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**COURSE TITLE: RENAL PHYSIOLOGY, BODY FLUID AND TEMPERATURE REGULATION.**

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 **QUESTIONS.**

1. Dis cuss the role of the kidney in glucose homeostasis.
2. Discuss the process of micturition.
3. Explain the juxtaglomerular apparatus,
4. Discuss the role of the kidney in regulation of blood pressure.
5. Discuss the role of the kidney in calcium homeostasis.

 **ANSWERS.**

1. The Role of the Kidney in Glucose Homeostasis.

The Kidneys’ contributions to maintaining glucose homeostasis are significant 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 tubule. 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 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. In hyperglycemia, the kidneys may play an exacerbating role by reabsorbing excess glucose, ultimately contributing to chronic hyperglycemia, which in turn contributes to chronic glycemic burden and the risk of microvascular consequences.

1. 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. It is a reflex process. In healthy humans the process of urination is under voluntary control. In infants, some elderly individuals, and those with neurological injury, urination may occur as a reflex. It is normal for adult humans to urinate up to seven times during the day. 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.

The main organs involved in urination are the urinary bladder and the urethra. The smooth muscle of the bladder, known as the detrusor, is innervated by sympathetic nervous system fibers from the lumbar spinal cord and parasympathetic fibers from the sacral spinal cord. Fibers in the pelvic nerves constitute the main afferent limb of the voiding reflex; the parasympathetic fibers to the bladder that constitute the excitatory efferent limb also travel in these nerves. Part of the urethra is surrounded by the male or female external urethral sphincter, which is innervated by the somatic pudendal nerve originating in the cord, in an area termed Onuf's nucleus.

Smooth muscle bundles pass on either side of the urethra, and these fibers are sometimes called the internal urethral sphincter, although they do not encircle the urethra. Further along the urethra is a sphincter of skeletal muscle, the sphincter of the membranous urethra (external urethral sphincter). The bladder's epithelium is termed transitional epithelium which contains a superficial layer of dome-like cells and multiple layers of stratified cuboidal cells underneath when evacuated. When the bladder is fully distended the superficial cells become squamous (flat) and the stratification of the cuboidal cells is reduced in order to provide lateral stretching. Stages of Micturition

The urinary bladder has two distinct stages or phases:

1. Resting or filling stage.
2. Bladder Emptying and Micturition reflex.
3. 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 filling phase is characterized by voluntary contraction of the external urethral sphincter, with sympathetic contraction of the inner urethral sphincter. The sympathetic nervous system also enables the detrusor to distend without reflex contractions, unlike that which happens in most voluntary muscles. Urethral reflexes, called ‘the guarding reflex,’ also play a part in inhibiting involuntary bladder emptying during this process. The afferents are all conveyed through the pelvic nerves to initiate a spinal reflex.

1. Bladder Emptying and Micturition Reflex.

The micturition or emptying phase displays a coordinated relaxation of the inner and outer urethral sphincters, under sympathetic and somatic regulation respectively, with strong contractions of the detrusor muscle due to parasympathetic impulses. Micturition is thus characterized by:

- Relaxation of the striated sphincter (somatic innervation).

- Relaxation of the smooth muscle sphincter and opening of the bladder neck (sympathetic innervation).

- Detrusor contraction (parasympathetic innervation).

The distension of the urinary bladder wall causes wall tension to rise very slightly. However, when the bladder is almost full, at about 300-400 ml, the inherent contractility of the detrusor causes reflex contractions to occur, which are less powerful than the voiding contraction. Afferent firing frequency increases with filling, but cortical control still overrides the micturition reflex until voluntary voiding is determined upon. During micturition, urinary flow is assisted by additional detrusor contractions and external sphincter relaxation which further lowers resistance to the passage of urine. The abdominal wall and pelvic floor musculature also participates by increasing the force on the bladder to help achieve complete emptying.

Higher Centers for Micturition.

- Spinal Reflex Arcs.

The act of micturition is an autonomic reflex at the level of the spinal cord. This reflex also helps to complete micturition when the act is voluntarily initiated, or when it follows a period of inhibition by the brain, by relaxing the external sphincter. The control of this process is mediated via afferent signals from stretch and volume receptors in the bladder, as well as from the muscles of the pelvic floor, the vagina/penis, and the rectum, which informs the brain about the extent of filling, initiating several spinal reflexes. These serve to inhibit micturition until filling is complete, while activating the voluntary external urethral sphincter via the pudendal nerve. At the same time, detrusor activity is inhibited and the internal urethral sphincter is stimulated via sympathetic activity. Impulses from the filling bladder are carried to the spinal cord via the pelvic and hypogastric nerves, whereas the pudendal and hypogastric nerves carry impulses from the neck of the bladder and the Urethra.

- Pontine Micturition Center

The pontine micturition center (PMC) in the brainstem is activated via afferent signals from the urinary bladder as it is filling. This center sends inhibitory impulses to the spinal reflex arcs to enable bladder voiding. In the absence of any other regulation, the afferents from the bladder and urethra to the midbrain and pons and the efferents to the spinal cord would act as an on-off switch, to cause either reflex voiding or storage depending only on the urine volume stored in the bladder. This means that during the filling or storage phase, the voiding reflex is off, but it is switched on to the highest level when the bladder is distended beyond a critical point, activating the tension receptors in the wall.

- Central Nervous System Regulation.

As the bladder fills, the conscious sensation is perceived and the cortical signals are triggered. This inhibits the purely involuntary firing of the voiding reflex and instead helps the individual to control voiding until the time and place are appropriate. This includes social, sensory, and emotional states, including the degree to which bladder stretching is sensed to be safe and tolerable. The cell group in the periaqueductal gray (PAG) plays a role in detecting the bladder distension, as well as in relaying bladder afferents to higher centers in the brain and enabling the person to feel the sensation. It also regulates the feed to the pontine center, while receiving afferents from higher brain centers such as the anterior cingulate and the prefrontal cortex. These help to inhibit the voiding reflex via suppression of PMC excitation.

The PMC neurons are released from inhibition and fire maximally once the voluntary signal for voiding is produced. This causes excitation of the sacral neurons which stimulate detrusor contractions and induce a sudden increase in turn of intravesical pressure, as well as relaxing the external or voluntary urethral sphincter. Once the intravesical pressure overcomes the urethral resistance, urine flows out through the urethra.

Micturition is thus under cortical control as well as mediated by the spinal reflex arc, which inhibits the pontine center until it is deemed appropriate to void. In addition, the motor cortex controls the voluntary muscle of the external urethral sphincter. The decision to void implies that the prefrontal cortex suppresses the tonic inhibition of the afferents from the PAG to the PMC.

- Urethral Reflexes.

The flow of urine and the mechanical distension of the urethra together cause detrusor contractions to occur, which encourages complete bladder emptying.

1. 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.

The juxtaglomerular apparatus consists of three types of cells:

1. The macula densa, a part of the distal convoluted tubule of the same nephron.
2. Juxtaglomerular cells, (also known as granular cells) which secrete renin.
3. Extraglomerular mesangial cells.

Structure.

The juxtaglomerular apparatus is part of the kidney nephron, next to the glomerulus. It is found between afferent arteriole and the distal convoluted tubule of the same nephron. This location is critical to its function in regulating renal blood flow and glomerular filtration rate.

Function.

a) Juxtaglomerular cells: The renin–angiotensin system. It is activated when juxtaglomerular cells are poorly perfused. Renin is produced by juxtaglomerular cells. These cells are similar to 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.

- 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.

b) Extraglomerular mesangial cells: 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 is also found in these cells.

c) Macula densa: At the point where the afferent arterioles enter the glomerulus and the efferent arteriole leaves it, the tubule of the nephron touches the arterioles of the 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. 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 signaling. 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.

Clinical significance.

Excess secretion of renin by the juxtaglomerular cells can lead to excess activity of the renin–angiotensin system, hypertension and an increase in blood volume. This is not responsive to the usual treatment for essential hypertension, namely medications and lifestyle modification. One cause of this can be increased renin production due to narrowing of the renal artery, or a tumor of juxtaglomerular cells that produces renin. These will lead to secondary hyperaldosteronism, which will cause hypertension, high blood sodium, low blood potassium, and metabolic alkalosis.

1. The Role of the Kidney in Regulation of Blood Pressure.

The juxtaglomerular apparatus of the kidney secretes a hormone called renin which acts in the renin-angiotensin system which helps to regulate blood pressure.

- The Renin- Angiotensin System.

When renin is released into the blood, it acts on a specific plasma protein called angiotensinogen or renin substrate. It is the α2-globulin. 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. Actions of Angiotensins.

- Angiotensin I

 Angiotensin I is physiologically inactive and serves only as the precursor of angiotensin II.

- Angiotensin II

Angiotensin II is the most active form. Its actions are:

1. On blood vessels:
2. Angiotensin II increases arterial blood pressure by directly acting on the blood vessels and causing vasoconstriction. It is a potent constrictor of arterioles. Earlier, when its other actions were not found it was called hypertensin.
3. It increases blood pressure indirectly by increasing the release of noradrenaline from postganglionic sympathetic fibers. Noradrenaline is a general vasoconstrictor.
4. On adrenal cortex: 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.
5. On brain:
6. Angiotensin II inhibits the baroreceptor reflex and thereby indirectly increases the blood pressure. Baroreceptor reflex is responsible for decreasing the blood pressure.

- Angiotensin III

Angiotensin III increases the blood pressure and stimulates aldosterone secretion from adrenal cortex. It has 100% adrenocortical stimulating activity and 40% vasopressor activity of angiotensin.

5. The Role of the Kidney in Calcium Homeostasis.

Plasma calcium concentration is maintained within a narrow range (8.5-10.5 mg/dL) by the coordinated action of parathyroid hormone (PTH), 1,25(OH)2D3, calcitonin, and ionized calcium (iCa2+) itself. The kidney plays a key role in this process by the fine regulation of calcium excretion. 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 through paracellin-1 (claudin-16). The calcium sensing receptor (CaSR) in the basolateral membrane of the thick ascending limb senses the change in iCa2+ and inhibits calcium reabsorption independent to PTH and 1,25(OH)2D3. The fine regulation of calcium excretion occurs in the distal convoluted tubules and connecting tubules despite the fact that only 10-15% of filtered calcium is reabsorbed there. Transient receptor potential vanilloid 5 (TRPV5) and 6 (TRPV6) in the apical membrane act as the main portal of entry, calbindin-D28K delivers Ca2+ in the cytoplasm, and then Na2+/Ca2+ exchanger (NCX1) and plasma membrane Ca2+-ATPase in the basolateral membrane serve as an exit. In the cortical collecting duct, TRPV6 is expressed, but the role might be negligible. In addition to PTH and 1,25(OH)2D3, acid-base disturbance, diuretics, and estrogen effect on these calcium channels. Recently, klotho and fibroblast growth factor 23 (FGF23) are suggested as new players in the calcium metabolism. Klotho is exclusively expressed in the kidney and co-localized with TRPV5, NCX1, and calbindin-D28K. Klotho increases calcium reabsorption through trafficking of TRPV5 to the plasma membrane, and also converts FGF receptor to the specific FGF23 receptor. FGF23: klotho complex bound to FGF receptor inhibits 1α-hydroxylase of vitamin D, and contributes to calcium reabsorption and phosphate excretion in the kidney.