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QUESTIONS

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

ANSWERS

1) ROLE OF KIDNEY IN GLUCOSE HOMEOSTASIS

Kidneys play a role in glucose homeostasis by reabsorbing all the filtered glucose, an adaptive mechanism that ensures sufficient energy is available during fasting periods.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.

A) THE RENAL GLUCONEOGENESIS

i) *Post Absorptive Phase*:

After a 14- to 16-h overnight fast, glucose is released into the circulation at a rate of approximately 10 μmol/(kg min). Approximately 50% of this is the result of the breakdown of glycogen (glycogenolysis) stored in the liver and the other half is because of the production of new glucose molecules from precursors such as lactate, glycerol, alanine and other amino acids (gluconeogenesis) by liver and kidneys. The kidney is unable to release glucose through glycogenolysis because it contains very little glycogen and those renal cells that are able to synthesise glycogen lack the enzyme glucose-6-phosphatase and therefore cannot release glucose. In humans, only the liver and kidney contain significant amounts of the enzyme glucose-6-phosphatase and therefore are the only organs that are able to perform gluconeogenesis. Research over the last 15–20 years has established that the human liver and kidneys provide about equal amounts of glucose via gluconeogenesis in the post-absorptive state . Consequently, after an overnight fast, 75–80% of glucose released into

the circulation derives from the liver and the remaining 20–25% derives from the kidneys. As the duration of fasting increases, glycogen stores in the liver become further depleted until, after 48 h, virtually all the glucose released into the circulation is derived from gluconeogenesis. Consequently, as the length of fast increases, the proportion of overall glucose release accounted for by renal gluconeogenesis increases.

NOTE: The kidney and the liver differs in their glycogenic precursors and the effect of hormones in their release of glucose.

ii) *Post Prandial State*:

Postprandial glucose levels are critically influenced by insulin and glucagon levels

B) RENAL GLUCOSE UTILIZATION

In the post-absorptive setting after an overnight fast, the kidneys utilise approximately 10% of all glucose utilised by the body. After meal ingestion their glucose utilisation increases in an absolute sense. In terms of whole-body glucose economy, normally approximately 45% of ingested glucose is thought to be converted to glycogen in the liver, approximately 30% is taken up by skeletal muscle and later converted to glycogen, approximately 15% is taken up by the brain, approximately 5% is taken up by the adipose tissue and approximately 10% is taken up by the kidneys

The metabolic fate of glucose is different in different regions of the kidney. Because of its low oxygen tension, and low levels of oxidative enzymes, the renal medulla is an obligate user of glucose for its energy requirement and does so anaerobically. Consequently, lactate is the main metabolic end product of glucose taken up in the renal medulla, not carbon dioxide (CO_2) and water. In contrast, the renal cortex has little glucose phosphorylating capacity but a high level of oxidative enzymes. Consequently, this part of the kidney does not take up and use very much glucose, with oxidation of Free FattyAcids acting as the main source of energy. A major energy-requiring process in the kidney is the reabsorption of glucose from glomerular filtrate in the proximal convoluted tubule.

C) RENAL GLUCOSE REABSORPTION

In addition to releasing glucose into the circulation by synthesising new glucose molecules via gluconeogenesis and its utilisation of glucose, the kidney can also influence glucose homeostasis by returning glucose to the circulation via the reabsorption of glucose from glomerular filtrate. Renal

reabsorption is the primary way in which the kidney influences glucose homeostasis.
Reabsorption of glucose from glomerular filtrate occurs by means of sodium–glucose co-transporters (SGLTs) in the proximal convoluted tubulae.
SGLT2 is thought to be located exclusively on the luminal surface of the epithelial cells lining the S1 and S2 segments of the proximal tubule. Transport of sodium and glucose by SGLT2 occurs in a 1:1 ratio. The remaining approximately 10% of glucose reabsorption is mediated by SGLT1, a high-affinity, low-capacity glucose/galactose transporter protein; sodium:glucose coupling ratio = 2:1) located on the luminal surface of epithelial cells lining the S3 segment of the proximal tubule. SGLT1 is also extensively expressed in the small intestine and in other tissues. Glucose reabsorbed from the proximal tubules by SGLTs is then released into the circulation through the action of facilitative glucose transporters (GLUTs) at the basolateral membrane of the epithelial cells lining the proximal tubules (GLUT2 in the S1/2 segments and GLUT1 in the S3 segment). SGLT-mediated glucose transport is an active process, moving glucose against a concentration gradient, utilising energy derived from the sodium electrochemical potential gradient across the brush border membrane and maintained by the transport of intracellular sodium into the blood via sodium:potassium adenosine triphosphatase (ATPase) pumps at the basolateral membrane. In contrast, GLUTs facilitate passive transport (equilibration) of glucose across membranes and do not require an energy source.
Reabsorption of filtered glucose also increases linearly until the maximal reabsorptive capacity is exceeded. This is often referred to as the renal threshold and equates to a filtration rate of 260–350 mg/min per 1.73 m2, which occurs at plasma glucose concentrations of 11.0 mmol/l in healthy adults Above this plasma glucose concentration, the percentage of filtered glucose that is reabsorbed decreases and the percentage of the filtered load of glucose that is excreted in the urine increases, resulting in GLUCOSORIA.

2) **PROCESS OF MICTURITION**

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

- 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 pre- vent urination even when the detrusor muscle contracts strongly.
- The neural controls that influence bladder structures during the phases of filling and micturition.
- 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 fibres, 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.
- 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.

- We have thus far described micturition as a local spinal reflex, but descending pathways from the brain can also profoundly influence this reflex, determining the ability to prevent or initiate micturition voluntarily.

- Loss of these descending pathways as a result of spinal cord damage eliminates the ability to voluntarily control micturition.
- As the bladder distends, the input from the bladder stretch receptors causes, via ascending pathways to the brain, a sense of bladder fullness and the urge to urinate. But in response to this, urination can be voluntarily prevented by activating descending pathways that stimulate both the sympathetic nerves to the internal urethral sphincter and the somatic motor nerves to the external urethral sphincter.
- In contrast, urination can be voluntarily initiated via the descending pathways to the appropriate neurons. Complex interactions in different areas in the brain control micturition. Briefly, there are areas in the brain-stem that can both facilitate and inhibit voiding. Furthermore, an area of the midbrain can inhibit voiding, and an area of the posterior hypothalamus can facilitate voiding.
- Finally, strong inhibitory input from the cerebral cortex, learned during toilet training in early childhood, prevents involuntary urination.

3) **JUXTAGLOMERULAR APPARATUS**

It refers to the collection of specialised cells located very near to the glomerulus. It forms the major component of RENIN-ANGIOTENSIN-ALDOSTERONE system. It comprises three types of cells.

- Juxtaglomerular cells
- Macula densa cells
- Mesangial cells

A) JUXTAGLOMERULAR CELLS

They are specialised myoepithelial(modified vascular Smooth muscle) cells located in the media of the afferent arteriole in the region of juxtaglomerular apparatus. They have well developed Golgi apparatus and endoplasmic reticulum, abundant mitochondria and ribosomes. They synthesise, stope and release an enzyme called renin. Renin is stored in the secretory granules of juxtaglomerular cells and therefore, these are also called GRANULAR CELLS. They act as baroreceptors(tension receptors)

and respond to changes in the transmural pressure gradient between the afferent arterioles and the interstitium. They are densely innervated by the sympathetic nerve fibres and release their renin content in response to the sympathetic discharge. As these cells act as vascular volume receptors, they monitor renal perfusion pressure and are stimulated by hypovolaemia or decreased renal perfusion pressure.

B) MACULA DENSA CELLS

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

C) MESANGIAL CELLS

They are the interstitial cells of the juxtaglomerular apparatus. They are in contact with both the macula dense cells (on one side) and juxtaglomerular cells(on the other side). Functionally, these cells positly relay the signals from macula dense to the granular cells after modulation the signals. In this way, a decreased intraluminal Na+ load, Cl- load or both in the region of macula dense stimulates the juxtaglomerular cells to secrete renin.

NOTE: The combination of macula densa and juxtaglomerular cells is known as the juxtaglomerular apparatus.

4) ROLE OF KIDNEY IN REGULATION OF BLOOD PRESSURE

The kidneys play 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 pressures natriuresis and influences the activity of various vasoactive systems such as renin-angiotensin

aldosterone system. Along with vessel morphology, blood viscosity is the renin angiotensin system or the renin angiotensin aldosterone system, a hormone system that regulates blood pressure and water balance.

The blood pressure in the body depends upon:

- The force by which the heart pumps out blood from the centricles of the heart- and this is dependent on how much the heart muscle gets stretched by the inflowing blood into the ventricles.
- The degree to which the arteries and arterioles constrictt- increases the resistance to blood flow, thus requiring a higher blood pressure.
- The volume of blood circulating round the body; if the volume is high, the ventricles get more filled, and the heart muscle gets more stretched.

The kidney influences blood pressure by

- Causing the arteries and veins to constrict
- Increasing the circulating blood volume

Specialised cells called macula dense are located in a portion of the distal tubule located near and in the wall of the afferent arteriole. These cells sense the Na in the filtrate, while the arterial cells(juxtaglomerular cells) sense the blood pressure. When the blood pressure drops, the amount of filtered Na also drops. The arterial cell sense the drop in blood pressure and the decrease in Na concentration is relayed to them by the macula densa cells. The juxtaglomerular cells then release an enzyme called Renin.

Renin converts angiotensinogen (a peptide, or amino acid derivative) into angiotensin-1. Angiotensin-1 is thereafter converted to angiotensin-2 by an angiotensin-converting enzyme (ACE), found in the lungs. Angiotensin-2 causes blood vessels to contract, the increased blood vessel constrictions elevate the blood pressure. When the volume of blood is low, arterial cells in the kidneys secrete renin directly into circulation. Plasma renin then carries out the conversion of angiotensinogen released by the liver to angiotensin-1. Angiotensin-1 is subsequently converted to angiotensin-2 by the enzyme angiotensin converting enzyme found in the lungs.

Angiotensin-2m a potent vasoactive peptide causes blood vessels to constrict, resulting in increased blood pressure. Angiotensin-2 also stimulates the secretion of the hormone aldosterone from the adrenal cortex . Aldosterone causes the tubules of the kidneys to increase the reabsorption of sodium and water into the blood. This increases the volume of fluid in the body, which also increases blood pressure. If the renin-angiotensin-aldosterone system is too active, blood pressure will be too high. Many drugs interrupt different steps in this system to lower blood pressure. These drugs are one of the main ways to control high blood pressure (hypertension), heart failure, kidney failure, and harmful effects of diabetes. It is believed that angiotensin-1 may have some minor activity, but angiotensin-2 is the major bioactive product. Angiotensin-2 has a variety of effects on the body: throughout the body, it is a potent vasoconstrictor of arterioles.

5) **ROLE OF KIDNEY IN CALCIUM HOMEOSTASIS**

Calcium balance are controlled primarily by parathyroid hormone and 1,25-$(OH)_2$D. Approximately 60% of plasma calcium is available for filtration in the kidney. The remaining plasma calcium is protein- bound or complexed with anions. Because calcium is so important in the function of every cell in the body, the kidneys have very effective mechanisms to reabsorb calcium ion from the tubular fluid. More than 60% of calcium ion reabsorption is not under hormonal control and occurs in the proximal tubule. The hormonal control of calcium ion reabsorption occurs mainly in the distal convoluted tubule and early in the cortical collecting duct. When plasma calcium is low, the secretion of parathyroid hormone (PTH) from the parathyroid glands increases. Parathyroid hormone stimulates the opening of calcium channels in these parts of the nephron, thereby increasing calcium ion reabsorption. Another important action of PTH in the kidneys is to increase the activity of the 1-hydroxylase enzyme, thus activating 25(OH)-D to 1,25-$(OH)_2$D, which then goes on to increase calcium and phosphate ion absorption in the gastrointestinal tract. About half of the plasma phosphate is ionised and is filterable. Like calcium, most of the phosphate ion that is filtered is reabsorbed in the proximal tubule. Unlike calcium ion, phosphate ion reabsorption is decreased by PTH, thereby increasing the excretion of phosphate ion.

Therefore, when plasma calcium is low, and PTH and calcium ion reabsorption are increased as a result, phosphate ion excretion is increased.