ASSIGNMENT ON RENAL PHYSIOLOGY

BODY FLUID AND TEMPERATURE REGULATION

BY

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Question 1: Discuss the role of kidney in glucose homeostasis.

The kidneys' contributions to maintaining glucose homeostasis are significant and include such functions as:
i. release of glucose into the circulation via gluconeogenesis

ii. uptake of glucose from the circulation to satisfy their energy needs

iii. reabsorption of glucose at the level of the proximal tubule.

Release of glucose into the circulation via gluconeogenesis

The kidneys synthesize glucose from amino acids and other precursors during prolonged fasting, a process referred to as gluconeogenesis. The kidneys' capacity to add glucose to the blood during prolonged periods of fasting rivals that of the liver. Renal release of glucose into the circulation is the result of glycogenolysis and gluconeogenesis, respectively involving the breaking down and formation of glucose-6-phosphate from precursors (e.g. lactate, glycerol, amino acids).

With chronic kidney disease or acute failure of the kidneys, these homeostatic functions are disrupted, and severe abnormalities of body fluid volumes and composition rapidly occur

Reabsorption of glucose at the level of the proximal tubule.

With regard to renal reabsorption of glucose, the kidneys normally 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. The process of renal glucose reabsorption is mediated by active (sodium-coupled glucose cotransporters) and passive (glucose transporters) transporters.

Question 2: Discuss the process of micturition

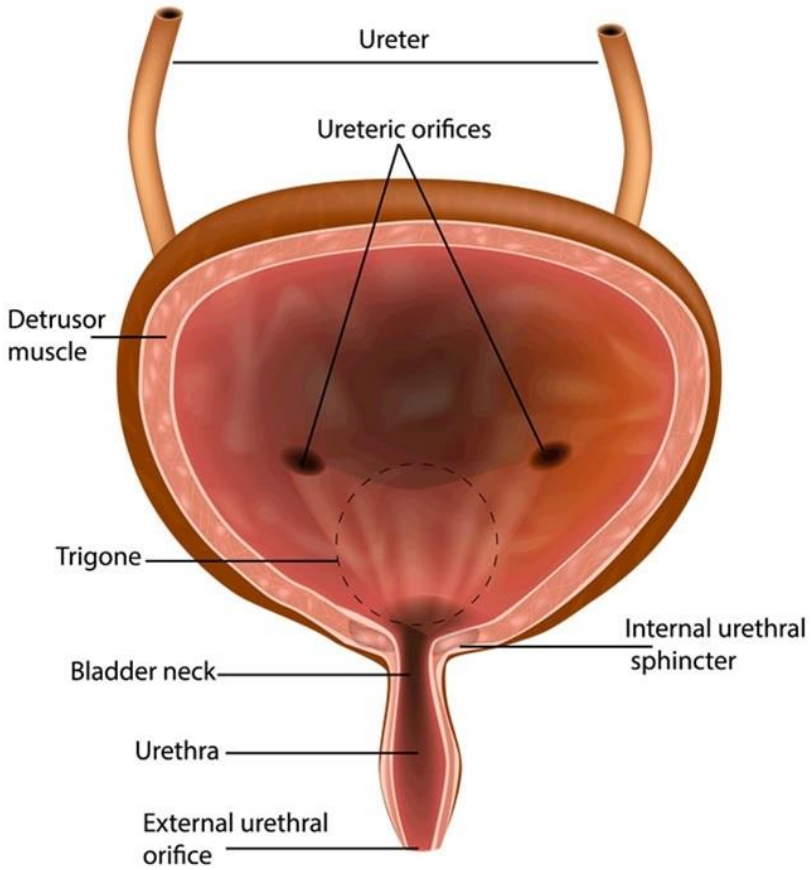
Urine flow through the ureters to the bladder is propelled by contractions of the ureter wall smooth muscle. The urine is stored in the bladder and intermittently ejected during urination, or micturition.

Micturition is the process by which the urinary bladder empties when it becomes filled. It is an autonomic spinal cord reflex, it can also be inhibited or facilitated by centers in the cerebral cortex or brain stem. However, in grown up children and adults, it can be controlled voluntarily to some extent.

This involves two main steps:

First, the bladder fills progressively until the tension in its walls rises above a threshold level;

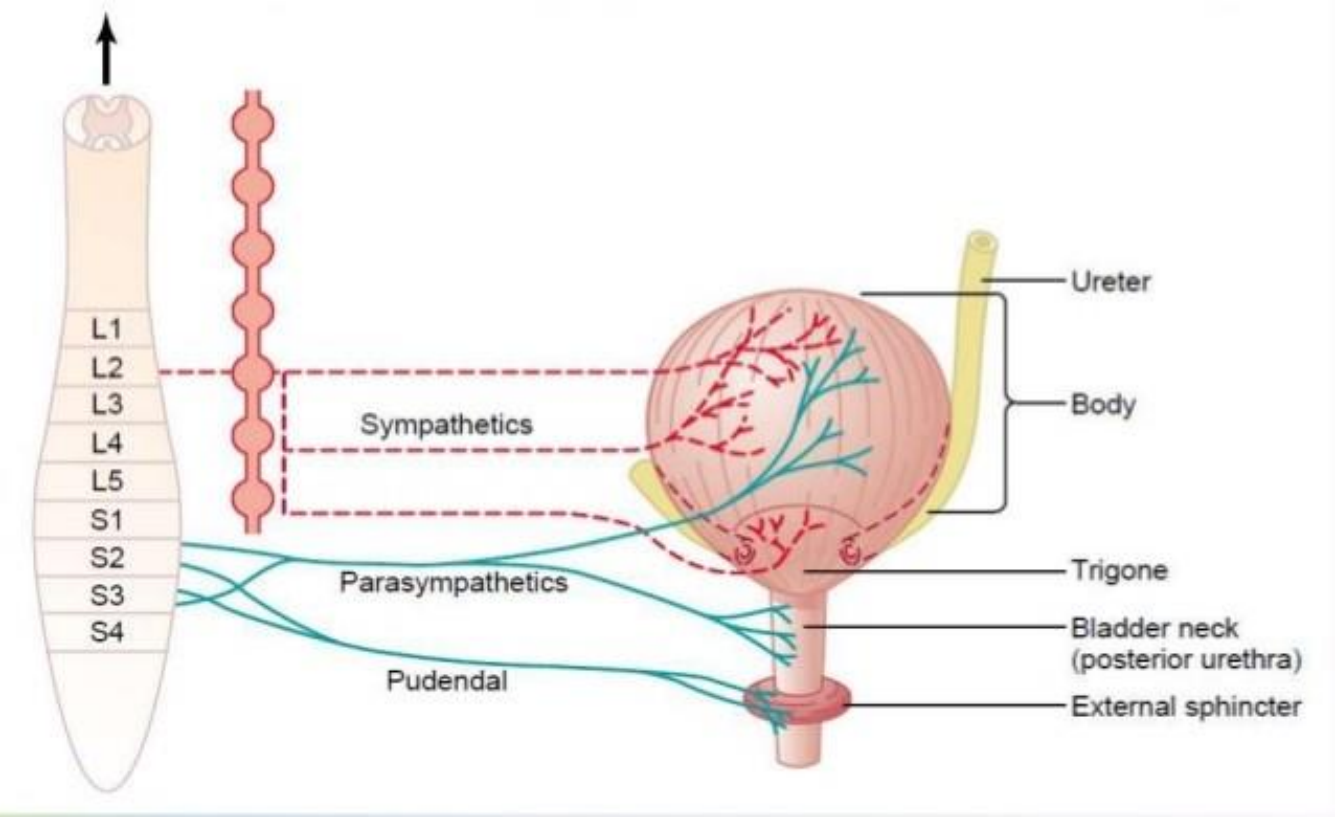
this elicits the second step, which is a nervous reflex called the micturition reflex that empties the bladder or, if this fails, at least causes a conscious desire to urinate.



The bladder is a balloon-like chamber with walls of smooth muscle collectively termed the detrusor muscle. The contraction of the detrusor muscle squeezes on the urine in the bladder lumen to produce urination. That part of the

detrusor muscle at the base (or “neck”) of the bladder where the urethra begins functions as the internal urethral sphincter. Just below the internal urethral sphincter, a ring of skeletal muscle surrounds the urethra. This is the external urethral sphincter, the contraction of which can prevent urination even when the detrusor muscle contracts strongly.

While the bladder is filling, the parasympathetic input to the detrusor muscle is minimal, and, as a result, the muscle is relaxed. Because of the arrangement of the smooth muscle fibers, when the detrusor muscle is relaxed, the internal urethral sphincter is passively closed. Additionally, there is strong sympathetic input to the internal urethral sphincter and strong input by the somatic motor neurons to the external urethral sphincter. Therefore, the detrusor muscle is relaxed and both the internal and external sphincters are closed during the filling phase.



During micturition, as the bladder fills with urine, the pressure within it increases, which stimulates stretch receptors in the bladder wall. The afferent neurons from these receptors enter the spinal cord and stimulate the parasympathetic neurons, which then cause the detrusor muscle to contract. When the detrusor muscle contracts, the change in shape of the bladder pulls open the internal urethral sphincter. Simultaneously, the afferent input from the stretch receptors reflexively inhibits the sympathetic neurons to the internal

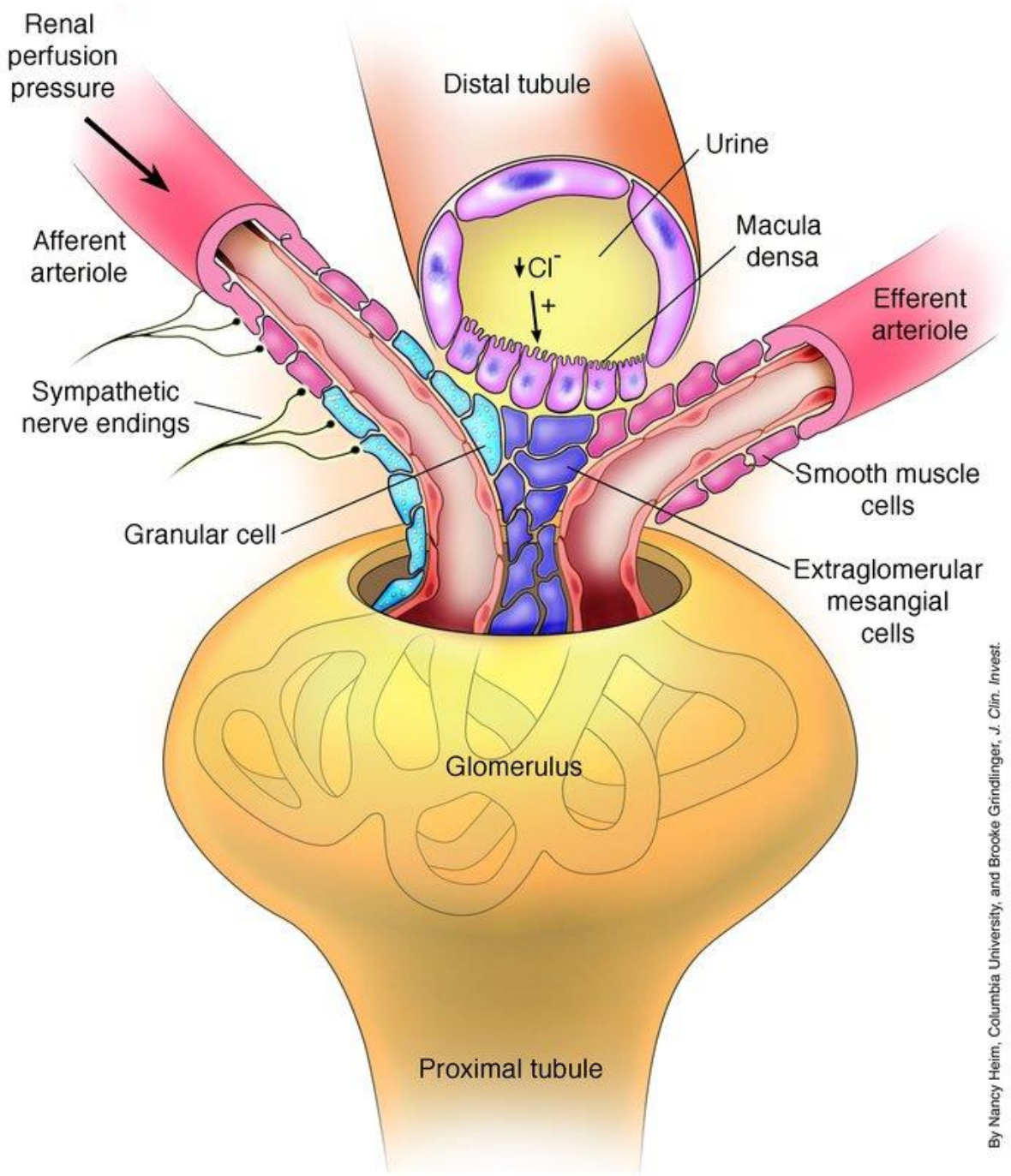
urethral sphincter, which further contributes to its opening. In addition, the afferent input also reflexively inhibits the somatic motor neurons to the external urethral sphincter, causing it to relax. Both sphincters are now open, and the contraction of the detrusor muscle can produce urination.

Muscle	Innervation		
	Type	During filling	During micturition
Detrusor (smooth muscle)	Parasympathetic (causes contraction)	Inhibited	Stimulated
Internal urethral sphincter (smooth muscle)	Sympathetic (causes contraction)	Stimulated	Inhibited
External urethral sphincter (skeletal muscle)	Somatic motor (causes contraction)	Stimulated	Inhibited

Question 3: Explain juxtaglomerular apparatus

Juxtaglomerular apparatus is a specialized organ situated near the glomerulus of each nephron (juxta = near). It is formed by three different structures:

i. Macula densa
ii. Extraglomerular mesangial cells
iii. Juxtaglomerular cells.



Macula densa

It is a specialized group of epithelial cells in the end portion of thick ascending segment before it opens into distal convoluted tubule. It is in close contact with afferent and efferent arterioles of the same nephron. It is very close to afferent arteriole.

The macula densa cells contain Golgi apparatus, which are intracellular secretory organelles directed toward the arterioles, suggesting that these cells may be secreting a substance toward the arterioles. Cells in the macula densa respond to changes in the sodium chloride levels in the distal tubule of the nephron via the tubuloglomerular feedback (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 signalling. An increase in the salt concentration causes several cell signals to eventually cause the adjacent afferent arteriole to constrict. 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).

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 and Prostaglandins to vasodilate the afferent arterioles and increase renin release.

Extraglomerular mesangial cells

These cells are situated in the triangular region bound by afferent arteriole, efferent arteriole and macula densa. These cells are also called agranular cells, lacis cells or Goormaghtigh 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. Glomerular mesangial cells are phagocytic in nature. These cells also secrete glomerular interstitial matrix, prostaglandins and cytokines.

Juxtaglomerular cells

These are specialized smooth muscle cells situated in the wall of afferent arteriole just before it enters the Bowman capsule. These smooth muscle cells

are mostly present in tunica media and tunica adventitia of the wall of the afferent arteriole. Juxtaglomerular cells are also called granular cells because of the presence of secretary granules in their cytoplasm.
Juxtaglomerular cells form a thick cuff called polar cushion or polkissen around the afferent arteriole before it enters the Bowman capsule.
Renin is produced by juxtaglomerular cells. The juxtaglomerular cells secrete renin in response to:

- Stimulation of the 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.

The juxtaglomerular apparatus functions in

- secretion of hormones; renin and prostaglandin.
- Regulation of glomerular blood flow and glomerular filtration rate.

Secretion of hormones; renin and prostaglandin:
Juxtaglomerular cells secrete renin. Along with angiotensins, renin forms the renin-angiotensin system, which is a hormone system that plays an important role in the maintenance of blood pressure. Renin is stimulated by:
i. Fall in arterial blood pressure
ii. Reduction in the ECF volume
iii. Increased sympathetic activity
iv. Decreased load of sodium and chloride in macula densa

When renin is released into the blood, it acts on a specific plasma protein called angiotensinogen or renin substrate. By the activity of renin, the angiotensinogen is converted into a decapeptide called angiotensin I. Angiotensin I is converted into angiotensin II, which is an octapeptide by the activity of angiotensin-converting enzyme (ACE) secreted from lungs. Most of the conversion of angiotensin I into angiotensin II takes place in lungs. Angiotensin II has a short half-life of about 1 to 2 minutes. Then it is rapidly degraded into a heptapeptide called angiotensin III by angiotensinases, which are present in RBCs and vascular beds in many tissues. Angiotensin III is converted into angiotensin IV, which is a hexapeptide.

Angiotensin I is physiologically inactive and serves only as the precursor of angiotensin II. Angiotensin II is the most active form. It:

i. increases arterial blood pressure by directly acting on the blood vessels and causing vasoconstriction. It is a potent constrictor of arterioles.

ii. It increases blood pressure indirectly by increasing the release of noradrenaline from postganglionic sympathetic fibers. Noradrenaline is a general vasoconstrictor

iii. It stimulates zona glomerulosa of adrenal cortex to secrete aldosterone. Aldosterone acts on renal tubules and increases retention of sodium, which is also responsible for elevation of blood pressure.

iv. It constricts the efferent arteriole, which causes decrease in filtration after an initial increase and contracts the glomerular mesangial cells leading to decrease in surface area of glomerular capillaries and filtration.

v. It increases sodium reabsorption from renal tubules. This action is more predominant on proximal tubules.

vi. Angiotensin II inhibits the baroreceptor reflex and thereby indirectly increases the blood pressure.

Other substances secreted are: Extraglomerular mesangial cells of juxtaglomerular apparatus secrete cytokines like interleukin-2 and tumour necrosis factor and Macula densa secretes thromboxane A2.

Regulation of glomerular blood flow and glomerular filtration rate.
Macula densa of juxtaglomerular apparatus plays an important role in the feedback mechanism called tubuloglomerular feedback mechanism, which regulates the renal blood flow and glomerular filtration rate.

Question 4: Discuss the role of kidney in regulation of blood pressure

Kidneys play an important role in the long-term regulation of arterial blood pressure. When blood pressure alters slowly in several days /months /years, the nervous mechanism adapts to the altered pressure and loses the sensitivity for the changes. It cannot regulate the pressure any more.
In such conditions, the renal mechanism operates efficiently to regulate the blood pressure. Therefore, it is called long-term regulation.
by two ways:
i. By regulating the volume of extracellular fluid
ii. Through renin-angiotensin mechanism.

Regulation of extracellular fluid volume:

When the blood pressure increases, kidneys excrete large amounts of water and salt, particularly sodium, by means of pressure diuresis and pressure natriuresis.
Pressure diuresis is the excretion of large quantity of water in urine because of increased blood pressure. Even a slight increase in blood pressure doubles the water excretion.
Pressure natriuresis is the excretion of large quantity of sodium in urine.
Because of diuresis and natriuresis, there is a decrease in ECF volume and blood volume, which in turn brings the arterial blood pressure back to normal level.

When blood pressure decreases, the reabsorption of water from renal tubules is increased. This in turn, increases ECF volume, blood volume and cardiac output, resulting in restoration of blood pressure

Through renin-angiotensin mechanism:

<u>Actions of Angiotensin II</u>

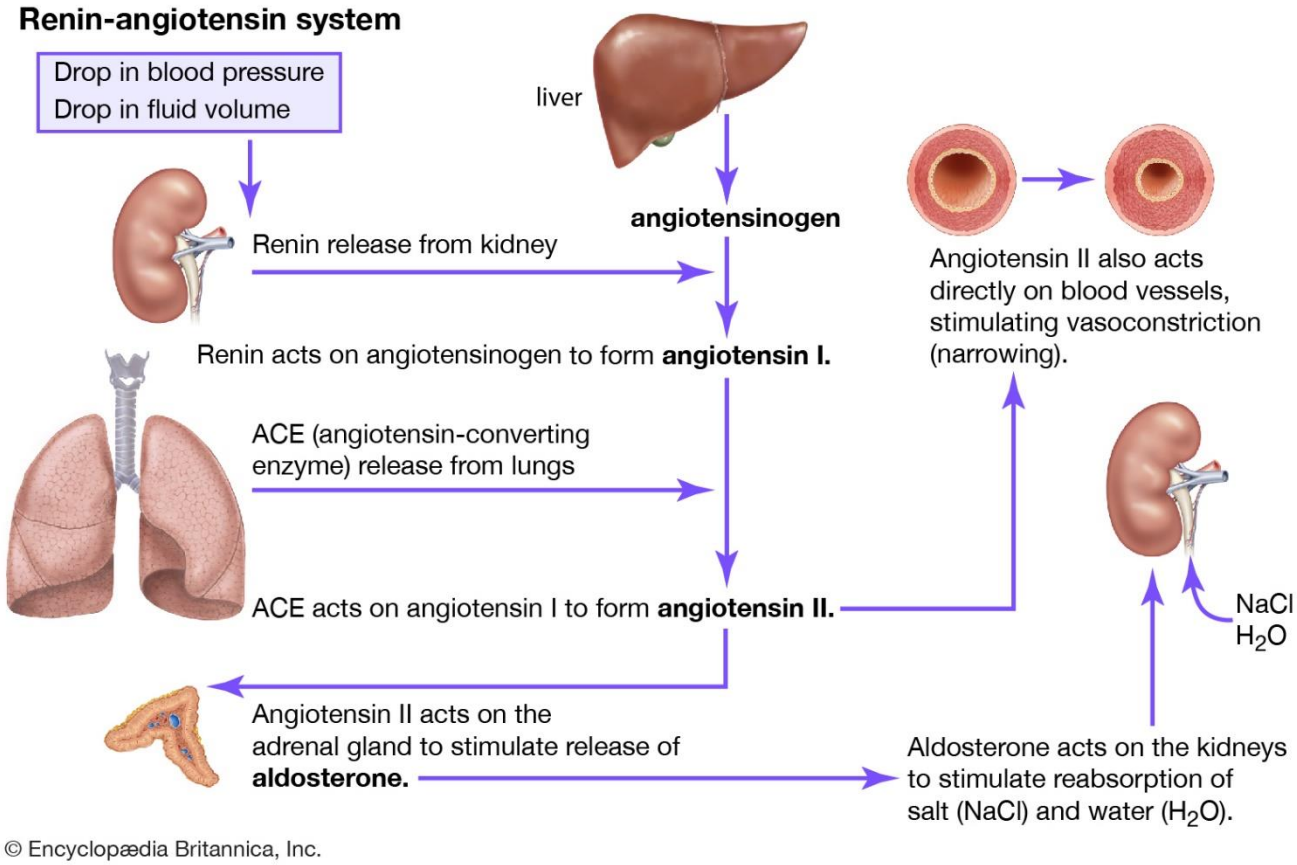
When blood pressure and ECF volume decrease, renin secretion from kidneys is increased. It converts angiotensinogen into angiotensin I. This is converted into angiotensin II by ACE (angiotensin-converting enzyme).

Angiotensin II acts in two ways to restore the blood pressure:

i. It causes constriction of arterioles in the body so that the peripheral resistance is increased and blood pressure rises. In addition, angiotensin II causes constriction of afferent arterioles in kidneys, so that glomerular filtration reduces. This results in retention of water and salts, increases ECF volume to normal level. This in turn increases the blood pressure to normal level.

ii. Simultaneously, angiotensin II stimulates the adrenal cortex to secrete aldosterone. This hormone increases reabsorption of sodium from renal tubules.

Sodium reabsorption is followed by water reabsorption, resulting in increased ECF volume and blood volume. It increases the blood pressure to normal level.



Regulation of blood pressure by renin-angiotensin mechanism. ACE = Angiotensin-converting enzyme.

Actions of Angiotensin III and Angiotensin IV

Like angiotensin II, the angiotensins III and IV also increase the blood pressure and stimulate adrenal cortex to secrete aldosterone**.**

Question 5: Discuss the role of kidney in calcium homeostasis

Calcium is both filtered and reabsorbed in the kidneys but not secreted, the rate of renal calcium excretion is calculated as:

Renal calcium excretion = Calcium filtered - Calcium reabsorbed

Only about 50 per cent of the plasma calcium is ionized, with the remainder being bound to the plasma proteins or complexed with anions such as phosphate. Therefore, only about 50 per cent of the plasma calcium can be filtered at the glomerulus. Normally, about 99 per cent of the filtered calcium is reabsorbed by the tubules, with only about 1 per cent of the filtered calcium being excreted. About 65 per cent of the filtered calcium is reabsorbed in the proximal tubule, 25 to 30 per cent is reabsorbed in the loop of Henle, and 4 to 9 per cent is reabsorbed in the distal and collecting tubules. This pattern of reabsorption is similar to that for sodium.

As is true with the other ions, calcium excretion is adjusted to meet the body's needs. With an increase in calcium intake, there is also increased renal calcium excretion, although much of the increase of calcium intake is eliminated in the faces. With calcium depletion, calcium excretion by the kidneys decreases as a result of enhanced tubular reabsorption.

One of the primary controllers of renal tubular calcium reabsorption is PTH. With increased levels of PTH, there is increased calcium reabsorption in the thick ascending loops of Henle and distal tubules, which reduces urinary excretion of calcium. Conversely, reduction of PTH promotes calcium excretion by decreasing reabsorption in the loops of Henle and distal tubules.

In the proximal tubule, calcium reabsorption usually parallels sodium and water reabsorption. Therefore, in instances of extracellular volume expansion or increased arterial pressure—both of which decrease proximal sodium and water reabsorption—there is also reduction in calcium reabsorption and, consequently, increased urinary excretion of calcium. Conversely, with extracellular volume contraction or decreased blood pressure, calcium excretion decreases primarily because of increased proximal tubular reabsorption.

Another factor that influences calcium reabsorption is the plasma concentration of phosphate. An increase in plasma phosphate stimulates PTH, which increases calcium reabsorption by the renal tubules, thereby reducing calcium excretion. The opposite occurs with reduction in plasma phosphate concentration.

Calcium reabsorption is also stimulated by metabolic acidosis and inhibited by metabolic alkalosis. Most of the effect of hydrogen ion

concentration on calcium excretion results from changes in calcium reabsorption in the distal tubule.