moves through leakage channels into interstitial fluid and then into vasa recta. K^+ ions that are brought in by symporters move down the concentration gradient back into tubular fluid.

Movement of positively charged K into the tubular fluid leaves a relative negativity in the interstitial fluid, which promotes reabsorption of cations like sodium, calcium, magnesium.

Reabsorption and Secretion in DCT

Early or initial part of DCT reabsorbs 10-15% filtered water, 5% Na and 5% Cl. Reabsorption of Na and Cl happens through Na^+/Cl^- symporters.

Early DCT is a major site where parathyroid hormone stimulates reabsorption of Ca^{2+}.

In late DCT, two types of cells are present: **principle cells** and **interc-alated cell**

Principle cells reabsorb Na^+ and secrete K^+. Intercalated cells reabsorb K^+ and $HCO3^-$ and secrete H^+.

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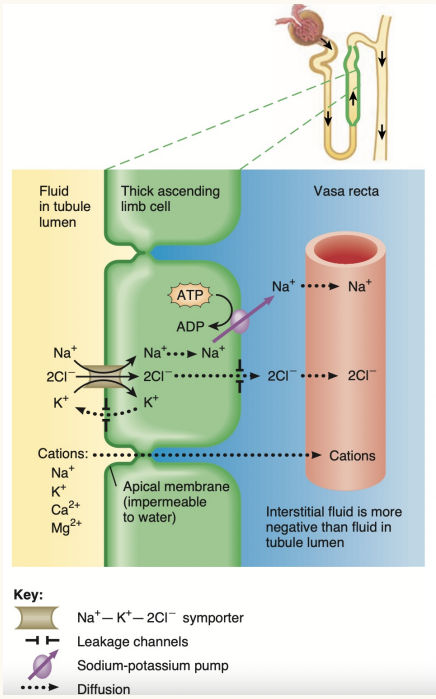
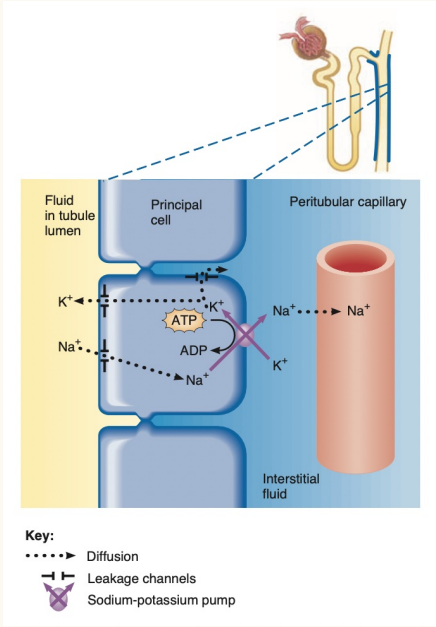


Na^+–K^+–$2Cl^-$ symporter in the thick ascending limb of the loop of Henle.

Figure:



Reabsorption of Na^+ and secretion of K^+ by principal cells in the last part of the distal convoluted tubule and in the collecting duct.

Formation of Dilute Urine

When dilute urine is formed, osmolarity of he tubular fluid increases as it flows down the descending loop of Henle, increases as it flows up the ascending limb and decreases more as it flows through the rest of the nephron and collecting ducts.

1. Osmolarity of the interstitial fluid of the medulla becomes progressively greater, more and more water is reabsorbed by osmosis as tubular fluid moves along descending limb of loop of Henle. Hence, fluid in the lumen becomes more and more concentrated.

2. Cells lining the thick ascending loop will have symporters that actively reabsorb Na, K and Cl from the tubular fluid.

3. Although solutes are being reabsorbed in the thick ascending limb, the water permeability is quite low

4. While fluid flows along DCT, additional solutes but very few water molecules are absorbed.

5. Principle cells in the DCT and collecting ducts are impermeable to water when ADH levels are low. Thus tubular fluid becomes for diluted as it flows onwards.

osmolarity of tubular fluid increases=water concentration decreases

Formation of Concentrated Urine

When water intake is low, or water loss is high, the kidneys are capable of producing small amount of highly concentrated urine under the influence of ADH in order to conserve water.

Ability of ADH to cause excretion of concentrated urine depends on the presence of an osmotic gradient of solutes in the interstitial fluid of medulla.

Two main factors contribute to building and maintaining the osmotic gradient in the renal medulla:

1. difference in solute and water permeability and reabsorption in different sections of the long loops of Henle and collecting ducts.

2. countercurrent flow of the flow of fluid through the tube shaped structures in the renal medulla.

Counter current flow refers to the flow of fluid in opposite directions.

Countercurrent Multiplication

Formation of Concentrated Urine (cont)

Countercurrent multiplication is the process by which a progressively increasing osmotic gradient is formed in the interstitial fluid of the renal medulla as a result of countercurrent flow.

Production of concentrated urine in the kidneys occurs in the following way:

1. Symporters in the thick ascending limb of the loop of Henle cause a buildup of Na^+ and Cl^- in the renal medulla. Water is not reabsorbed in this section as it is impermeable to water.

2. Countercurrent flow through the descending and ascending limbs of loop of Henle establishes an osmotic gradient in the renal medulla.

3. Cells in the collecting ducts reabsorb more water and urea with increase in ADH. With loss of water, urea left behind in the collecting ducts becomes increasingly concentrated and diffuses from the fluid in the duct into the interstitial fluid of the medulla.

4. Urea recycling causes buildup of urea in the renal medulla. As urea accumulates in the interstitial fluid, some of it diffuses into the tubular fluid in the descending and thin ascending limbs of the long loops of Henle. However, while the fluid flows through the thick ascending limb, distal convoluted tubule, and cortical portion of the collecting duct, urea remains in the lumen because cells in these segments are impermeable to it.

Constant transfer of urea between segments of the renal tubule and interstitial fluid is termed urea recycling.

Countercurrent Exchange

Countercurrent exchange is the process by which solutes and water are passively exchanged between the blood of the vasa recta and interstitial fluid of the renal medulla.

Countercurrent flow between the descending and the ascending limbs of the vasa recta allows for the exchange of solutes and water between blood and interstitial fluid of renal medulla.

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