Lecture 3

RENAL PHYSIOLOGY AND ACID-BASE BALANCE

Kidney

The kidney is surrounded by tough fibrous capsule. Each kidney consists of 8-10 conical pyramids. The pyramid has its base outward and its apex toward the pelvis. Pyramids consist of outer cortex and inner medulla. About 1.3 million nephrons are present in each kidney. These are the structural and functional units of kidney.

The renal artery provides the blood flow to the kidney. It gives off several segmental arteries which further branch to multiple interlobar arteries that ascend through the renal columns to reach the cortex. In turn, interlobar arteries branch into arcuate arteries and then interlobular arteries (or called cortical radiate arteries). Afferent arterioles arise from interlobular arteries to serve nephrons.

After passing through the renal corpuscle (glomerulus), the capillaries form the efferent arteriole. Efferent arteriole branches around the renal tubules of the same nephron to form peritubular capillaries and vasa recta, before returning to the venous system which runs the same (but reverse) course.

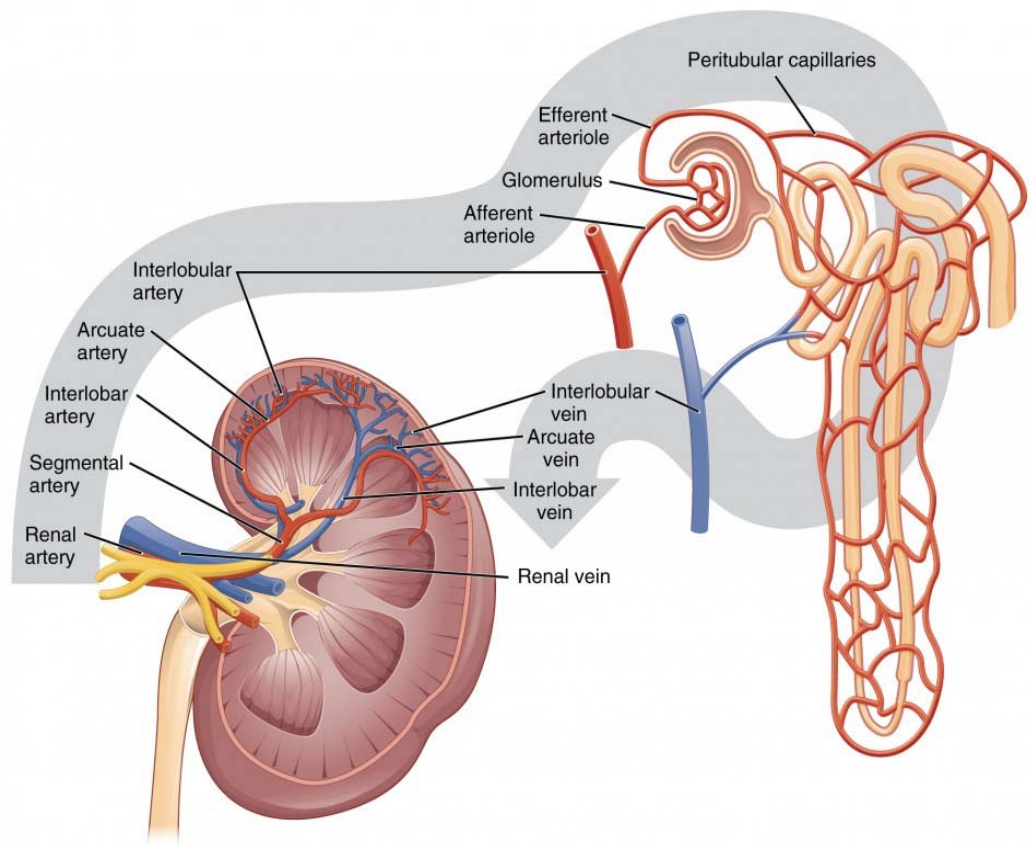

Figure 31: Renal blood supply

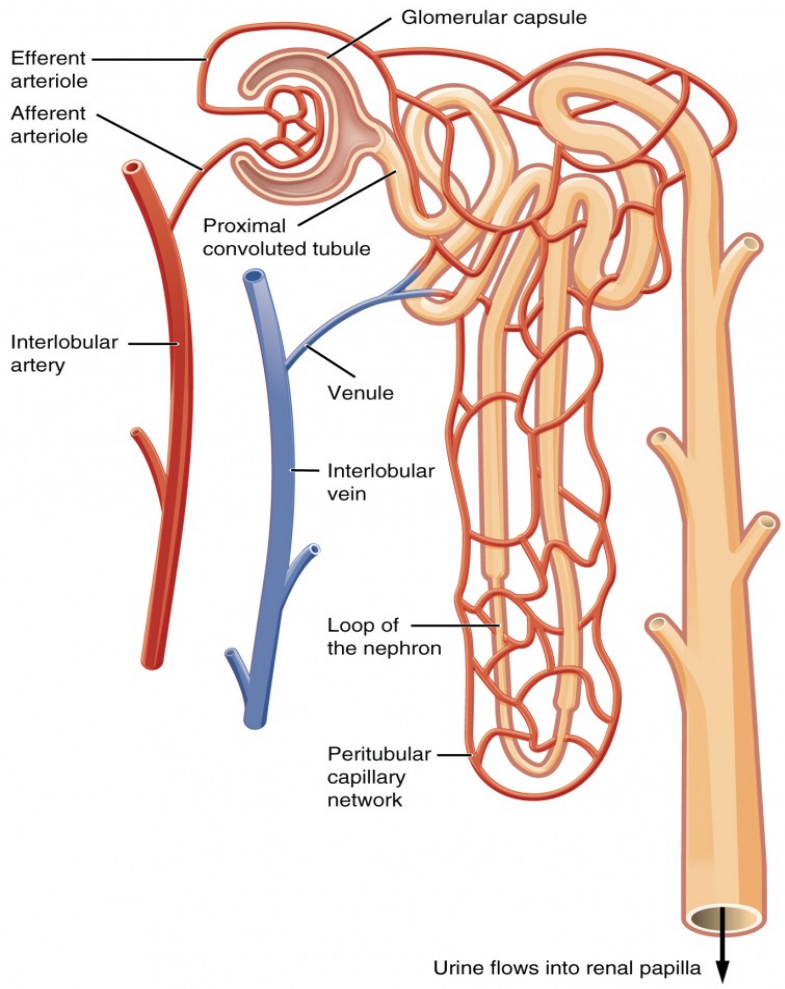

Figure 32: Nephron

Renal blood flow (RBF) is about 25% of the resting cardiac output (about 1.25 L/min) with much greater blood flow to the cortex than to the medulla (97% and 3% respectively). About 45% of the blood volume is in the form of cells. This ratio is called the packed cell volume (PCV) or the hematocrit. The other 55% represents the plasma.

PCV or Hematocrit = 0.45 (about 0.5)
Renal plasma flow (RPF) = RBF * (1- Hematocrit)
RPF = 1.25 * 0.5 = 0.625 L/min

The filtrate of plasma leaves Bowman's capsule and moves to the renal tubule, where it is further processed to form urine. The components of the renal tubule are:

-Proximal convoluted tubule (PCT).

-Loop of Henle (descending and ascending limbs). The loop is also divided into thin and thick segments.

-Distal convoluted tubule (DCT).

-Collecting tubule.

-Collecting duct.

-The main duct of pyramid (previously known as the papillary duct of Bellini).

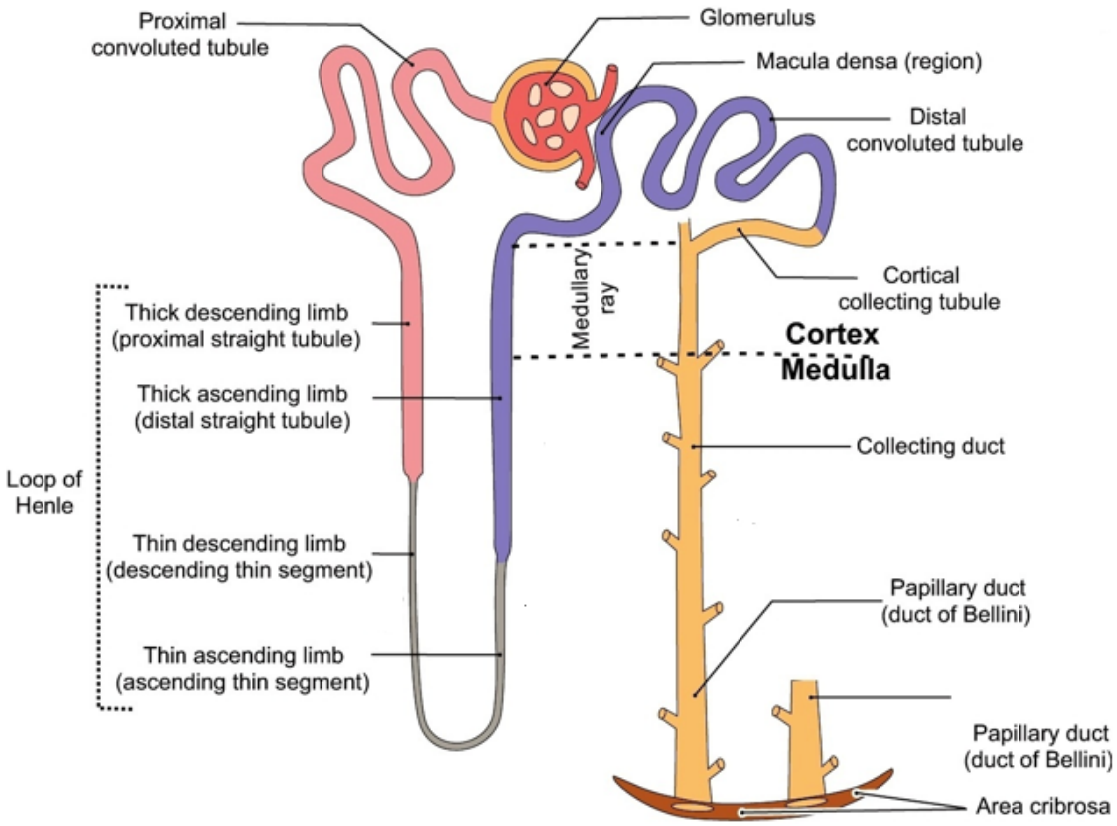

Figure 33: Renal tubules

Each pyramid pours its urine into a minor calyx. Every 2-3 calyces unite to form a major calyx. Major calyces unite to form the renal pelvis. Renal pelvis leads urine through the ureter which emerges through the hilum of kidney. At the hilum also, renal artery enters and renal vein leaves. Two ureters pour into single urinary bladder from which urethra emerges.

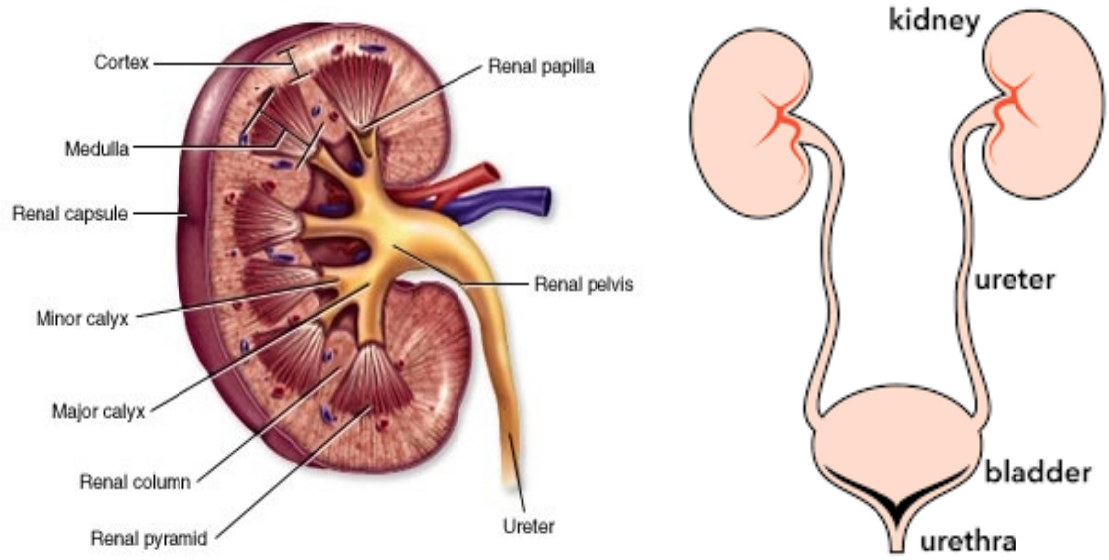

Figure 34: Urinary system

Glomerular capillary membrane

Filtration occurs across that membrane which is composed of 3 layers:

1- Single layer of capillary endothelial cells.
2- Basement membrane.
3- Visceral layer of Bowman's capsule which is called podocytes.

The endothelial layer is fenestrated. All blood components are filtered across fenestrae except some large plasma proteins and cells. The basement membrane is very highly permeable. Filtered materials and ions (but not proteins) can pass easily through the membrane and the slit pores between the feet of podocytes.

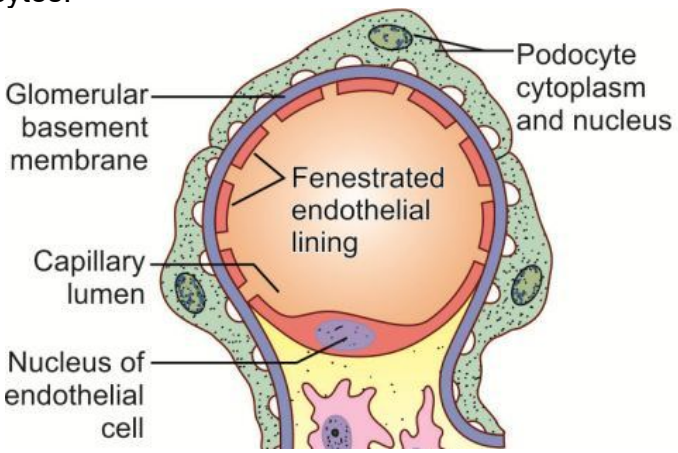

Figure 35: Glomerular filtration membrane

Functions of kidney

1- Regulation of extracellular fluid (ECF) volume, osmolarity and composition.
2- Regulation of blood pressure.
3- Regulation of acid-base balance.
4- Regulation of bone metabolism by regulation of excretion of calcium and phosphate ions and formation of active the form of vitamin-D (1, 25 dihydroxycholecalcipherol).
5- Production of erythropoietin hormone (production of red blood cells).
6- Excretion of various metabolic waste products, drugs, toxic substances and poisons.

Urine formation

When certain amount of substance (x) is cleared away from plasma and excreted in urine, this is called renal clearance of that substance (C_x). Not all of the substance filtered from glomerular capillaries appears in urine, instead; some of this substance may be reabsorbed back to the blood via peritubular capillaries, while additional amounts of the same substance may be secreted from tubular cells to tubular lumen to appear in urine. So:

$$C_x = GFR - TR + TS$$

GFR is the glomerular filtration, TR is the tubular reabsorption, TS is the tubular secretion.

Hence, about 180 liters of plasma are filtered by renal glomeruli every day. But, about 179 liters are reabsorbed by renal tubules back to the circulation and only about 1 liter is excreted as urine every day.

Glomerular filtration

Glomerular filtration is passive non-selective process. The GFR is equal to 125 ml/min. When renal plasma flows from afferent to efferent arterioles, about 20% of its contents is filtered by glomerular filtration from glomerular capillaries to Bowman's capsule. This ratio is called the filtration fraction (FF).

$$GFR = RPF * FF$$

$$GFR = 0.625\ L/min\ * 20\% = 0.125\ L/min = 125\ ml/min$$

In order to measure the GFR, the clearance of creatinine (endogenous substance) or inulin (exogenous substance) are measured. The clearance of paraaminohippuric acid (C_{PAH}) is used to measure renal plasma flow.

$$RPF = C_{PAH} / 0.9$$

Control of GFR

1- Sympathetic nervous activity: Vasoconstriction of afferent arteriole reduces renal blood flow and, hence, reduces the glomerular capillaries hydrostatic pressure. This, in turn, decreases GFR. Slight vasoconstriction of efferent arteriole increases the glomerular capillaries hydrostatic pressure. This, in turn, increases GFR.

Severe vasoconstriction of efferent arteriole, however, decreases GFR. This is due to that much time is allowed for plasma water and electrolytes to be filtered out the glomerulus while the plasma proteins cannot escape the glomerular capillaries. Presence of higher protein concentration increases the glomerular capillaries osmotic pressure which counters the GFR.

2- Hormones and autacoids: Some chemicals decrease GFR like epinephrine (also called adrenaline), nor-epinephrine (also called nor-adrenaline), angiotensin II, aspirin and endothelin. Some chemicals increase GFR like nitric oxide, prostaglandin and bradykinin.

3- Autoregulation:The afferent arteriolar wall is composed of smooth muscles When RBF is increased, these smooth muscles are stretched resulting in vasoconstriction of afferent arteriole which reduces GFR. This myogenic mechanism provides autoregulation for GFR.

Another autoregulation process is provided by the Juxtaglomerular apparatus (JGA). It is a special contact between the macula densa of distal convoluted tubule and the juxtaglomerular cells of afferent arteriole. The macula densa is specialized epithelial cells that detect sodium concentration of the fluid in the tubule. When GFR is increased, sodium concentration inside the renal tubules is elevated. The macula densa cells trigger contraction of the afferent arteriole, reducing RBF and GFR.

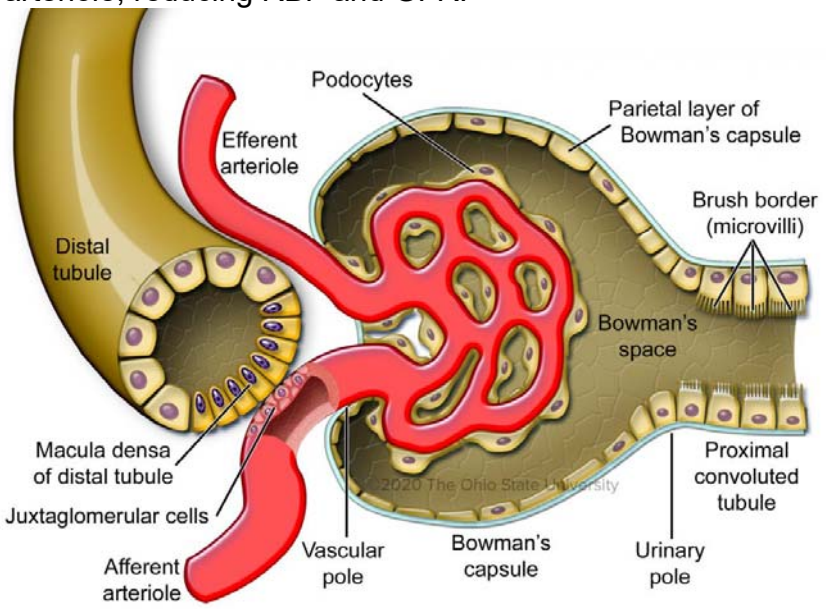

Figure 36: Juxtaglomerular apparatus

4- Plasma levels of amino acids and glucose: Up to physiological limits, renal tubules completely reabsorb essential substances like amino acids and glucose. Increased levels of amino acids and glucose in the blood plasma will increase renal reabsorption of these substances along with sodium. The JGA detects the decrease in sodium concentration and responds by vasodilatation of afferent arteriole leading to an increase in GFR.

Tubular reabsorption and secretion

Tubular reabsorption is a highly selective process that might be passive or active. Some substances are completely reabsorbed (up to physiological limits) like amino acids and glucose. The active transport processes of reabsorption might be saturated when the tubular lumen is overloaded with filtered substances. The maximum tubular load of certain substance (X) above which an active transport process of tubular reabsorption is saturated and reabsorption is ceased is called transport maximum of that substance (TmX).

The maximum plasma concentration of certain substance above which this substance starts to appear in urine is called renal threshold of that substance which equals TmX/GFR. Transport maximum of glucose (TmG) is about 325 mg/min and its ideal renal threshold is 325/125 which is equal to 2.6 mg/ ml (or 260 mg/100 ml). But the actual renal threshold for glucose is about 180 mg/100 ml and this difference might be due to that not all of renal tubules have the same TmG and that some of the filtered glucose molecules before TmG bypass reabsorption.

Some substances are mostly reabsorbed like bicarbonates and some other electrolytes. Some substances are mostly reabsorbed in the presence of specific hormones like water (in the presence of antidiuretic hormone), and Na^+ (in the presence of aldosterone and/or angiotensin-II hormones).

Many substances are reabsorbed along with other substances (Cl^- follows Na^+, and NaCl follows H_2O). Some substances are 50% reabsorbed like urea. Some substances are about completely excreted like creatinine and some drugs and poisons.

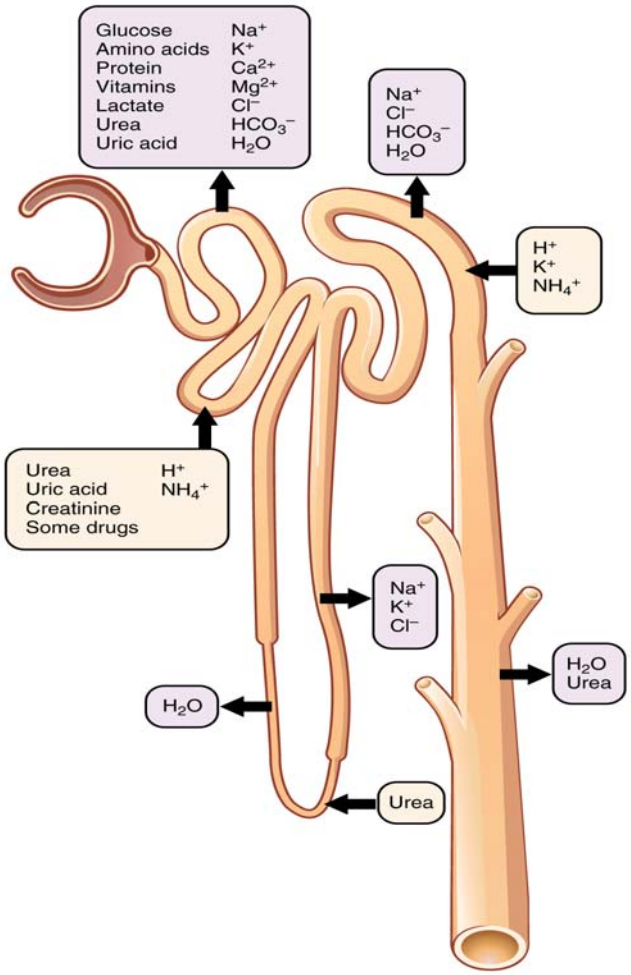

Figure 37: Tubular reabsorption

Table 6: Substances secreted or reabsorbed in the nephron an their locations

Substance	PCT	Loop of Henle	DCT	Collecting ducts
Glucose	Almost 100 percent reabsorbed; secondary active transport with Na^+			
Oligopeptides, proteins, amino acids	Almost 100 percent reabsorbed; symport with Na^+			
Vitamins	Reabsorbed			
Lactate	Reabsorbed			
Creatinine	Secreted			
Urea	50 percent reabsorbed by diffusion; also secreted	Secretion, diffusion in descending limb		Reabsorption in medullary collecting ducts; diffusion
Sodium	65 percent actively reabsorbed	25 percent reabsorbed in thick ascending limb; active transport	5 percent reabsorbed; active	5 percent reabsorbed, stimulated by aldosterone; active
Chloride	Reabsorbed, symport with Na^+, diffusion	Reabsorbed in thin and thick ascending limb; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; symport
Water	67 percent reabsorbed osmotically with solutes	15 percent reabsorbed in descending limb; osmosis	8 percent reabsorbed if ADH; osmosis	Variable amounts reabsorbed, controlled by ADH, osmosis
Bicarbonate	80–90 percent symport reabsorption with Na^+	Reabsorbed, symport with Na^+ and antiport with Cl^-; in ascending limb		Reabsorbed antiport with Cl^-
H^+	Secreted; diffusion		Secreted; active	Secreted; active
NH_4^+	Secreted; diffusion		Secreted; diffusion	Secreted; diffusion
HCO_3^-	Reabsorbed; diffusion	Reabsorbed; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; antiport with Na^+
Some drugs	Secreted		Secreted; active	Secreted; active
Potassium	65 percent reabsorbed; diffusion	20 percent reabsorbed in thick ascending limb; symport	Secreted; active	Secretion controlled by aldosterone; active
Calcium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion		Reabsorbed if parathyroid hormone present; active
Magnesium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion	Reabsorbed	
Phosphate	85 percent reabsorbed, inhibited by parathyroid hormone, diffusion		Reabsorbed; diffusion	

Proximal convoluted tubule

Approximately two-thirds (65%) of the filtered sodium is reabsorbed in the proximal tubule (PCT). The basolateral Na^+-K^+ ATPase creates the gradient for Na+ entry into the cell and its removal from the cell back into the bloodstream. About two-thirds of the filtered H_2O, K^+ and almost two-thirds of the filtered Cl^- follow the sodium, and the osmolarity at the end of the proximal tubule remains close to 300 mmol/L (isosmotic reabsorption).

Normally, all of the filtered glucose, proteins, peptides, amino acids, and ketone bodies are reabsorbed in the PCT via secondary active transport linked to sodium. Therefore, the concentration

of the above should be zero in the tubular fluid leaving the proximal tubule. Glucose is reabsorbed by sodium glucose-linked transporter (SGLT-2).

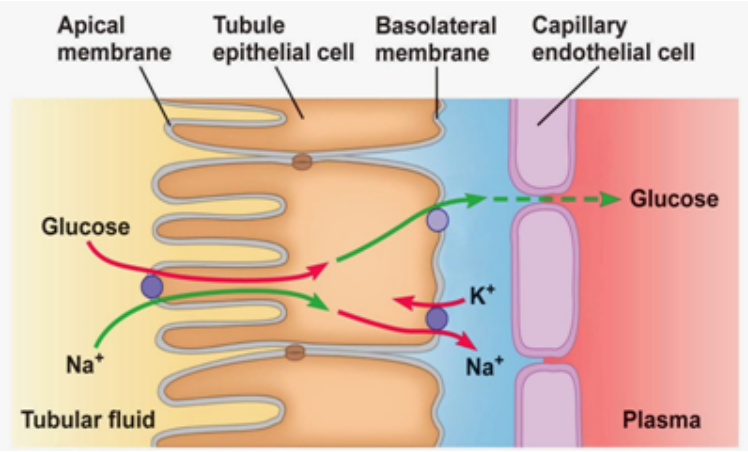

Figure 38: Glucose reabsorption in the proximal tubule

About 80% of the filtered bicarbonate is reabsorbed here. Bicarbonate combines with free H^+ in tubular lumen and is converted into CO_2 and H_2O, catalyzed by the luminal carbonic anhydrase enzyme (CA). The CO_2, being very soluble, crosses the luminal membrane where it combines with water to reform H^+ and bicarbonate. The H^+ is then pumped back into the lumen by Na^+-H^+ antiporter, while bicarbonate exits the baslolateral membrane to complete its reabsorption. Bicarbonate reabsorption is dependent upon H^+ secretion and the activity of CA. Angiotensin-II stimulates the Na^+-H^+ antiporter. Thus, in volume depleted states, bicarbonate reabsorption increase.

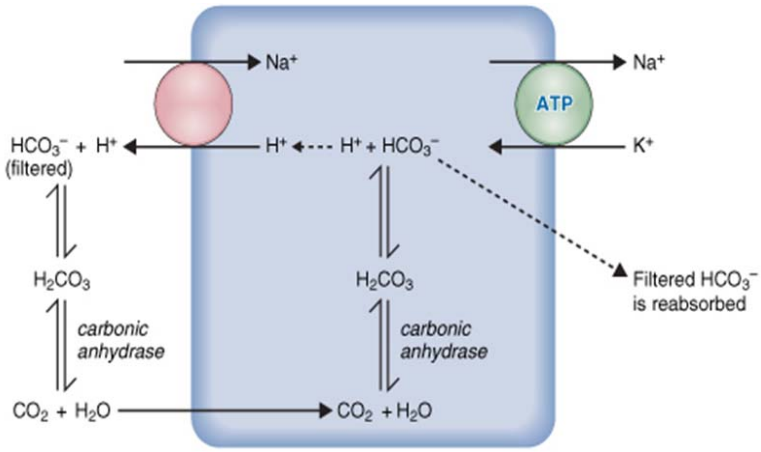

Figure 39: Bicarbonates reabsorption in the proximal tubule

Urate (uric acid) is formed by the breakdown of nucleotides. About 90% of the filtered urate is reabsorbed by the proximal tubule. If the filtration of urate is high enough and the luminal pH is low, then more of the urate exists as uric acid, which can precipitate and form a kidney stone.

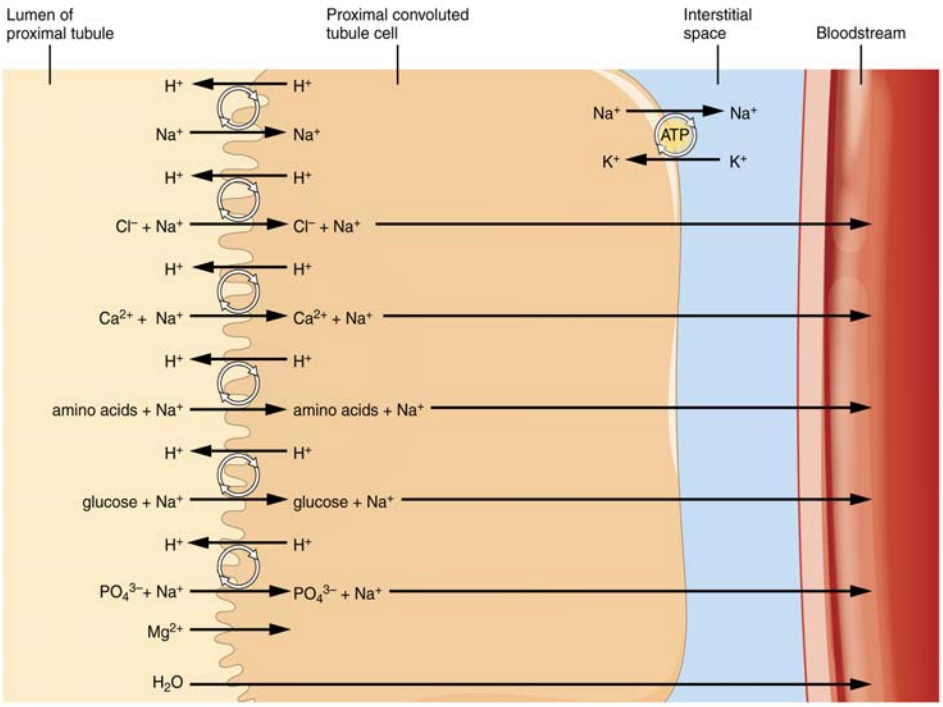

Figure 40: Reabsorption in the proximal tubule

Loop of Henle The descending and ascending limbs of Henle's loop and vasa recta run a long distance parallel, counter and in close proximity to each other carrying solutes toward medulla and water toward systemic circulation resulting in hyperosmotic medulla. Descending limbs of Henle's loop are called countercurrent multipliers because they continuously bring new NaCl to medulla while ascending vasa recta are called countercurrent exchangers because they continuously draw back water from medulla to the systemic circulation. The osmolarity will change from isosmotic with blood (about 280–300 mmol/L) to both a very hypertonic solution of about 1200 mmol/L and a very hypotonic solution of about 100 mmol/L. The majority of the descending loop has aquaporin channel proteins that allow unrestricted movement of water from the descending loop into the surrounding hyperosmotic interstitium. This results in reabsorption of up to 15 percent of the water entering the nephron. Little amounts of urea, Na^+, and other ions are also reabsorbed here. The ascending loop is completely impermeable to water due to the absence of aquaporin proteins, but ions, mainly Na^+, are actively pumped out of the loop by large quantities of the Na^+/K^+ ATPase pump. This has two significant effects: removal of Na^+ while retaining water leads to a hypotonic filtrate by the time it reaches the DCT; pumping Na^+ into the interstitial space contributes to the hyperosmotic environment in the kidney medulla.

The Na^+/K^+ ATPase pumps in the basal membrane create an electrochemical gradient, allowing reabsorption of Cl^- by Na^+/Cl^- symporters in the apical membrane. At the same time that Na+ is actively pumped from the basal side of the cell into the interstitial fluid, Cl^- follows the Na^+ from the lumen into the interstitial fluid by a paracellular route between cells through leaky tight junctions. These are found between cells of the ascending loop, where they allow certain solutes to move according to their concentration gradient. Most of the K^+ that enters the cell via symporters returns to the lumen (down its concentration gradient) through leaky channels in the apical membrane.

Note the environment now created in the interstitial space: With the “back door exiting” K^+, there is one Na+ and two Cl^- ions left in the interstitium surrounding the ascending loop. Therefore, in comparison to the lumen of the loop, the interstitial space is now a negatively charged environment. This negative charge attracts cations (Na^+, K^+, Ca^{++}, and Mg^{++}) from the lumen via a paracellular route to the interstitial space and vasa recta.

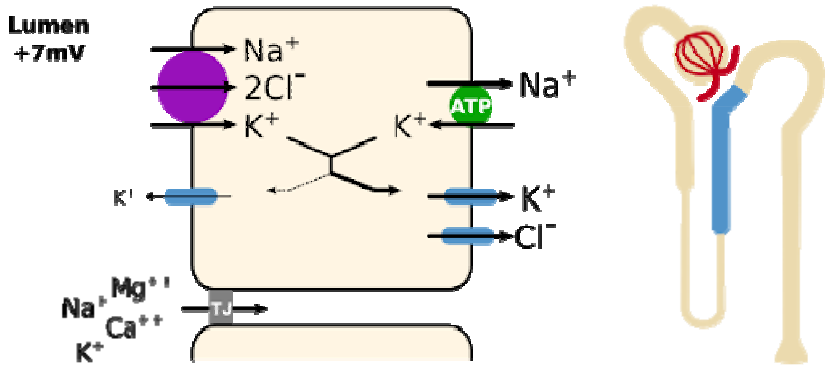

Figure 41: Reabsorption in the thick ascending limb of Henle's loop

Calcium-sensing receptor

The basolateral membranes of cells in thick segment of loop of Henle contain a calcium-sensing receptor (CaSR), this receptor is influenced by the plasma concentration of calcium. When plasma calcium level is high, CaSR is activated which, in turn, activates Gq-proteins leading to reducing intracellular cAMP. The net effect of these changes in intracellular signaling pathways is inhibition of the Na^+-K^+-$2Cl^-$ transporter. This will decrease K^+ movement from cell into tubular lumen reducing the positive luminal potential which in turn, decreases calcium reabsorption and return plasma calcium concentration to its normal level. (Note: CaSR also present in cells of the parathyroid gland).

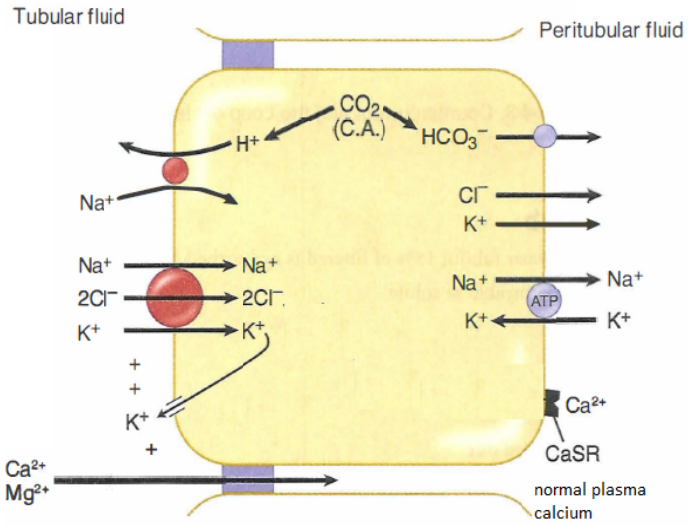

Figure 42: Calcium reabsorption in the thick ascending limb of Henle's loop

Early distal convoluted tubule

Aldosterone increases the amount of Na+/K+ ATPase in the basal membrane of the DCT and collecting duct. The movement of Na+ out of the lumen of the collecting duct creates a negative charge that promotes the movement of Cl– out of the lumen into the interstitial space by a paracellular route across tight junctions. Peritubular capillaries receive the solutes and water, returning them to the circulation. The early distal tubule reabsorbs Na+, Cl_, and Ca++. This section is impermeable to water. Thus, osmolality decreases further. In fact, the ultrafiltrate in the early distal tubule has the lowest osmolality of the entire nephron.

NaCl crosses the apical membrane via Na^+-Cl^- symporter and pumped across the basal membrane by Na^+/K^+-ATPase proteins. Calcium enters the cell from the luminal fluid passively through calcium channels. The opening of these channels is primarily regulated by parathyroid hormone (PTH). Ca^{++} actively extruded into peritubular fluid via Ca^{++}-ATPase or a $3Na^+$-Ca^{++} antiporter. These cells also express the calcium binding protein, calbindin, which facilitates calcium reabsorption.

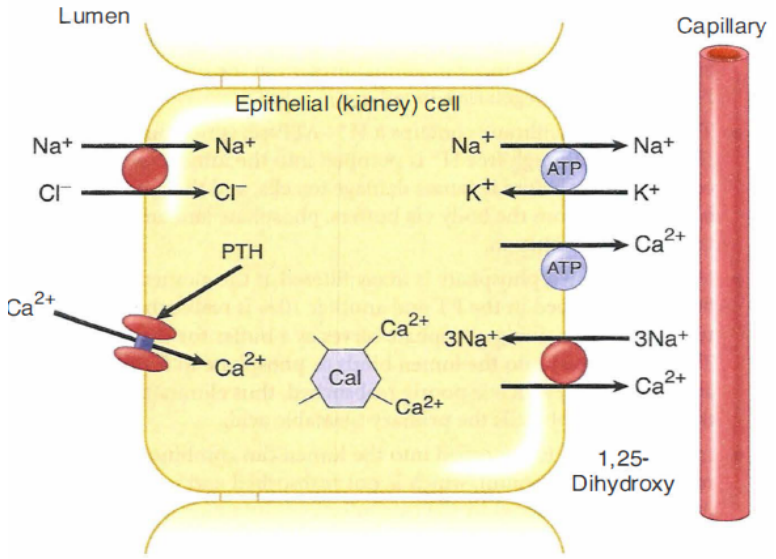

Figure 43: Calcium reabsorption in the distal tubule

Late distal tubule and collecting ducts

The late distal tubule and collecting duct are lined by two type of cells:

1. Principal cells

The luminal membrane of principal cells contains epithelial Na+ channels (ENaC), through which sodium follows its electrochemical gradient (created by the basolateral Na^+-K^+ ATPase) into the cell. The reabsorption of sodium linked to potassium secretion and its under control of aldosterone.

Aldosterone increases the number of luminal ENaC channels, increases their open time, and increases the synthesis of the basolateral Na^+-K^+ ATPase. The net effect is increased sodium reabsorption and potassium secretion.

Antidiuretic hormone (ADH), also known as arginine vasopressin (AVP) is a hormone secreted by posterior lobe of pituitary gland and acts on V2 receptors to cause insertion of aquaporins to luminal membrane which in turn, causes water (and urea) reabsorption.

2. Intercalated cells

The luminal membrane contains a H^+-ATPase, which pumps H^+ into the lumen. H^+ is eliminated from the tubule via buffers, and help to maintain acid- base balance. The main two buffer of H^+ ion are phosphate and ammonia:

a. Monoprotonated phosphate is freely filtered at the glomerulus. About 80% is reabsorbed in the PCT and another 10% is reabsorbed in the distal tubule. The remaining phosphate bind to H^+ to form diprotonated phosphate, which is excreted in the urine.

b. In addition, the H^+ pumped into the lumen can combine with ammonia to form ammonium, which is not reabsorbed and is thus excreted. Ammonia is produced by the catabolism of glutamine and this occurs in cells of the PCT. Aldosterone stimulates the H^+-ATPase of intercalated cells. Thus, excess aldosterone results in a metabolic alkalosis.

For every H^+ excreted by the above buffers, bicarbonate is added to the body.

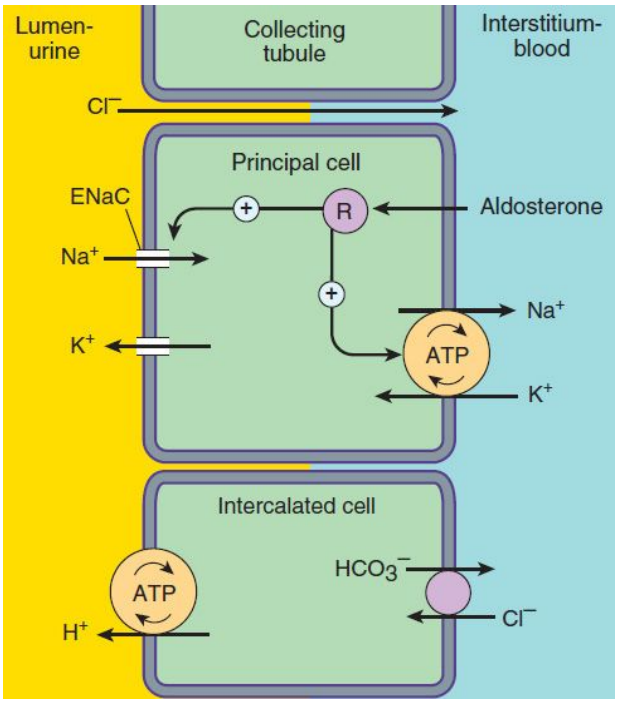

Figure 44: Reabsorption in the distal and collecting tubules

Regulation of urine volume and osmolarity are major functions of the collecting ducts. By varying the amount of water that is reabsorbed, the collecting ducts play a major role in maintaining the body's normal osmolarity. If the blood becomes hyperosmotic, the collecting ducts reabsorb more water to dilute the blood; if the blood becomes hyposmotic, the collecting ducts reabsorb less water, leading to concentration of the blood.

This function is regulated by the posterior pituitary hormone ADH (vasopressin). With mild dehydration, plasma osmolarity rises slightly. This increase is detected by osmoreceptors in the hypothalamus, which stimulates the release of ADH from the posterior pituitary gland. If plasma osmolarity decreases slightly, the opposite occurs.

When stimulated by ADH, aquaporin channels are inserted into the apical membrane of principal cells, which line the collecting ducts. As the ducts descend through the medulla, the osmolarity surrounding them increases due to the countercurrent mechanisms. If aquaporin water

channels are present, water will be osmotically pulled from the collecting duct into the surrounding interstitial space and into the peritubular capillaries. Therefore, the final urine will be more concentrated. If less ADH is secreted, fewer aquaporin channels are inserted and less water is recovered, resulting in dilute urine. By altering the number of aquaporin channels, the volume of water reabsorbed or lost is altered. This, in turn, regulates the blood osmolarity, blood pressure, and osmolarity of the urine.

As Na^+ is pumped from the forming urine, water is passively recaptured for the circulation; this preservation of vascular volume is critically important for the maintenance of a normal blood pressure.

Aldosterone is secreted by the adrenal cortex in response to angiotensin II stimulation. As an extremely potent vasoconstrictor, angiotensin II functions immediately to increase blood pressure. By also stimulating aldosterone production, it provides a longer-lasting mechanism to support blood pressure by maintaining vascular volume (water reabsorption).

In addition to receptors for ADH, principal cells have receptors for the steroid hormone aldosterone. While ADH is primarily involved in the regulation of water reabsorption, aldosterone regulates Na^+ reabsorption. Aldosterone stimulates principal cells to manufacture luminal Na^+ and K^+ channels as well as Na^+/K^+ ATPase pumps on the basal membrane of the cells. When aldosterone output increases, more Na^+ is reabsorbed from the forming urine and water follows the Na^+ passively. As the pump reabsorbs Na^+ for the body, it is also pumping K^+ into the forming urine, since the pump moves K^+ in the opposite direction. When aldosterone decreases, more Na^+ remains in the forming urine and more K^+ is reabsorbed in the circulation. Symport channels move Na^+ and Cl^- together. Still other channels in the principal cells secrete K^+ into the collecting duct in direct proportion to the reabsorption of Na^+. Intercalated cells play significant roles in regulating blood pH. Intercalated cells reabsorb K^+ and HCO_3^- while secreting H^+. This function lowers the acidity of the plasma while increasing the acidity of the urine.

Control of tubular reabsorption

1-Sympathetic control: (increases tubular reabsorption of sodium ions).
2- Hormonal control:
a- Aldosterone: increases reabsorption of Na^+ and excretion of K^+.
b- Angiotensin-II: acts directly (or indirectly after stimulation of aldosterone) to increase Na^+reabsorption.
c- Antidiuretic hormone (ADH or called vasopressin): increase water reabsorption.
d- Atrial natriuretic peptide (ANP): decreases Na^+ and water reabsorption.
e- Parathyroid hormones: increases Ca^{++} and Mg^{++} reabsorption and decreases phosphate reabsorption.

Reabsorption of water and electrolytes

The major bulk of tubular reabsorption of water and solutes (about 65%) occurs in proximal tubules. About 15% of water reabsorption occurs in thin descending loop of Henle. Very little amounts of solutes are passively reabsorbed in thin ascending loop of Henle. The major active reabsorption of electrolytes occurs in thick ascending loop of Henle (about 30%). The remaining reabsorption processes of electrolytes (about 5%) occur in distal segments. Further water reabsorption (about 19%) from collecting ducts in the presence of ADH and only about 1% of filtered water is excreted in urine. Without ADH, about 20% of filtered water is excreted.

Regulation of acid - base balance

Regulation of [H^+] is by chemical acid-base buffer systems, respiratory regulation, and renal regulation.

a. Buffer systems

The buffer systems are:

1- Bicarbonate buffer system: It is the most important buffer system in ECF.
When HCO_3^- decreases; pH is decreased and there will be metabolic acidosis.
When CO_2 increases; pH is decreased and there will be respiratory acidosis.
When HCO_3^- increases; pH is increased and there will be metabolic alkalosis.
When CO_2 decreases; pH is increased and there will be respiratory alkalosis.
2- Phosphate buffer system: It is important in ICF and renal tubular fluids.
3- Protein buffer systems: The most available ICF buffer systems but also work in ECF. Hemoglobin in red blood cells is a protein buffer.
4- Ammonium buffer system: It is the last choice buffer system in renal tubules.

b. Respiratory regulation

Increased breathing reduces CO_2 and raises pH from 7.4 to 7.63 and vice versa. Respiratory regulation of acid-base balance is by stimulation or inhibition of the respiratory center in the brain stem. Central chemosensitive areas are sensitive to changes in H^+ and partial pressure of carbon dioxide (P_{CO2}). They stimulate the respiratory center and result in hyperventilation or inhibit or the respiratory center and result in hypoventilation.

c. Renal regulation

Renal regulation occurs by excretion of acidic or alkaline urine. Normally, daily renal secretion of H^+ is about 4400 mmol. Bicarbonates system buffers 4320 mmol in renal tubules and the other 80 mmol are buffered by phosphates and then ammonium buffer systems. Most of renal tubular cells utilize secondary active transport to secrete H^+ and reabsorb Na^+ (Na^+- H^+ countertransport). Other distal tubular cells utilize primary active transport called proton pump.