PHYSIOLOGY ASSIGNMENT

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QUESTION 1

Discuss the role of kidney in glucose homeostasis

The kidneys' contributions to maintaining glucose homeostasis are significant in preventing hyperglycemia and hypoglycaemia in the body and include such functions as release of glucose into the circulation via **gluconeogenesis**, **uptake of glucose** from the circulation to satisfy their energy needs, and **reabsorption of glucose** at the level of the proximal convoluted tubule.

Renal release of glucose into the circulation is the result of **glycogenolysis** and **gluconeogenesis**, respectively involving the breaking down of glycogen and formation of glucose-6-phosphate from precursors (eg, lactate, glycerol, amino acids). With regard to renal reabsorption of glucose, the kidneys normally retrieve as much glucose as possible, rendering the urine virtually glucose free.

Chronically uncontrolled **hyperglycemia** leads to a higher risk of macrovascular and microvascular complications, such as cardiovascular disease, nephropathy, neuropathy, and retinopathy. **Hypoglycemia,** on the other hand, may lead to a myriad of central nervous system complications (eg, confusion, behavioral changes, seizures, loss of consciousness, and even death), since the brain is the body's largest consumer of glucose in the fasting or "postabsorptive" state.

The kidney carries out the following to ensure glucose balance in the body:

Glycogenolysis involves the breakdown of glycogen to glucose-6-phosphate from precursors (eg, lactate, glycerol, amino acids) and its subsequent hydrolysis (via glucose-6-phosphatase) to free glucose.

Gluconeogenesis involves formation of glucose-6-phosphate from those same precursors and subsequent conversion to free glucose. Interestingly, the liver

and skeletal muscles contain most of the body's glycogen stores, but only the liver contains glucose-6-phosphatase. As such, the breakdown of hepatic glycogen leads to release of glucose, whereas the breakdown of muscle glycogen leads to release of lactate. Lactate (generated via glycolysis of glucose by blood cells, the renal medulla, and other tissues) may be absorbed by organs and reformed into glucose.

- **RENAL GLUCONEOGENESIS:** From the point of view of glucose utilization, the kidney is considered as 2 separate organs; ***the renal medulla is characterized mainly by glucose utilization and the renal cortex is responsible for glucose release.*** The separation of these activities represents the consequence of differences in the distribution of numerous enzymes along the nephron.
  The cells in the **renal medulla** can use only glucose for their needs (like the brain) and they have enzymes capable of glucose-phosphorylation and glycolysis. They can therefore phosphorylate important amounts of glucose and accumulate glycogen but, because these cells do not have glucose-6-phosphatase or any other gluconeogenic enzymes, they are unable to release glucose into the bloodstream.
  Moreover, the cells in the **renal cortex** have gluconeogenic enzymes and they can produce and release glucose into the circulation. However these cells cannot synthesize glycogen because they have little phosphorylating capacity.

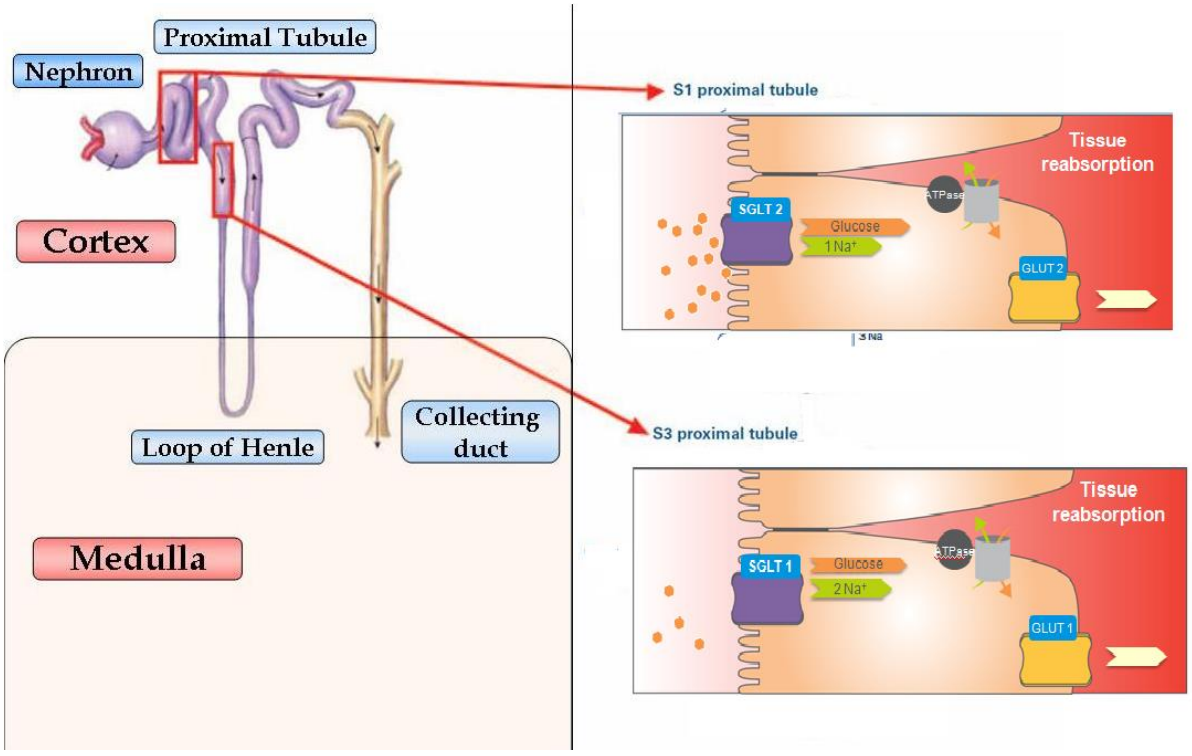
Glucose Reabsorption:
In addition to their important role in gluconeogenesis, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. Under normal conditions as well as when there is excess glucose in the body, the kidneys retrieve as much glucose as possible, rendering the urine virtually glucose free. The glomeruli filter from plasma approximately 180 grams of D-glucose per day, all of which is reabsorbed through **glucose transporter proteins** that are present in cell membranes within the proximal tubules. If the capacity of these transporters is exceeded, glucose appears in the urine. This maximum capacity, known as the tubular maximum for glucose (TmG), ranges from 260 to 350 mg/min/1.73 m^2 in healthy adults and children, and corresponds to a plasma glucose level of approximately 200 mg/dL.

Once the TmG (the threshold) is reached and transporters are unable to reabsorb all the glucose, **glucosuria ocurrs** and this is associated with diabetes mellitus**.**

Renal Glucose Reabsorption *is the part of kidney (renal) physiologythat deals with the retrieval of filtered glucose, preventing it from disappearing from the body through the urine.*

How does glucose reabsorption work?

Firstly, the glucose in the proximal tubule is co-transported with sodium ions into the proximal convoluted tubule walls via the **SGLT2 cotransporter**. Some (typically smaller) amino acids are also transported in this way. Once in the tubule wall, the glucose and amino acids diffuse directly into the blood capillaries along a concentration gradient. This blood is flowing, so the gradient is maintained.



QUESTION 2

Discuss the process of Micturition.

Micturition or urination is the process of expelling urine from the bladder. This act is also known as voiding of the bladder. The excretory system in humans

includes a pair of kidneys, two ureters, a urinary bladder and a urethra. The kidneys filter the urine and it is transported to the urinary bladder via the ureters where it is stored till its expulsion. The process of micturition is regulated by the **nervous system** and the **muscles of the bladder** and urethra. The urinary bladder can store around 350-400ml of urine before it expels it out.

Nerve Supply to the Urinary Bladder and Sphincters:

Urinary bladder and the internal sphincter are supplied by **sympathetic** and **parasympathetic divisions** of autonomic nervous system where as, the external sphincter is supplied by the **somatic nerve fibers**.

Stages of Micturition

The urinary bladder has two distinct stages or phases:

1. Resting or filling stage
2. Voiding stage

Resting or Filling Stage:

It is in this phase of the bladder that the urine is transported from the kidneys via the ureters into the bladder. The ureters are thin muscular tubes that arise from each of the kidneys and extend downwards where they enter the bladder obliquely.
The oblique placement of the ureters in the bladder wall serves a very important function. The opening of the ureter into the urinary bladder is not guarded by any sphincter or muscle. Therefore, this oblique nature of opening prevents the urine from re-entering the ureters. At the same time, the main muscle of the urinary bladder, the **detrusor muscle**, is relaxing allowing the bladder to distend and accommodate more urine.

The stimulation of **sympathetic (hypogastric) nerve** causes **relaxation of detrusor muscle** and **constriction of the internal sphincter**. It results in filling of urinary bladder and so, the sympathetic nerve is called **nerve of filling**.

Voiding Stage:

During this stage, both the urinary bladder and the urethra come into play together. The detrusor muscle of the urinary bladder which was relaxing so far starts to contract once the bladder's storage capacity is reached.

The urethra is controlled by two sets of muscles: The internal and external urethral sphincters. The internal sphincter is a **smooth muscle** whereas the external one is **skeletal**. Both these sphincters are in a contracted state during the filling stage.

Stimulation of **parasympathetic (pelvic) nerve** causes **contraction of detrusor muscle** and **relaxation of the internal sphincter** leading to emptying of urinary bladder. So, parasympathetic nerve is called the **nerve of emptying** or **nerve of micturition**. Pelvic nerve has also the sensory fibers, which carry impulses from stretch receptors present on the wall of the urinary bladder and urethra to the central nervous system.

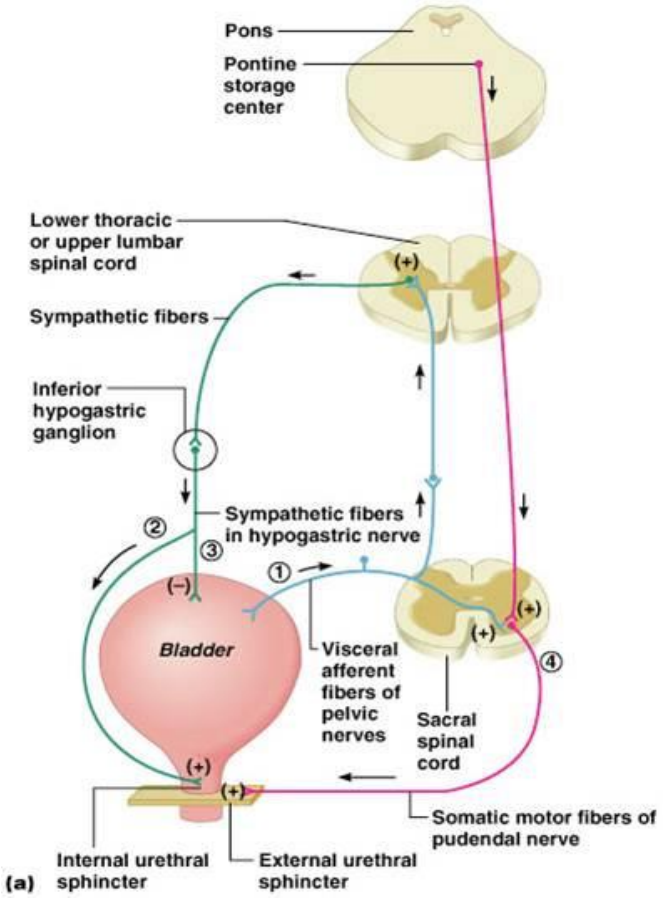
NOTE: External sphincter is innervated by the **somatic nerve** called **pudendal nerve**. Pudendal nerve maintains the tonic contraction of the skeletal muscle fibers of the external sphincter and **keeps the external sphincter constricted always**. During micturition, this nerve is inhibited. It causes relaxation of external sphincter leading to voiding of urine. Thus, **the pudendal nerve is responsible for voluntary control of micturition.**

MICTURITION REFLEX

The process of micturition is governed by both the nervous and muscular systems. Within the nervous system, the process is governed by the **autonomous nervous system** and the **somatic system**. Once the urinary bladder reaches its maximum capacity, the **stretch receptors** in the walls of the bladder send an impulse via the sensory fibers of the **pelvic nerve** to the brain via the **spinal cord**.

- Sensory (afferent) impulses from the receptors reach the sacral segments of spinal cord via the sensory fibers of pelvic (parasympathetic) nerve.
- Motor (efferent) impulses produced in spinal cord, travel through motor fibers of pelvic nerve towards bladder and internal sphincter. **Motor impulses cause contraction of detrusor muscle and relaxation of internal sphincter so that, urine enters the urethra from the bladder.**
- Once urine enters urethra, the stretch receptors in the urethra are stimulated and send afferent impulses to spinal cord via pelvic nerve fibers.
- The impulses generated from spinal centers inhibit pudendal nerve. So, the external sphincter relaxes and micturition occurs.

Once a micturition reflex begins, **it is self-regenerative**, i.e. the initial contraction of bladder further activates the receptors to cause further increase in sensory impulses from the bladder and urethra. These impulses, in turn cause further increase in reflex contraction of bladder. The cycle continues repeatedly until the force of contraction of bladder reaches the maximum and the urine is voided out completely. ***During micturition, the flow of urine is facilitated by the increase in the abdominal pressure due to the voluntary contraction of abdominal muscles***



QUESTION 3

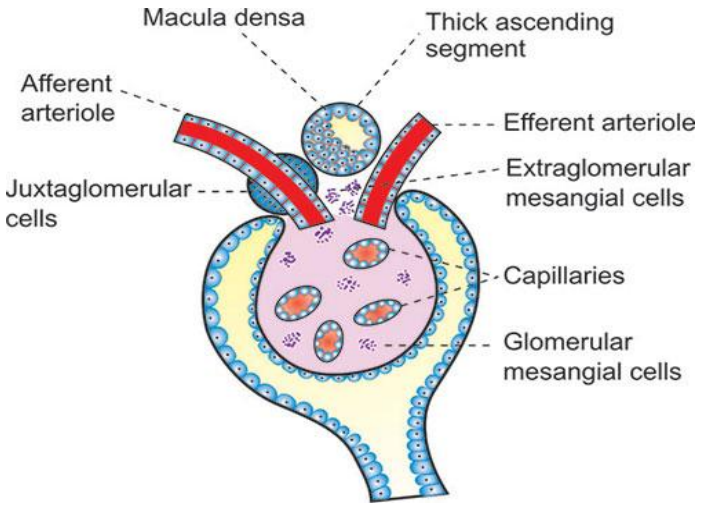
Explain the Juxtaglomerular apparatus.

The **juxtaglomerular apparatus** (also known as the **juxtaglomerular complex**) is a structure in the kidney that regulates the function of each nephron, the functional units of the kidney. The juxtaglomerular apparatus is named because it is next to (juxta-) the glomerulus.

It is a specialized structure formed by the **distal convoluted tubule** and the **glomerular afferent arteriole**. It is located near the vascular pole of the glomerulus and its main function is to regulate blood pressure and the filtration rate of the glomerulus.

The juxtaglomerular apparatus consists of three types of cells:

1. Macula densa.
2. Juxtaglomerular cells.
3. Extraglomerular mesangial cells.



MACULA DENSA:

In the kidney, the **macula densa** is an area of closely packed cuboidal cells lining the wall of the distal tubule, at the point where the **thick ascending limb** of the Loop of Henle meets the **distal convoluted tubule**. The macula densa is the thickening where the distal tubule touches the glomerulus.
The cells of the macula densa are sensitive to the concentration of sodium chloride in the distal convoluted tubule. A decrease in sodium chloride concentration initiates a signal from the macula densa that has two effects:

(1) It decreases resistance to blood flow in the afferent arterioles, which raises glomerular hydrostatic pressure and helps return the glomerular filtration rate (GFR) toward normal.
(2) It increases renin release from the juxtaglomerular cells of the afferent and efferent arterioles, which are the major storage sites for renin.

As such, **an increase in sodium chloride concentration would result in vasoconstriction of afferent arterioles**, and reduced paracrine stimulation of

juxtaglomerular cells. This demonstrates the macula densa feedback, where compensatory mechanisms act in order to return GFR to normal.

JUXTAGLOMERULAR CELLS:

The **juxtaglomerular cells** (JG cells, or granular cells) are cells in the kidney that synthesize, store, and secrete the enzyme **renin**. They are specialized smooth muscle cells mainly in the walls of the afferent arterioles (and some in the efferent arterioles) that deliver blood to the glomerulus. They play a critical role in the **renin–angiotensin system** and thus in **autoregulation** of the kidney.

Juxtaglomerular cells secrete renin in response to a drop in pressure detected by **stretch receptors** in the vascular walls, or when stimulated by **macula densa** cells. Macula densa cells are located in the distal convoluted tubule, and stimulate juxtaglomerular cells to release renin when they detect a drop in sodium concentration in tubular fluid.

Similar to cardiac tissue, juxtaglomerular cells harbor **β1 adrenergic receptors**. When stimulated by **epinephrine** or **norepinephrine**, these receptors induce the **secretion of renin**.
These cells also respond directly to a decrease in systemic blood pressure which is manifested as a lower renal perfusion pressure.

EXTRAGLOMERULAR MESANGIAL CELLS:

Extraglomerular mesangial cells (also known as **Lacis cells**, **Polkissen cells**, or **Goormaghtigh cells**) are light-staining pericytes in the kidney found outside the glomerulus, near the vascular pole. They are a type of **smooth muscle** cell; they play a role in **autoregulation** of blood flow to the kidney and regulation of systemic blood pressure through the **renin-angiotensin** system.

NOTE: Glomerular Mesangial Cells:
Besides extraglomerular mesangial cells there is another type of mesangial cells situated in between glomerular capillaries called **glomerular mesangial** or **intraglomerular mesangial cells**. Glomerular mesangial cells support the glomerular capillary loops by surrounding the capillaries in the form of a cellular network. These cells play an important role in regulating the glomerular filtration by their contractile property

SIGNIFICANCE OF THE JUXTAGLOMERULAR APPARATUS

- Juxtaglomerular apparatus secretes two hormones:
  I. **Renin:** Renin's primary function is therefore to eventually cause an increase in blood pressure, leading to restoration of perfusion pressure in the kidneys in response to low blood pressure, causing the transformation of angiotensinogen to angiotensin I.
  II. **Prostaglandin**: Prostaglandins (PGs) with best-defined renal functions are PGE_2 and prostacyclin (PGI_2). These vasodilatory PGs increase renal blood flow and glomerular filtration rate under conditions associated with decreased actual or effective circulating volume, resulting in greater tubular flow and secretion of potassium.
- They help in maintaining the blood pressure and glomerular filtration rate through rennin-angiotensin system.
- They result in aldosterone production and thus regulate the salt absorption from the filtrate and regulate the blood pressure.

QUESTION 4:

Discuss the role of kidney in blood pressure regulation.

The kidney plays a central role in the regulation of arterial blood pressure. A large body of experimental and physiological evidence indicates that renal control of extracellular volume and renal perfusion pressure are closely involved in maintaining the arterial circulation and blood pressure. Renal artery perfusion pressure directly regulates sodium excretion-a process known as pressure **natriuresis-**and influences the activity of various vasoactive systems such as the **renin-angiotensin-aldosterone system**.

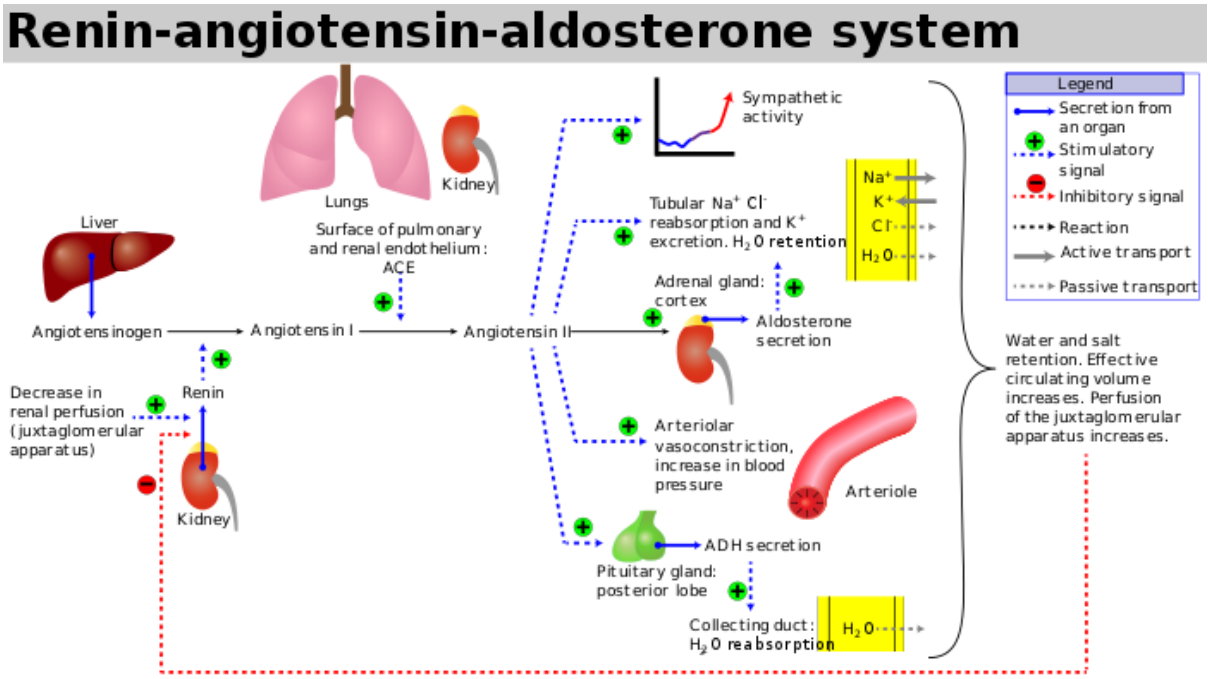
RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system or RAS **regulates blood pressure** and fluid balance in the body. When blood volume or sodium levels in the body are low, or blood potassium is high, cells in the kidney release the enzyme, **renin**.

Renin converts **angiotensinogen**, which is produced in the liver, to the hormone **angiotensin I**. An enzyme known as **ACE** or angiotensin-converting enzyme found in the lungs metabolizes **angiotensin I into angiotensin II**.

Angiotensin II raises the blood pressure by the following ways:

1. Angiotensin II causes blood vessels to constrict which increases the **Total Peripheral Resistance** and in turn, causes blood pressure to increase. It increases blood pressure indirectly by increasing the release of **noradrenaline** from postganglionic sympathetic fibers. Noradrenaline is a general vasoconstrictor.
2. Angiotensin II stimulates the release of the hormone **aldosterone** in the adrenal glands, which causes the renal tubules to retain sodium and water and excrete potassium. The reabsorption of electrolytes together with water, leads to and increase in blood volume which causes the venous return to increase and in turn, leads to and increase in cardiac output. Together, angiotensin II and aldosterone work to raise blood volume, blood pressure and sodium levels in the blood to restore the balance of sodium, potassium, and fluids.
3. Angiotensin II stimulates the release of **antidiuretic hormone** (ADH) by the posterior pituitary gland. ADH, or vasopressin, acts to increase water reabsorption in the kidney by inserting aquaporin channels at the collecting duct. The reabsorption of water increases blood volume, which in turn, leads to and increase in cardiac output, thereby raising the blood pressure.
4. Angiotensin II stimulates thirst centres, which leads to an increase in the intake of water, increasing the blood volume and raising the blood pressure in return.



However, the hyperactivity of this system may lead to High Blood Pressure.

QUESTION 5:

Discuss the role of kidney in calcium homeostasis

The kidney, one of the major organs of the excretory system, regulates Ca^{2+} homeostasis by filtration and reabsorption. Approximately 60% of the Ca^{2+} in plasma is filtered, and 99% of that is reabsorbed by the kidney tubules, which preserves blood calcium levels. If tubular reabsorption of calcium decreases, calcium is lost by excretion into urine.

Vitamin D and **parathyroid hormone** (PTH) help regulate how much calcium is absorbed and how much calcium the kidneys eliminate. Healthy kidneys turn vitamin D into an active hormone (calcitriol), which helps increase calcium absorption from the intestines into the blood. More than 95% of filtered **calcium** is **reabsorbed** along the renal tubules. In the proximal tubules, 60% of filtered calcium is reabsorbed by passive mechanisms. In the thick ascending limb, 15% of calcium is reabsorbed by paracellular diffusion.

Ca^{2+} filtration and reabsorption in the kidney, together with intestinal absorption, bone resorption, and deposition, determine total body Ca^{2+} balance. The ionized Ca^{2+} in the blood and extracellular fluids is filtered every

2hours, and any change in the capacity to reabsorb Ca^{2+}, even small changes, can significantly affect Ca^{2+} balance.

The reabsorptive capacity of the kidney involves two pathways: the **paracellular** and the **transcellular pathway**. Movement of Ca^{2+} through the tight junctions between epithelial cells proceeds through the paracellular pathway, whereas the transcellular pathway involves the transport of Ca^{2+} through epithelial cells.

As the filtrate runs along the nephron the tubular Ca^{2+} concentration decreases, thus decreasing the drive for the paracellular pathway, which triggers the transcellular component.

The transcellular pathway includes Ca^{2+} entry across the apical membrane via **Ca^{2+}-permeable ion channels**, followed by intracellular diffusion of Ca^{2+} from the apical to the basolateral membrane mediated by calcium-binding proteins and buffers (such as calbindins) and, finally, exit through the basolateral membrane via the Ca^{2+} pump or the **Na^{+}/Ca^{2+} exchanger**.

Although the majority of Ca^{2+} is reabsorbed via the energy-saving paracellular route, the transcellular route is important in fine-tuning the total body Ca^{2+} homeostasis, a process tightly regulated by vitamin D and parathyroid hormone .