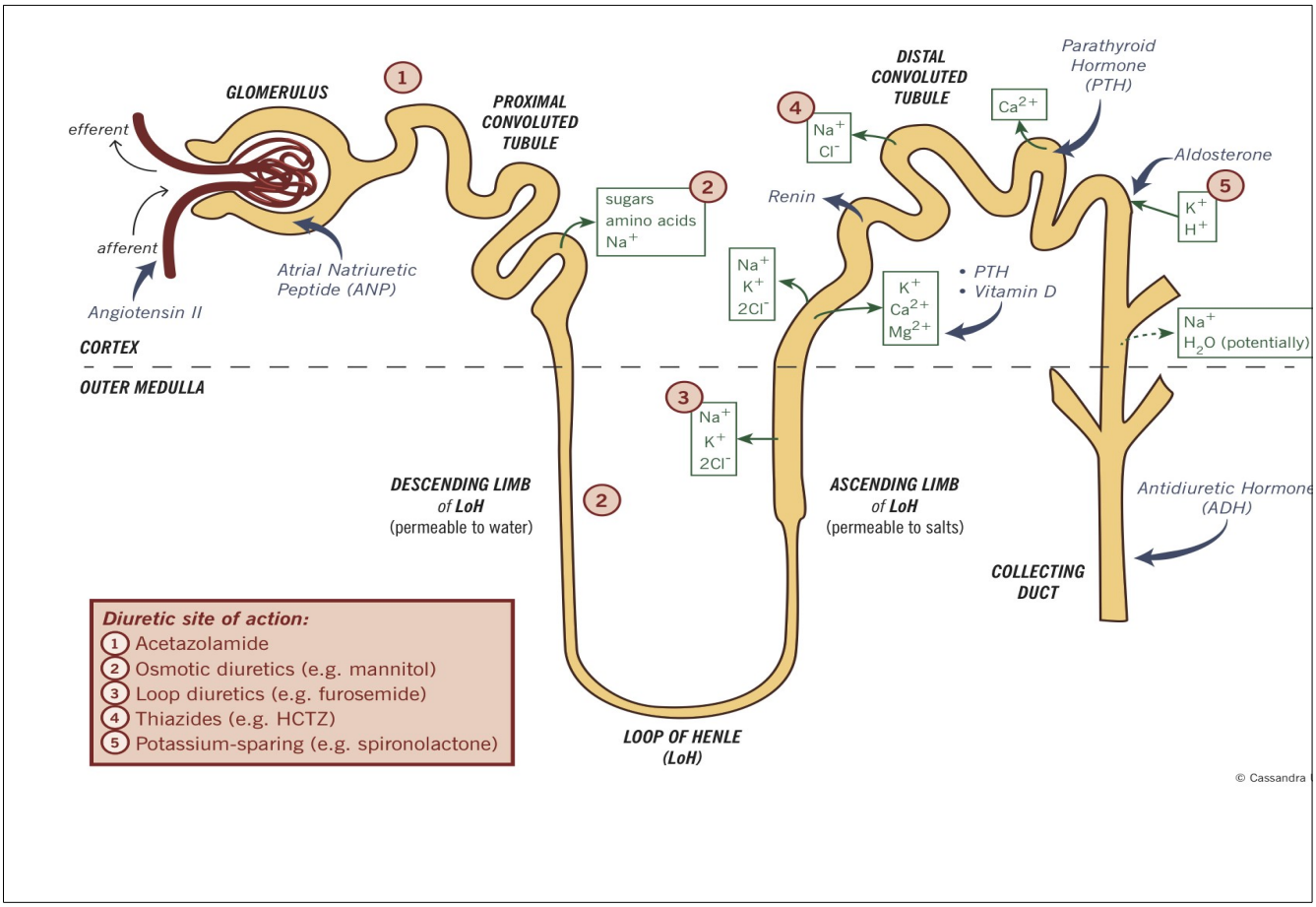
Urine Formation

Urine formation begins with the delivery of blood to the glomerulus followed by its filtration past the glomerular barrier. The filtered portion of plasma continues through the nephron whereas the unfiltered portion passes into the peritubular capillaries. As the filtered portion travels through the nephron, water and certain solutes are resorbed back into the peritubular capillaries whilst other solutes are secreted from the peritubular capillaries into the nephron. Whatever fluid is remains at the end of the nephron is discarded as urine. Here we discuss the basic mechanistic that which are involved in formation of urine.

Functional organization of the glomerulonephronic unit:

Blood enters the glomerulus via the afferent arteriole and leaves via the efferent arteriole to enter the peritubular capillaries that surround the nephron. The glomerular filtrate then enters the nephron and travels through it. At the different stages of the nephron the filtrate is modified by mechanisms which specifically resorb or secrete small molecules including water, into or out of the filtrate. These molecules enter the interstitial fluid where they non-specifically enter and exit the peritubular capillaries. Whatever fluid and molecules remain in the nephron at its end are excreted as urine.

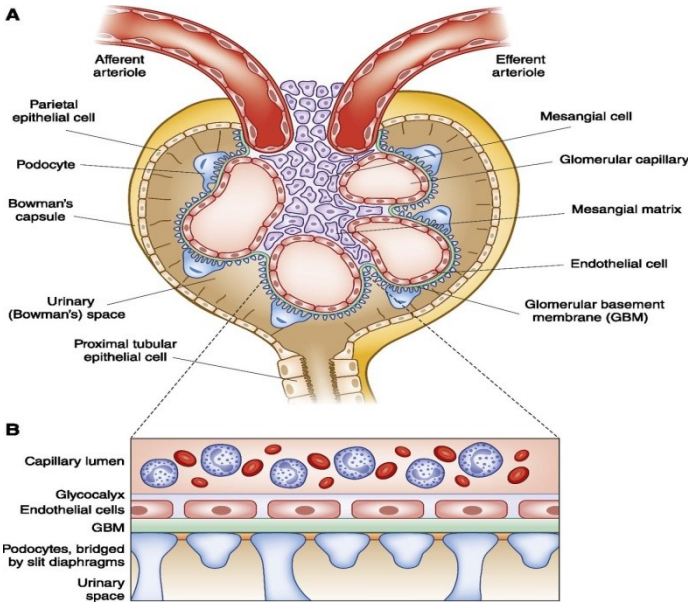


Glomerular filtration

Filtration of blood through the glomerular barrier, known as "Glomerular Filtration", is the first step in the process of urine formation. Blood entering the glomerular capillaries is filtered into Bowman's Capsule from where it enters the remainder of the nephron. The glomerular barrier is highly permeable and nearly 20% of the plasma volume entering the glomerular capillaries is filtered through into the nephron. However, filtration is also highly selective and only allows water and small molecules pass through the glomerular barrier. Here we discuss the physical basis by which the glomerular barrier can achieve both high permeability and selectivity.

The glomerular barrier is composed of three basic layers which separate blood from Bowman's Space (See Glomerular Histology for a more in-depth discussion). The first layer is that of glomerular capillary endothelial cells which are fenestrated, allowing for high fluid permeability. The second layer is that of the glomerular basement membrane which invests the fenestrated endothelial cells. The third layer is that of podocytes, a specialized type of epithelial cells with foot-like processes that support the glomerular basement membrane.

The glomerular capillaries display an enormous permeability to water and small molecules far beyond that of most other capillary beds. The physical basis of this incredible permeability is the fenestrated nature of the glomerular endothelium which facilitates molecular transport across the glomerular capillaries.



Functional Features of the Glomerular Barrier
The glomerular barrier allows for large volumes of fluid filtration into bowman's space but also exerts some selectivity on the molecules that are allowed to cross. The barrier itself is composed of

Although highly permeable to water and small solutes, the glomerular barrier is also highly selective and prevents the passage of nearly all plasma proteins and cells. Studies have shown that the glomerular barrier selects for two basic molecular features: size and charge. As the molecular weight of a molecule increases, its capacity for filtration progressively and rapidly declines. Furthermore, for any given sized molecules, its capacity for filtration progressively and rapidly declines as its charge becomes more negative. Because plasma proteins are typically large and negatively charged, they are almost totally prevented from crossing the glomerular barrier.

The physical basis for the size and charge selectivity of glomerular filtration is that of the glomerular basement membrane and its supporting podocytes, although the basement membrane appears to be most important. The glomerular basement membrane is a tight meshwork of negatively charged glycoproteins. This meshwork not only provides a physical barrier to large molecules, its negative charge repels other negatively-charged molecules. Podocyte foot processes also appear to display a strong negative charge which enhances the repulsive power of the basement membrane.

Glomerular filtration rate:

The Glomerular Filtration Rate (GFR) is the volume of fluid filtered through the body's glomeruli per unit time (Measured in ml/min). The principles governing the GFR are in reality a specialized application of the principles discussed in microcirculatory physiology and are thus ultimately governed by Starling Forces. Below we discuss the physical determinants of GFR and how they can be physiologically modulated.

Physical determinants of the glomerular filtration rate:

The Glomerular Filtration Rate (GFR) is a quantitation of the volume of fluid filtered through the glomerular barrier per unit time.

The GFR is essentially determined by a special case of the starling equation and is given above. The primary physiological modulators of GFR are the afferent and efferent arteriolar resistances (RA and RE). As expected, increasing the afferent arteriolar resistance (RA) drops the pressure within the glomerulus and thus reduces GFR. The relationship between the efferent arteriolar resistance (RE) and GFR is more complicated. Initially, increasing RE boosts the pressure within the glomerulus and thus increases GFR. However, at higher values of RE the total blood flow through the glomerulus decreases and thus GFR drops.

Systemic Arterial Pressure

Naturally, increased or decreased incoming systemic arterial blood pressures will increase or decrease the hydrostatic pressures within the glomerular capillaries. However, due to autoregulatory mechanisms discussed in Autoregulation of GFR and RBF incoming arterial pressures into the glomerulus are largely constant over a wide range of systemic arterial pressures and thus are not a major source of regulation.

Renal Afferent Arteriolar Resistance

Whatever the incoming arterial pressure, the resistance offered by the renal afferent arteriole is a major determinant of the ultimate hydrostatic pressure within the glomerulus. If afferent arteriolar resistance is increased, the hydrostatic pressure within the glomerulus declines and so too does the glomerular filtration rate. Conversely, if the afferent arteriolar resistance is decreased, the hydrostatic pressure within the glomerulus increases and so too does the glomerular filtration rate. Consequently, regulation of renal afferent arteriolar resistance is a major source of modulation of the GFR.

Renal Efferent Arteriolar Resistance

The relationship between the resistance of the renal efferent arteriole with GFR is more complex and not well-understood. A hand-waving explanation is that increased renal efferent arteriolar resistance causes backup of blood into the glomerulus and consequently increases glomerular hydrostatic pressures and thus GFR. However, as efferent arteriolar resistance increases, the renal blood flow also declines, resulting in reduced GFR. Empirically, these two antagonistic phenomenon result in a biphasic relationship to increased efferent arteriolar resistance and GFR. Initial increments in efferent arteriolar resistance increase GFR; however, larger increments in efferent resistance result in decreased GFR.

Permeability Coefficient

The permeability of the glomerular barrier can decline due to thickening of the glomerular basement membrane as occurs in diabetic nephropathy. Additionally, total glomerular permeability can decline due to reductions in the total number of functional glomeruli, thus reducing the total glomerular surface area as occurs in hypertension.

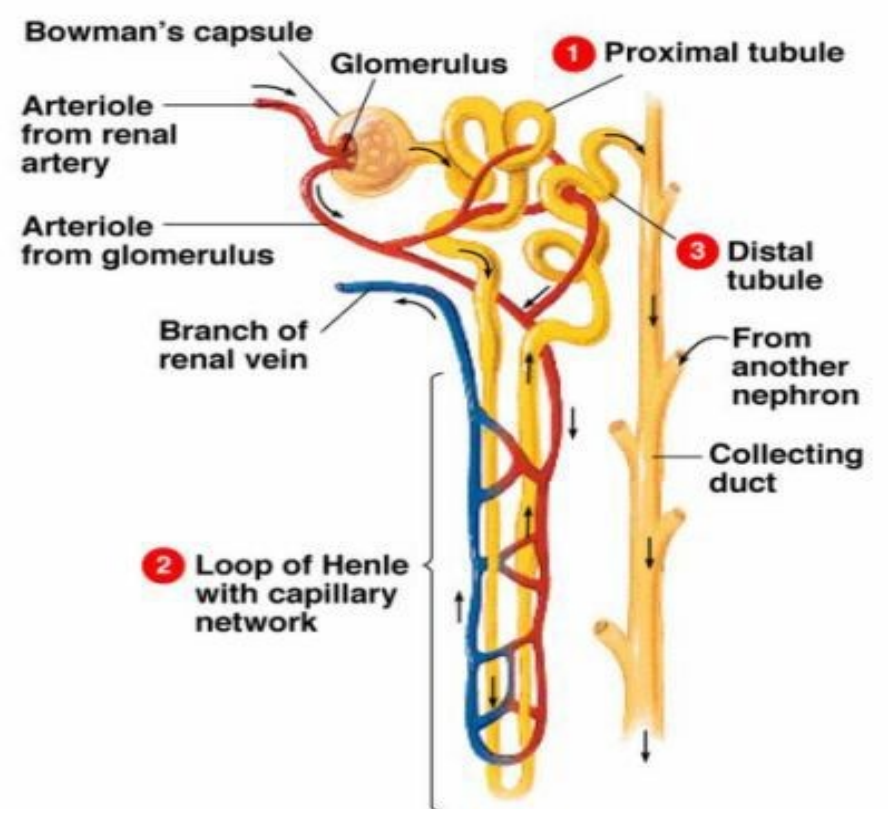
Bowman's Space Hydrostatic Pressure

In cases of urinary tract obstruction resulting in hydronephrosis, fluid backup into Bowman's Space can increase its hydrostatic pressure and thus reduce GFR.

Renal absorption and secretion

As the glomerular filtrate enters the renal tubules, it flows sequentially through the successive parts of the tubule:
The proximal tubule → the loop of Henle(1) → the distal tubule(2) → the collecting tubule → finally ,the collecting duct, before it is excreted as urine.
A long this course, some substances are selectively reabsorbed from the tubules back into the blood, whereas others are secreted from the blood into the tubular lumen.
The urine represent in the sum of three basic renal processes: glomerular filtration, tubular reabsorption, and tubular secretion:

Urinary excretion = Glomerular Filtration – Tubular reabsorption + Tubular secretion.



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Mechanisms of cellular transport in the nephron

1. **Active transport**

   "Active transport can move a solute **against an electrochemical gradient** and **requires energy** derived from metabolism"

movement of two molecules in opposite direction based on their concentration.

i. Primary active transport

Transport that is coupled directly to an energy source such as **ATP Sodium-potassium pump** (found in **basolateral membrane** along renal tubules)

H+-pump

ii. Secondary active transport

Transport that is coupled indirectly to an energy source due to **concentration gradient of ion Na-K-2Cl co-transport glucose-sodium co-transport (SGLT) amino acid-sodium co-transport H+/Na counter-transport**

2. **Passive Transport**

   "Pasive transport can move a solute **down the electrochemical gradient** and **do not requires energy** "

   i. **i. Simple diffusion (without carrier protein)**

   Simple diffusion is basically the **diffusion** of substances through a membrane without needing the help from other substances

   Ex-Cl, HCO_3-, urea , creatinine

   ii. **Facilitated diffusion (require carrier protein)**

   It is the process of spontaneous passive transport (as opposed to active transport) of molecules or ions across a biological membrane via specific transmembrane integral proteins.

   Ex- Glucose and amino acids at the basalateral border (GLUT)

3. **Osmosis**

   Water is always reabsorbed by a passive (nonactive) physical mechanism called osmosis , which means water diffusion from a region of **low solute concentration (high water concentration)** to one of **high solute concentration (low water concentration).**

4. **Pinocytosis\ exocytosis**

   The proximal tubule, reabsorb **large molecules such as proteins** by pinocytosis. In this process, the protein attaches to the brush border of the luminal membrane, then invaginates to the interior of the cell until it is completely pinched off and a vesicle is formed containing the protein. Once inside the cell the protein is digested into its constituent amino acids, which are reabsorbed through the **basolateral membrane** into the interstitial fluid. Because pinocytosis requires energy, it is considered a form of **active transport.**

Tubular Reabsoption

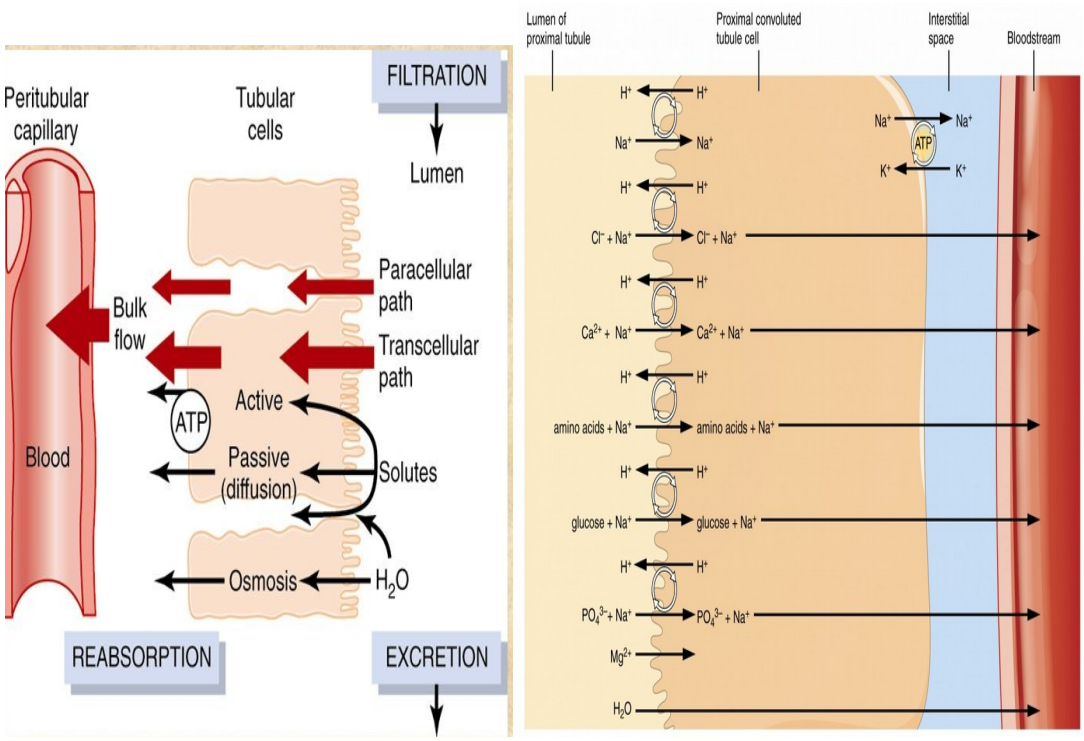
The ways of transport:

1- From lumen of tubules (Apical membrane"1") to epithelial cells then from epithelial cells to interstitium (Basolateral membrane):

A-Transcellular route: (through the cell membrane)
B-Paracellular route: (between spaces of tight cell junction)

2- From interstitium (basolateral space) to the Peritubular capillaries:

By **ultrafiltration (bulk flow)** that is mediated by:
hydrostatic and colloid osmotic forces .

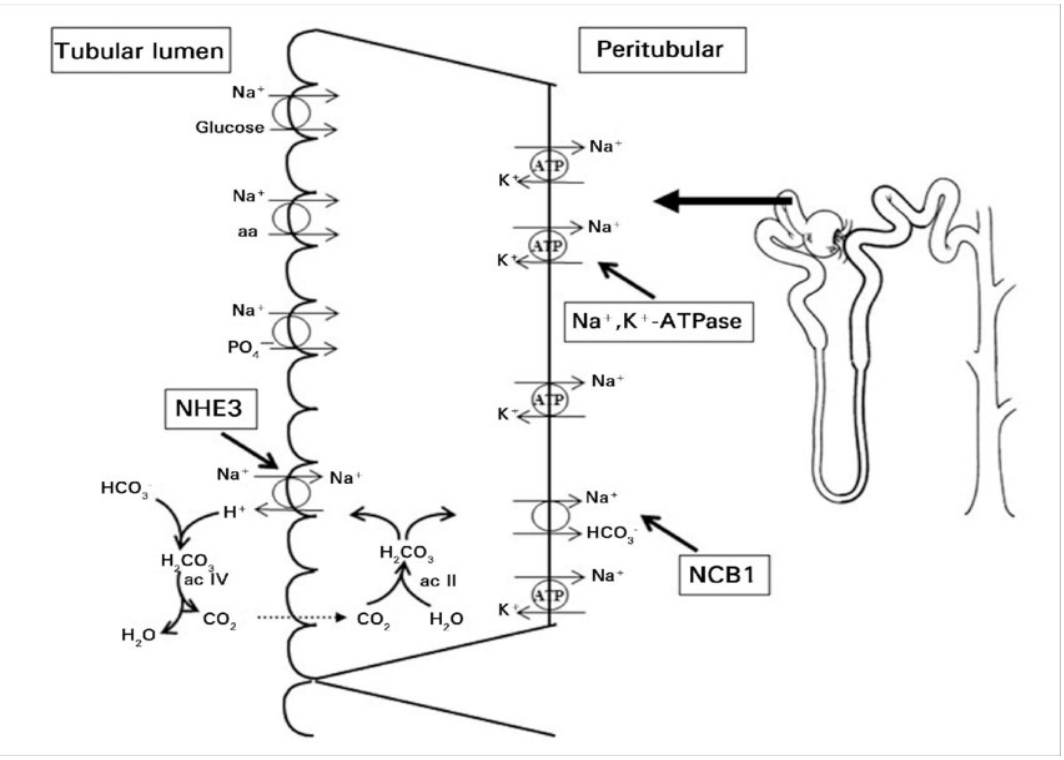


(1)**Co-transport:** Movement of two molecules in the same direction but they opposite in concentration gradient

(2)**Counter-transport:** Movement of two molecules in the opposite direction based on their concentration gradient.

Mechanisms of transportation from tubules to interstitiam:

- Sodium diffuses across the luminal membrane (also called the apical membrane) into the cell down an electrochemical gradient (with other substances such as glucose, amino acids etc.) established by the sodium -potassium ATPase pump on the basolateral side of the membrane.
- Other molecules like water and Cl^- , Ca^{+2} etc. by osmosis and diffusion
- Sodium is transported across the basolateral membrane against an electrochemical gradient by the sodium -potassium ATPase pump
- other substances will across the basolateral membrane by passive diffusion
- Sodium , water , and other substances are reabsorbed from the interstitial fluid into the Peritubular capillaries by ultrafiltration (bulk flow ”1”), a passive process driven by the hydrostatic and colloid osmotic pressure gradients .

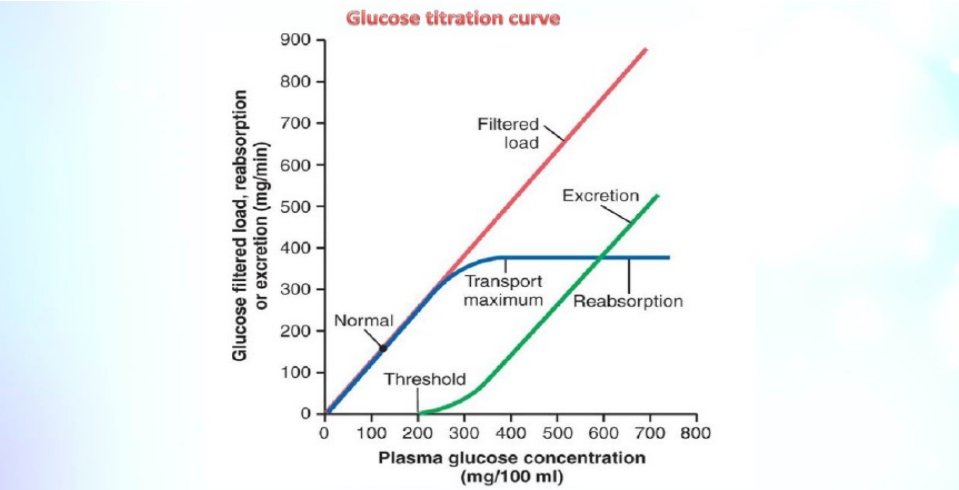


Reabsorption of glucose

•Glucose inter the tubular cells by secondary active transport "co-transport", It use **SGLT** "a specific transport protein "which needs Na" .

•Then it's cross the cell membrane into the interstitial spaces by facilitated transport "passive transport" which use **GLUT's** "do not need Na".

•Glucose reabsorption occurs in proximal tubule.
•Essentially all glucose is reabsorbed
•The renal **threshold** for glucose= 180 mg/dl
•The **tubular transport maximum** for glucose Tmg = 375 mg/min in men and 300 mg/min in women.



Relations among the filtered load of glucose, the rate of glucose reabsorption by the renal tubules, and the rate of glucose excretion in the urine

Renal threshold : it's the rate that glucose begins to appear in the urine .

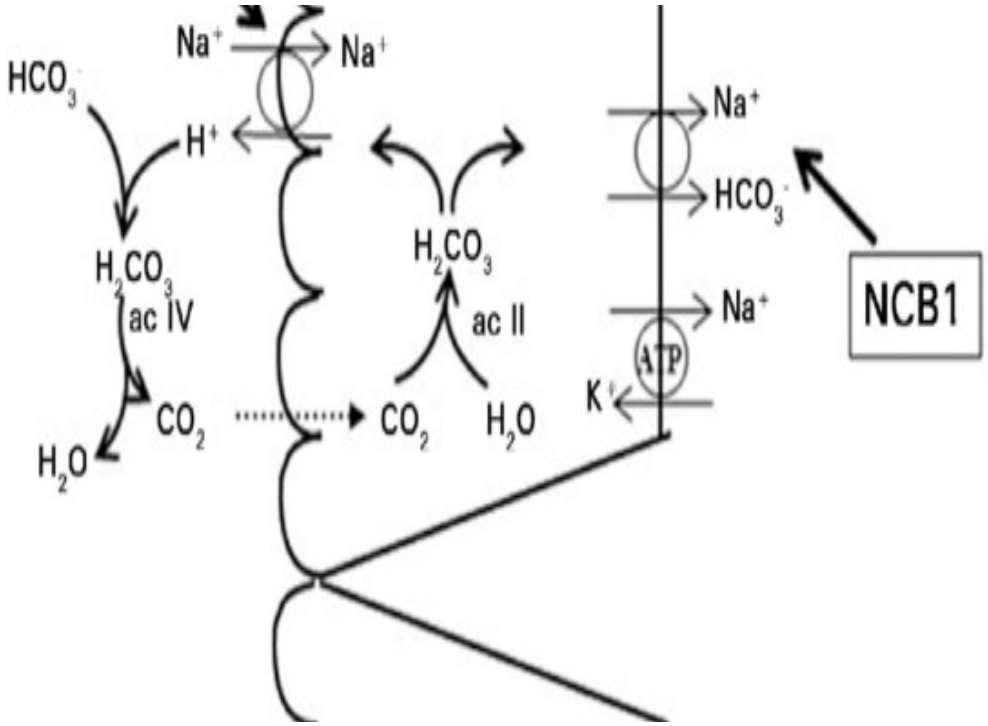
transport maximum for glucose : all nephrons have reached their maximal capacity to reabsorb glucose maximum saturation of transporters.

What cause the excretion of glucose in urine before reach to its maximum transport?

Not all nephrons have the same transport maximum for glucose, and some of the nephrons therefore begin to excrete glucose before others have reached their transport maximum

Reabsorption of bicarbonate

- bicarbonate (HCO_3-) attaches itself with hydrogen (H+) then it becomes H_2CO_3 in the lumen
- Carbonic Anhydrase will break H_2CO_3 down to water (H_2O) + carbonic dioxide (CO_2) which diffuses into the proximal tubule
- Carbonic Anhydrase will convert the water (H_2O) + the carbon dioxide (CO_2) to HCO^{3-} + H^+
- Hydrogen will transport out and sodium (Na) will come in the proximal tubule
- Lastly, the HCO_3- will go into the blood

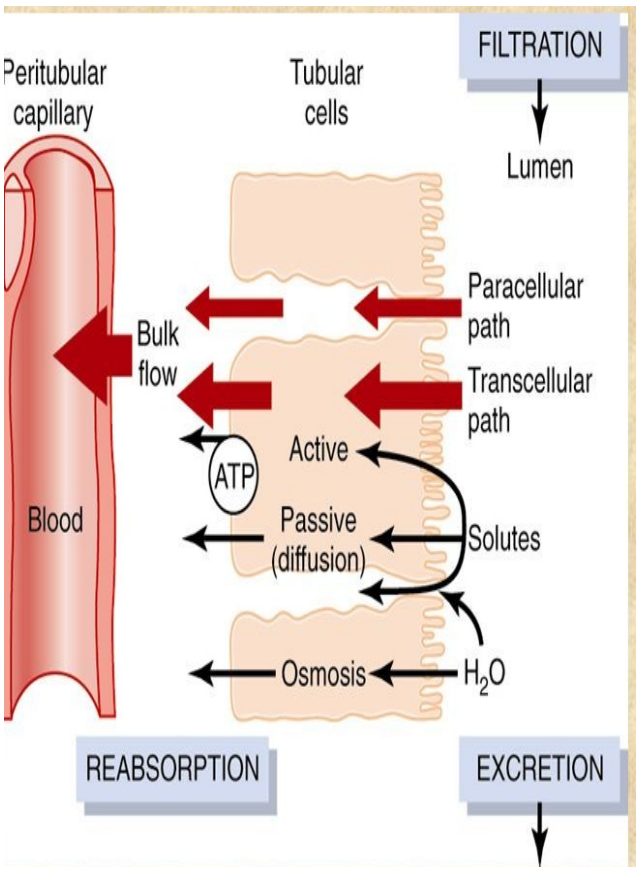


The process of ultrafiltration

In Peritubular capillaries the high plasma oncotic pressure is due to fluid filtration in glomerulus

increase GFR ◊ increase oncotic pressure & decrease hydrostatic pressure in efferent & Peritubular capillaries ◊ increase bulk flow from lateral space to Peritubular capillaries ◊ increse reabsorption

decrease GFR ◊ decrease oncotic pressure & increase hydrostatic pressure ◊ decrease bulk flow ◊ fluid go back to lumen through tight junction ◊ decrease reabsorption



General Characteristics of the tubules and their functions

Parts of nephron	Reabsorption	Secretion
Proximal convoluted tubules The convoluted portion of the vertebrate nephron that lies between Bowman's capsule and the loop of Henle and functions especially in the resorption of sugar, sodium and chloride ions, and water from the glomerular filtrate.	-Poorly reabsorbed creatinine and urea -60% - 75% of sodium and water -90% of HCO_3, K+, Ca and Cl- -100% Glucose and amino acids	H+ -Urea -ammonia
Thin decending loop of henle , The **thin descending limb** has low permeability to ions and urea, while being highly permeable to water. The loop has a sharp bend in the renal medulla going from **descending** to ascending **thin limb**.	-25% of water (H_2O) Sodium chloride (NaCl)	_____
Thick ascending loop of henle The **thin ascending limb** is found in the medulla of the kidney	-Sodium -Potassium -Chloride	_____
Distal convoluted tubules The **distal convoluted tubule** is the nephron segment that lies immediately downstream of the macula densa. Although short in length, the **distal convoluted tubule** plays a critical role in sodium, potassium, and divalent cation homeostasis.	- Sodium in response to **aldosterone** - Water in response of **ADH** - Calcium in response of **parathyroid hormone**	Potassium in response of **aldosterone**
Late distal tubule & Cortical Collecting ducts The connecting tubules join the distal convoluted tubules to the cortical **collecting duct.**	a. Principal cells: absorb Sodium Na+ & H_2O b. Intercalated cells: absorb Potassium K+ & HCO_3 -Water in response of **ADH** - Sodium in response to **aldosterone** - Calcium in response of **parathyroid hormone**	a. **Principal cells:** secert K+ b. **Intercalated cells**: secret H+ Potassium in response of **aldosterone** - H+

Medullary Collecting ducts	Water in response of **ADH** **- Highly permeable to urea (to maintain osmolarity of medulla)**	