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DEPARTMENT: MEDICINE AND SURGERY

LEVEL: 300L

COURSE: RENAL PHYSIOLOGY

1. ***Discuss the role of kidney in glucose homeostasis.***

The kidneys are involved in maintaining glucose homeostasis through three different mechanisms:

- Gluconeogenesis
- Glucose uptake from the blood for its own energy requests
- 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-6phosphatase 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-h overnight fast, approximately 10kg/min of 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-6phosphatase, 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.

GLUCOSE REABSORPTION

In addition to their important role in gluconeogenesis, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. Under normal conditions, 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 m2 in healthy adults and children, and corresponds to a plasma glucose level of approximately 200 mg/dL. Once the TmG is reached and transporters are unable to reabsorb all the glucose (as in type 2 diabetes mellitus), glycosuria occurs.

2. Discuss the process of micturition.

Micturition is the process by which urinary bladder empties when filled. The main physiological events in the process of micturition are:

- Filling of urinary bladder
- Emptying of urinary bladder.

FILLING OF URINARY BLADDER

Transport of urine into urinary bladder through ureters

As urine collects in the renal pelvis, the pressure in the pelvis increases and initiates a peristaltic contraction beginning in the pelvis and spreading along the ureter to force urine towards the bladder.

Capacity of the bladder

Physiological capacity of the bladder varies with age, being 20–50 mL at birth, about 200 mL at 1 year, and can be as high as 600 mL in young adult males. In all cases, the physiological capacity is about twice that at which the first desire to void is felt.

Volume and pressure changes in bladder during filling

The normal bladder is completely empty at the end of micturition and the intravesical pressure is equal to the intraabdominal pressure. As the bladder is filled up, it adjusts its tone and a fairly large volume of urine can be accommodated with minimal alterations in the intravesical pressure. This is possible because of the phenomenon of adaptation. The adaptation occurs because of the inherent property of plasticity, the smooth muscles of detrusor and because of law of Laplace.

Cystometry

This refers to the process of studying the relationship between the intravesical volume and pressure, the cystometrogram refers to a graphical record of this relationship.

Normal cystometrogram shows three phases of filling:

Phase Ia

It is the initial phase of filling in which pressure rises from 0 to 10 cm H2O, when about 50 mL of fluid is collected in the bladder.

Phase Ib

It is the phase of plateau which lasts till the bladder volume is 400 mL. During this phase, the pressure in the bladder does not change much and remains approximately at 10 cm H2O. This is because of adaptation of urinary bladder by relaxation.

Phase II

This phase starts beyond 400 mL volume when the pressure begins to rise markedly, triggering the micturition reflex. Normally, the voiding contraction raises the intravesical pressure by about 20–40 cm H2O. If voiding is avoided (not initiated), the pressure rises from 10 cm H2O onward. Beyond 600 mL, the urge to void urine becomes almost unbearable.

EMPTYING OF THE BLADDER

Emptying of the bladder is basically a reflex action called the micturition reflex, which is controlled by supraspinal centres and is assisted by contraction of perineal and abdominal muscles. Therefore, emptying of the urinary bladder focuses on:

- Micturition reflex
- Voluntary control of micturition
- Role of perineal and abdominal muscles in micturition.

Micturition reflex

Initiation: Micturition reflex is initiated by the stimulation of the stretch receptors located in the wall of urinary bladder.

Stimulus: Filling of bladder by 300–400 mL of urine in adults constitutes the adequate stimulus for the micturition reflex to occur.

Afferents: The afferents from the stretch receptors in the detrusor muscle and urethra travel along the pelvic splanchnic nerves and enter the spinal cord through dorsal roots to S2, S3 and S4 segments to reach the sacral micturition centre. Sacral micturition centre is formed by the sacral detrusor nucleus and sacral pudendal nucleus.

Efferents: Efferents arising from the sacral detrusor nucleus are the preganglionic parasympathetic fibres, which relay in the ganglia near or within bladder and urethra. The post-ganglionic parasympathetic fibres are excitatory to the detrusor muscle and inhibitory to the internal sphincter.

Response: Once micturition reflex is initiated, it is selfregenerative, i.e. initial contraction of the bladder wall further activates the receptors to increase the sensory impulses (afferents) from the bladder and urethra which cause further increase in the reflex contraction of detrusor muscle of the bladder. The cycle thus keeps on repeating itself again and again until the bladder has reached a strong degree of contraction. Once the micturition reflex becomes powerful enough, this causes another reflex which passes through pudendal nerves to external sphincter to cause its inhibition. If this inhibition is more

potent than the voluntary constrictor signals from brain, then urination will not occur. If not so, urination will not occur unless the bladder fills still more and micturition reflex becomes more powerful.

APPLIED PHYSIOLOGY

Nocturnal micturition: Nocturnal micturition is the involuntary voiding of urine during night. It is otherwise known as enuresis or bedwetting. It occurs due to the absence of voluntary control of micturition. It is a common and normal process in infants and children below 3 years. It is because of incomplete myelination of motor nerve fibers of the bladder. When myelination is complete, voluntary control of micturition develops and bedwetting stops.

If nocturnal micturition occurs after 3 years of age it is considered abnormal. It occurs due to neurological disorders like lumbosacral vertebral defects. It can also occur due to psychological factors. Loss of voluntary control of micturition occurs even during the impairment of motor area of cerebral cortex.

3. *Explain juxtaglomerular apparatus*.

Juxtaglomerular (JG) apparatus as the name indicates refers to the collection of specialised cells located very near to the glomerulus. It forms the major component of renin–angiotensin–aldosterone system. The JG apparatus comprises three types of cells:

- Juxtaglomerular cells
- Macula densa cells
- Extraglomerular mesangial cells.

JUXTAGLOMERULAR CELLS

JG cells are specialised myoepithelial (modified vascular smooth muscle) cells located in the media of the afferent arteriole in the region of JG apparatus.

Characteristic features of JG cells are:

I. They have well-developed Golgi apparatus and endoplasmic reticulum, abundant mitochondria and ribosomes.
II. They synthesize, store and release an enzyme called renin. Renin is stored in the secretory granules of JG cells and, therefore, these are also called granular cells.
III. They act as baroreceptors (tension receptors) and respond to changes in the transmural pressure gradient between the afferent arterioles and the interstitium.
IV. They are densely innervated by the sympathetic nerve fibres and release their renin content in response to the sympathetic discharge.
V. As these cells act as vascular volume receptors, they monitor renal perfusion pressure and are stimulated by hypovolaemia or decreased renal perfusion pressure.

MACULA DENSA CELLS

Macula densa cells refer to the specialised renal tubular epithelial cells of a short segment of the thick ascending limb of loop of Henle which passes between the afferent and efferent arterioles supplying its glomerulus of origin.

Characteristic features of macula densa cells are:

I. They are not well adapted for reabsorption.
II. They are not innervated.
III. These cells are in direct contact with the mesangial cells and in close contact with the JG cells.
IV. They act as chemoreceptors and are stimulated by decreased NaCl concentration and thereby causing increased renin release.

MESANGIAL CELLS

Mesangial cells or lacis cells are the interstitial cells of the JG apparatus.

Characteristic features of these cells are:

I. They are in contact with both the macula densa cells (on one side) and JG cells (on the other side).
II. Functionally, these cells possibly relay the signals from macula densa to the granular cells after modulating the signals. In this way, a decreased intraluminal Na+ load, Cl– load, or both in the region of macula densa stimulates the JG cells to secrete renin.
III. They also show granulation to secrete renin in conditions of extreme hyperactivity.
IV. They also secrete various substances and take up immune complexes.

FUNCTIONS OF JUXTAGLOMERULAR APPARATUS

Primary function of juxtaglomerular apparatus is the secretion of hormones (renin and prostaglandins). It also regulates the glomerular blood flow and glomerular filtration rate.

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. Kidneys regulate arterial blood pressure by two ways:

- Regulation of ECF volume
- Through renin-angiotensin mechanism.

BY 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.

RENIN-ANGIOTENSIN SYSTEM

Renin is produced by the juxtaglomerular apparatus of the kidney.When arterial pressure falls, renin which is released into the blood where it acts on a specific plasma protein produced by the liver, angiotensinogen. It converts it to angiotensin I which has slight vasoconstrictor properties but not enough to cause significant changes in circulatory function. Angiotensin converting enzyme (ACE) in the lungs then acts on angiotensin I to form angiotensin II. Angiotensin II is an extremely powerful vasoconstrictor that persists in blood only for 1 or 2 minutes because it is rapidly inactivated by angiotensinases present in blood and tissues. Its actions are:

I. **On blood vessels:**
   - It acts directly on blood pressure by acting on blood vessels and causing intense vasoconstriction of arterioles and mild vasoconstriction in veins; this is so that there is increased venous return of blood to the heart for it to pump against the increasing pressure. This causes increase in total peripheral resistance therby raising arterial pressure.
   - It acts indirectly by increasing release of norepinephrine by post-ganglionic sympathetic fibers. Norepinephrine is a general vasoconstrictor.

II. **On adrenal cortex:** It stimulates zona glomerulosa to secrete aldosterone which acts on renal tubules and increases retention of sodium and hence, water. This leads to increase in blood volume and therefore, increase in blood pressure.

III. **On Kidneys:**
   - It regulates glomerular filtration rate by constricting the efferent arteriole which causes decrease in filtration after initial release and contracting the glomerular mesangial cells leading to a decrease in surface area of glomerular capillaries and filtration.
   - It increases sodium reabsorption from renal tubules leading to increase in blood volume and then blood pressure. This is mostly in proximal tubules.

IV. **On brain:**

- It inhibits the baroreceptor reflex which is responsible for decreasing blood pressure.
- It increases water intake by stimulating thirst center.
- It increases corticotropin- releasing hormone (CRH) secretion from hypothalamus leading to increases adenocorticotropic hormone secretion from pituitary.
- It increases antidiuretic hormone secretion from hypothalamus to cause water retention by kidneys.

5. Discuss the role of kidney in calcium homeostasis.

Kidneys play an important role in regulating blood calcium by activating 1,25-dihydroxycalciferol into vitamin D which is necessary for normal calcium deposition in bone and calcium resorption by gastrointestinal tract. Also in terms of excretion, in humans who have a GFR of 170 litres per 24 hours, roughly 10 g of calcium is filtered per day. The amount of calcium excreted in the urine usually ranges from 100 to 200 mg per 24 hours; hence, 98%–99% of the filtered load of calcium is reabsorbed by the renal tubules. Approximately 60%–70% of the filtered calcium is reabsorbed in the proximal convoluted tubule, 20% in the loop of Henle, 10% by the distal convoluted tubule, and 5% by the collecting duct. The terminal nephron, although responsible for the reabsorption of only 5%–10% of the filtered calcium load, is the major site for regulation of calcium excretion.