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MATRIC NUMBER:17/MHS01/021

COURSE:PYHSIOLOGY 303 assignment

1. Discuss the role of kidney in glucose homeostasis.

 Along with the liver, the kidney has an important role in fulfilling the energy needs required by the body during fasting periods of fasting. This organ has a vital role in absorbing the entire quantity of the filtered glucose. Having a glomerular filtration rate of 180 liters per day, it filters approximately 180 grams of glucose per day, bringing its contribution in maintaining normal fasting plasma glucose (FPG) levels. The reabsorption of glucose is ensured by the sodium-glucose cotransporter (SGLT) 2, responsible for the reabsorption of 90% of glucose, and SGLT1, that reabsorbs the remaining glucose. In a given day, the kidneys can produce, via gluconeogenesis, 15–55g glucose and it can metabolize 25–35g glucose. Regarding the glucose metabolic pathways, it is obvious that renal reabsorption represents the main mechanism by which the kidney is involved in glucose homeostasis. Therefore, the change in tubular glucose reabsorption may have a considerable impact on glucose homeostasis.

 Despite the implication of the kidneys in glucose homeostasis, this organ is often overlooked as a key player in glucose metabolism. But the awareness of the renal mechanisms of glucose control is likely to increase due to the development of new types of glucose-lowering drugs that target this metabolic pathway.The plasma glucose concentration is determined by the amount of glucose synthesized, and the one removed from the circulation and metabolized. This concentration must be maintained within a relatively narrow range despite the wide daily fluctuations in glucose ingestion and glucose demands in various tissues. The regulation of endogenous production of glucose is determined by hormonal and neural factors.. In the acute phase, glucoregulatory mechanisms involve insulin, glucagon and catecholamines and they can effect changes in plasma glucose levels in a matter of minutes. Insulin is able to suppress glucose release in both the kidney and liver by direct enzyme activation ⁄ deactivation and by reducing the availability of gluconeogenic substrates. Glucagon has no effect on the kidneys, but it stimulates glycogenolysis and gluconeogenesis in the liver.. Catecholamines also have multiple acute actions. They can stimulate renal glucose release and glucagon secretion and inhibit insulin secretion. The kidneys are involved in maintaining glucose homeostasis through three different mechanisms: gluconeogenesis; glucose uptake from the blood for its own energy requests and reabsorption into the general circulation of glucose from glomerular filtrate in order to preserve energy.

###  **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.

After a 16 hour overnight fast glucose is released into the circulation.. Almost 50% of this is the result of glycogenolysis from the liver stocks and the other half is produced by liver and kidney gluconeogenesis. The renal cortex (like the liver) contains gluconeogenic enzymes and it can synthesize glucose-6-phosphate from precursors (lactate, glutamine, glycerol and alanine). Because it contains glucose-6-phosphatase, it is able to release glucose into the blood stream and the human liver and kidneys are the only organs that can perform gluconeogenesis. Therefore, after an overnight fast, the liver produces 75–80% of glucose released into the circulation and the remaining 20–25% is derived from the kidneys. Several studies have indicated that human kidneys and liver provide approximately the same amounts of glucose through gluconeogenesis in postabsorptive period. If the duration of fasting is increased, the glycogen stores are depleted and gluconeogenesis produces all the glucose released into circulation.

An important aspect is that kidney and liver use different gluconeogenic precursors and several hormones have different effects on their release of glucose. Lactate represents the predominant gluconeogenic precursor in both organs, but regarding the aminoacids, the kidney prefers to use glutamine, whereas the liver preferentially uses alanine.. Insulin can suppress glucose release in both organs with almost comparable efficacy,whereas glucagon stimulates hepatic glucose release only. Catecholamines normally have a direct effect only on renal glucose release ,but their effect on both hepatic and renal glucose release may be indirect by increasing the quantity of gluconeogenic substrates available and by suppressing insulin secretion. Other hormones, such as growth hormone, cortisol and thyroid hormones can stimulate hepatic glucose release over a great period of time.

In the postprandial state the situation changes significantly. Postprandial glucose levels in the plasma are determined by insulin and glucagon levels. After glucose ingestion, plasma glucose levels reach the peak in 60–90 minutes and they return to post-absorptive levels in almost 3–4 h. The plasma insulin increases four times and the plasma glucagon levels decrease by 50%. This indicated that endogenous glucose release is reduced by almost 60% and hepatic glycogenolysis drops to zero in the 4- to 6-h period after meal ingestion.This is happening because this period determines the refilling of hepatic glycogen stores and inhibition of endogenous glucose release is able to limit postprandial hyperglycaemia. There is also a reduction in hepatic gluconeogenesis by 82% and glucose molecules generated through hepatic gluconeogenesis are also directed into hepatic glycogen, not only released in the circulation. Renal gluconeogenesis can increase by approximately twofold and it can represent ~60% of endogenous glucose production in the postprandial state. This mechanism is believed to facilitate the repletion of glycogen stocks in the liver.

### **Glycogenolysis**

Glycogenolysis is the breakdown of glycogen to glucose-6-phosphate and a hydrolysis reaction (using glucose-6-phosphatase) in order to free glucose. The liver is the only organ that contains glucose-6-phosphatase. So, the cleavage of hepatic glycogen releases glucose, while the cleavage of glycogen from other sources can release only lactate. Lactate, that is generated via glycolysis, is often absorbed by other organs and helps regenerating glucose.

### **Glucose reabsorption**

Apart from the important role in gluconeogenesis and the role of renal cortex in glucose uptake, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. In normal conditions, the kidneys can reabsorb as much glucose as possible, the result being a virtually glucose free urine. Approximately 180 grams of glucose are filtered by the glomeruli from plasma, daily but all of this quantity is reabsorbed through glucose transporters that are present in cell membranes located in the proximal tubules.

Certain glucose transporters have a limited capacity of reabsorption. If this capacity is exceeded, glucose usually appears in the urine. The tubular maximum for glucose (TmG), the term used for the maximum capacity, can vary from 260 to 350 mg/min/1.73 m2 in healthy subjects. It corresponds to blood glucose levels of 180-200 mg/dL. When the blood glucose is very high and the TmG is reached, the transporters cannot reabsorb all the glucose and glucosuria occurs. Nevertheless, there can be slight differences between the nephrons and the inaccurate nature of biological systems may potentially lead to the development of glucosuria when blood glucose is low. Glucosuria may occur at lower plasma glucose levels in certain conditions of hyperfiltration (eg. pregnancy), but as a consequence of hyperfiltration and not of significant hyperglycemia.

Glucose is a polar compound with positive and negative charged areas; therefore it is soluble in water. Its transport into and across cells is dependent on two specialized carrier protein families: the GLUTs (facilitated glucose transporters) and the SGLTs (sodium-coupled glucose cotransporters). These transporters are responsible for glucose passage and reabsorption in several tissue types, including the proximal renal tubule, blood-brain barrier, small intestine. GLUTs are responsible for the passive transport of glucose across cell membranes, in order to equilibrate its concentrations across a membrane. SGLTs, on the other hand, are involved in active transport of glucose against a concentration gradient by means of sodium-glucose cotransport . SGLT2 is considered the most important because it is responsible for the reabsorption of 90% of the glucose filtered at the glomerulus. The other 10% of glucose reabsorbed in the proximal tubule is ensured by SGLT1. Of the family of GLUT proteins expressed in the kidneys, GLUT2 is the major transporter and it releases into circulation the glucose reabsorbed by SGLTs in the proximal tubular cells.

#### 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](https://www.toppr.com/guides/biology/excretory-products/human-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](https://www.toppr.com/guides/biology/control-and-coordination/nervous-system/) and the [muscles](https://www.toppr.com/guides/biology/locomotion-and-movement/muscle/) of the bladder and urethra. The urinary bladder can store around 350-400ml of urine before it expels it out.

## 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](https://www.toppr.com/guides/maths/relations-and-functions/functions/). The opening of the ureter into the urinary bladder is not guarded by any sphincter or muscle. Therefore, this oblique [nature](https://www.toppr.com/guides/business-studies/business-services/nature-and-types-of-services/) 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.

### **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](https://www.toppr.com/guides/biology/locomotion-and-movement/skeletal-system/). Both these sphincters are in a contracted state during the filling stage.

As mentioned earlier, the process of [micturition](https://www.toppr.com/guides/biology/excretory-products/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 pelvic nerve to the brain via the spinal cord.

The micturition reflex is ultimately generated from the level of the spinal cord after it receives reflexes from the pontine region in the brain. Once the bladder and the urethra receive the signals to empty the bladder, the two sphincters relax and the detrusor muscle causes the contractions of the bladder. Along with these muscles, the muscles of the abdomen also play a role by putting [pressure](https://www.toppr.com/guides/physics/force-and-pressure/introduction-to-pressure) on the bladder wall. This leads to complete emptying of the bladder.

1. Explain the juxtaglomerular apparatus.

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Bottom of Form

# Juxtaglomerular apparatus.

The juxtaglomerular apparatus (also known as the juxtaglomerularcomplex) is a structure in the [kidney](https://en.m.wikipedia.org/wiki/Kidney) that regulates the function of each [nephron](https://en.m.wikipedia.org/wiki/Nephron), the functional units of the kidney. The juxtaglomerular apparatus is named because it is next to the [glomerulus](https://en.m.wikipedia.org/wiki/Glomerulus_%28kidney%29). The juxtaglomerular apparatus consists of three types of cells:

1. the [macula densa](https://en.m.wikipedia.org/wiki/Macula_densa), a part of the distal convoluted tubule of the same nephron
2. [juxtaglomerular cells](https://en.m.wikipedia.org/wiki/Juxtaglomerular_cell), (also known as granular cells) which secrete [renin](https://en.m.wikipedia.org/wiki/Renin)
3. [extraglomerular mesangial cells](https://en.m.wikipedia.org/wiki/Extraglomerular_mesangial_cells)

The juxtaglomerular apparatus is part of the kidney [nephron](https://en.m.wikipedia.org/wiki/Nephron), next to the [glomerulus](https://en.m.wikipedia.org/wiki/Glomerulus_%28kidney%29). It is found between [afferent arteriole](https://en.m.wikipedia.org/wiki/Afferent_arteriole) and the [distal convoluted tubule](https://en.m.wikipedia.org/wiki/Distal_convoluted_tubule) of the same nephron. This location is critical to its function in regulating renal blood flow and [glomerular filtration rate](https://en.m.wikipedia.org/wiki/Glomerular_filtration_rate).

**The**[**renin–angiotensin system**](https://en.m.wikipedia.org/wiki/Renin%E2%80%93angiotensin_system)- It is activated when juxtaglomerular cells are poorly perfused. [Renin](https://en.m.wikipedia.org/wiki/Renin) is produced by [juxtaglomerular cells](https://en.m.wikipedia.org/wiki/Juxtaglomerular_cells). These cells are similar to [epithelium](https://en.m.wikipedia.org/wiki/Epithelium) and are located in the tunica media of the afferent arterioles as they enter the glomeruli. The juxtaglomerular cells secrete renin in response to:

* Stimulation of the [beta-1 adrenergic receptor](https://en.m.wikipedia.org/wiki/Beta-1_adrenergic_receptor)
* Decrease in renal perfusion pressure (detected directly by the granular cells)
* Decrease in NaCl concentration at the macula densa, often due to a decrease in [glomerular filtration rate](https://en.m.wikipedia.org/wiki/Glomerular_filtration_rate).

### Extraglomerular mesangial cells.

[Extraglomerular mesangial cells](https://en.m.wikipedia.org/wiki/Extraglomerular_mesangial_cells) are located in the junction between the afferent and efferent arterioles. These cells have a contractile property similar to vascular smooth muscles and thus play a role in “regulating GFR” by altering the vessel diameter. [Renin](https://en.m.wikipedia.org/wiki/Renin) is also found in these cells.

### Macula densa

At the point where the afferent arterioles enter the glomerulus and the efferent arteriole leaves it, the tubule of the [nephron](https://en.m.wikipedia.org/wiki/Nephron) touches the arterioles of the [glomerulus](https://en.m.wikipedia.org/wiki/Glomerulus) from which it rose. At this location, in the wall of the distal convoluted tubule, there is a modified region of tubular epithelium called the [macula densa](https://en.m.wikipedia.org/wiki/Macula_densa). Cells in the macula densa respond to changes in the [sodium chloride](https://en.m.wikipedia.org/wiki/Sodium_chloride) levels in the distal tubule of the nephron via the [tubuloglomerular feedback](https://en.m.wikipedia.org/wiki/Tubuloglomerular_feedback%22%20%5Co%20%22Tubuloglomerular%20feedback) (TGF) loop.

The macula densa's detection of elevated sodium chloride, which leads to an increase in GFR, is based on the concept of [purinergic signaling](https://en.m.wikipedia.org/wiki/Purinergic_signaling). An increase in the [salt](https://en.m.wikipedia.org/wiki/Sodium_chloride) concentration causes several [cell signals](https://en.m.wikipedia.org/wiki/Signal_transduction) to eventually cause the adjacent afferent arteriole to [constrict](https://en.m.wikipedia.org/wiki/Vasoconstriction). This decreases the amount of blood coming from the afferent arterioles to the glomerular capillaries, and therefore decreases the amount of fluid that goes from the glomerular capillaries into the Bowman's space (the [glomerular filtration rate (GFR)](https://en.m.wikipedia.org/wiki/Glomerular_filtration_rate)).

When there is a decrease in the sodium concentration, less sodium is reabsorbed in the macular densa cells. The cells increase the production of [nitric oxide](https://en.m.wikipedia.org/wiki/Nitric_oxide) and [Prostaglandins](https://en.m.wikipedia.org/wiki/Prostaglandins) to vasodilate the afferent arterioles and increase renin release.

CLINICAL SIGNIFICANCE OF THE JUXTAGLOMERULAR APPARATUS

Excess secretion of renin by the [juxtaglomerular cells](https://en.m.wikipedia.org/wiki/Juxtaglomerular_cells) can lead to excess activity of the renin–angiotensin system, [hypertension](https://en.m.wikipedia.org/wiki/Hypertension) and an increase in [blood volume](https://en.m.wikipedia.org/wiki/Blood_volume). This is not responsive to the usual treatment for [essential hypertension](https://en.m.wikipedia.org/wiki/Essential_hypertension), namely medications and lifestyle modification.

One cause of this can be increased renin production due to [narrowing of the renal artery](https://en.m.wikipedia.org/wiki/Renal_artery_stenosis), or a tumour of juxtaglomerular cells that produces renin. These will lead to [secondary hyperaldosteronism](https://en.m.wikipedia.org/wiki/Secondary_hyperaldosteronism), which will cause hypertension, [high blood sodium](https://en.m.wikipedia.org/wiki/Hypernatremia), [low blood potassium](https://en.m.wikipedia.org/wiki/Hypokalemia), and metabolic alkalosis.

1. Discuss the role of kidney in regulation of blood pressure.

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. As a result, many researchers argue that identifying any marked rise in blood pressure requires resetting of the relationship between arterial blood pressure and urinary sodium excretion, which can occur by an array of systemic or local mechanisms. Almost all of the monogenic forms of hypertension affect sites in the kidney associated with sodium handling and transport. Increasing the salt intake of an animal increases blood pressure in the short term. It increases the osmolarity of the blood which therefore increases water movement from tissues to the blood causing an increased circulating volume. As a result of this increased osmolarity more ADH is released as the osmoreceptors in the hypothalamus are triggered. This results in increased water retention in the kidneys further increasing the circulating volume. Secondary to the increase in salt the thirst centre is stimulated to increase fluid intake to try and counter act the increased osmolarity. This would increase blood volume and therefore pressure temporarily.

1. Discuss the role of the kidney in calcium homeostasis.

The kidney is critcally important in calcium homeostasis. Under normal blood calcium concentrations, almost all of the calcium that enters glomerular filtrate is reabsorbed from the tubular system back into blood, which preserves blood calcium levels. If tubular reabsorption of calcium decreases, calcium is lost by excretion into urine. The maintenance of calcium homeostasis is very important because calcium is the main component of bony skeleton and serves as the intracellular and extracellular messenger in numerous essential cellular events such as neuronal network, immune response, muscle contraction, and hormone secretion. Calcium is a multivalent cation that is very important for many biologic and cellular functions. The kidneys play a central role in the homeostasis of this ion. Gastrointestinal absorption is balanced by renal excretion. When calcium levels in the body declines significantly gastrointestinal absorption, bone resorption, and renal tubular reabsorption increase to normalize it’s levels. Renal regulation of this ion occurs through a glomerular filtration and tubular reabsorption and/or secretion and is therefore an important determinant of plasma ion concentration. Under physiologic conditions, the whole body balance of calcium is maintained by fine adjustments of urinary excretion to equal the net intake.

Imbalances of calcium will result in a number of serious clinical complications, including arrhythmias, seizures, and respiratory difficulties. The kidney plays a critical role in regulating serum levels of this ion. Regulation of calcium occurs in different parts of the nephron and involves a number of different channels, transporters, and pathways.

Total body calcium in the adult human is about 1-2 kg and 99% of total calcium exists in bone. Even though only less than 1% of body calcium is in the extracellular space, maintaining the extracellular calcium concentration within a narrow range (8.5-10.5 mg/dL) is very important for calcium homeostasis. Approximately 40% of plasma calcium is protein-bound and 10% of calcium is in a complex with anions like phosphate, citrate, and sulfate etc. Only half of plasma calcium is in its free form (ionized form, iCa2+) and physiologically important. The ionized calcium is tightly regulated by hormones like parathyroid hormone (PTH), 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), calcitonin, and calcium itself. The kidney, intestine, and bone are the main target organs of these regulators, and the kidney plays a key role in the fine regulation of calcium excretion.

## **Renal calcium handling**

About 50% of plasma calcium (ionized and complexed form; ultrafilterable fraction, excluding the protein bound form) is freely filtered through the renal glomerulus, and 99% of the filtered calcium is actually reabsorbed along renal tubules. The excreted calcium in the final urine is about 200 mg per day in an adult person with an average diet. Several factors are involved in the regulation of calcium in renal tubules. PTH and activated vitamin D enhance calcium reabsorption in the thick ascending limb,distal convoluted tubule (DCT) and/or connecting tubule (CNT), and estrogen promotes calcium absorption in the DCT/CNT. Acidosis contributes to hypercalciuria by reducing calcium reabsorption in the proximal tubule (PT) and DCT, and alkalosis vice versa.Diuretics like thiazide and furosemide also alter calcium absorption in the renal tubules; thiazide promotes calcium reabsorption and furosemide inhibits it. Plasma calcium itself also controls renal calcium absorption through altered PTH secretion as well as via binding to the calcium sensing receptor in the TAL. To facilitate Ca2+ reabsorption along renal tubules; (i) voltage difference between the lumen and blood compartment should be favorable for Ca2+ passage, i.e., a positive voltage in the lumen; (ii) concentration difference should be favorable for Ca2+ passage with a higher Ca2+ concentration in the lumen; (iii) an active transporter should exist if the voltage or concentration difference is not favorable for Ca2+ reabsorption. Each renal tubular segment has a different Ca2+ concentration difference or voltage environment for its unique mechanism for calcium reabsorption.

## **Renal Ca2+ handling along the tubules**

Fifty to sixty percent of filtered calcium is absorbed in parallel with sodium and water in the PT, suggesting that the passive pathway is the main route of Ca2+ absorption in this segment. There is no evidence that Ca2+ reabsorption occurs in the thin descending and ascending limb. In the thick ascending limb, 15% of filtered calcium is absorbed, and the passive absorption through paracellular space is known as the main mechanism. The CaSR is a member of G protein-coupled receptors and suppresses PTH secretion by sensing high plasma Ca2+ level in the parathyroid glands. In the kidney, the CaSR is most highly expressed in the thick ascending limb. Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant disease due to the mutation of CaSR gene, and is manifested as hypercalcemia, hypophosphatemia, parathyroid hyperplasia, and unusually low renal clearance of calcium.

Although only 10-15% of filtered Ca2+ is absorbed in the DCT and CNT, these are the main sites in which the fine regulation of Ca2+ excretion and the major action of PTH and activated vitamin D occur. In the DCT and CNT, the luminal voltage is negative and Ca2+ concentration in the lumen is lower than that of plasma. Several Ca2+ transporting proteins are involved in this active transmembrane transport of Ca2+ in the DCT and CNT. Transcellular Ca2+ reabsorption can occur by three steps; (i) entry of Ca2+ through the calcium channels (TRPV5, TRPV6) in the apical membrane, (ii) binding of Ca2+ with calciumbinding protein (calbindin) and diffusion in the cytoplasm (which enables no significant change in the intracellular i[Ca2+], and (iii) Ca2+ extrusion via an ATP-dependent plasma membrane Ca2+-ATPase (PMCA1b) and an Na2+/Ca2+ exchanger (NCX1) in the basolateral membrane. In the collecting duct (CD), there is no evidence that Ca2+ reabsorption occurs even though calcium channel (TRPV6) was documented to be expressed in CD cells. Each renal tubule has a unique environment and plays a different role in Ca2+ reabsorption. The coordinated play of different renal tubules could maintain harmony of renal Ca2+ handling.

## **Renal calcium transport proteins**

The important renal calcium transport proteins are exclusively expressed in the DCT and CNT.

## **TRPV5 and TRPV6**

Transient receptor potential (TRP) channel is a superfamily of ion channels permeable to monovalent and/or divalent cations with six-transmembrane domains. The mammalian TRP family consists of six subfamilies like TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and TRPA (ankyrin). TRPV is one of them and consists of six members in mammalians; TRPV1 to TRPV6. TRPV5 (previously known as ECaC1) and TRPV6 (ECaC2), have characteristics distinguished from other TRPV channels; (i) constitutively active at low intracellular Ca2+ concentration, and (ii) exclusively selective for Ca2+.TRPV5 is exclusively expressed in the DCT and CNT in the kidney. On the contrary, TRPV6 is more distributed, especially in the intestine, and also found from the DCT to the CD in the kidney. Both TRPV5 and TRPV6 are located in the apical plasma membrane of the tubular epithelium, and serve as the entrance of Ca2+ from the lumen into the cytoplasm. Until now, TRPV5 is known as the main entry of Ca2+ in renal tubular epithelial cells in the DCT and CNT, and TRPV6 is also known to contribute to renal Ca2+ reabsorption in the distal nephron.

**CLINICAL CORRELATES**

* Hypocalcemia refers to low blood calcium concentration. Clinical signs of this disorder reflect increased neuromuscular excitability and include muscle spasms, tetany and cardiac dysfunction.
* Hypercalcemia indicates a concentration of blood calcium higher than normal. The normal concentration of calcium and phosphate in blood and extracellular fluid is near the saturation point; elevations can lead to diffuse precipitation of calcium phosphate in tissues, leading to widespread organ dysfunction and damage.

Maintaining normal blood calcium concentration is managed through the concerted action of three hormones that control fluxes of calcium in and out of blood and extracellular fluid:

[**Parathyroid hormone**](http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/thyroid/pth.html)**serves to increase blood concentrations of calcium.** Mechanistically, parathyroid hormone preserves blood calcium by several major effects:

* Stimulates production of the biologically-active form of vitamin D within the kidney.
* Facilitates mobilization of calcium and phosphate from bone. To prevent detrimental increases in phosphate, parathyroid hormone also has a potent effect on the kidney to eliminate phosphate (phosphaturic effect).
* Maximizes tubular reabsorption of calcium within the kidney. This activity results in minimal losses of calcium in urine.

[**Vitamin D**](http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/otherendo/vitamind.html)**acts also to increase blood concentrations of calcium.** It is generated through the activity of parathyroid hormone within the kidney. Far and away the most important effect of vitamin D is to facilitate absorption of calcium from the small intestine. In concert with parathyroid hormone, vitamin D also enhances fluxes of calcium out of bone.

[**Calcitonin**](http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/thyroid/calcitonin.html) is a hormone that functions to reduce blood calcium levels. It is secreted in response to hypercalcemia and has at least two effects:

* Suppression of renal tubular reabsorption of calcium. In other words, calcitonin enhances excretion of calcium into urine.
* Inhibition of bone resorption, which would minimize fluxes of calcium from bone into blood.