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Assignment

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?

ANSWER

1) ROLE OF KIDNEY IN GLUCOSE HOMEOSATSIS

Kidney plays an important role in glucose homeostasis, both in the post-absorptive and postprandial period. The human kidney is involved in the regulation of glucose homeostasis and in abnormalities found in diabetes mellitus via three different mechanisms: (i) release of glucose into the circulation via gluconeogenesis; (ii) uptake of glucose from the circulation to satisfy its energy needs; and (iii) reabsorption into the circulation of glucose from glomerular filtrate to conserve glucose carbon.

i. Renal gluconeogenesis

In the fasting (postabsorptive) state in healthy individuals, the kidneys contribute about 20% to 25% of the glucose released into the circulation via gluconeogenesis (15–55 g per day), with the liver responsible for the remainder via both glycogenolysis and gluconeogenesis. Renal gluconeogenesis occurs predominantly within proximal tubule cells in the renal cortex and is chiefly regulated by insulin and catecholamines (e.g., adrenaline). Insulin reduces renal gluconeogenesis directly, and also reduces the availability of gluconeogenic substrates, such as lactate, glutamine, and glycerol, thus reducing glucose release into the circulation. Adrenaline stimulates renal gluconeogenesis stimulates renal glucose release, inhibits insulin secretion, increases the supply of gluconeogenic substrates, and reduces renal glucose uptake.

In patients with T2DM, both renal and hepatic glucose release are increased as a result of increased gluconeogenesis. The relative increase in renal gluconeogenesis is thought to be substantially greater than in hepatic gluconeogenesis (300% vs 30%). Renal glycogenolysis is minimal in healthy individuals but may play a role in increased renal glucose release in patients with T2DM, due to accumulation of glycogen in diabetic kidneys.

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%. Meyer et al. 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.

ii. Uptake of glucose

In the post-absorptive setting after an overnight fast, the kidneys utilize approximately 10% of all glucose utilized by the body. After meal ingestion their glucose utilization 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, ∼30% is taken up by skeletal muscle and later converted to glycogen, ∼15% is taken up by the brain, ∼5% is taken up by the adipose tissue and ∼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 product of glucose taken up in the renal medulla, not carbon dioxide (CO_2) and water.

iii. Renal glucose reabsorption

In addition to releasing glucose into the circulation by synthesizing new glucose molecules via gluconeogenesis and its utilization of glucose, the kidney can also influence glucose homeostasis by returning glucose to the circulation via the reabsorption of glucose from glomerular filtrate. Normally, approximately 180 l of plasma are filtered by the kidneys each day. As the average plasma glucose concentration throughout a 24-h period is ∼5.5 mmol/l (100 mg/dl), ∼180 g of glucose is filtered by the kidneys each day. In healthy individuals, virtually all of this is reabsorbed into the circulation and the urine is essentially free from glucose. To put this into perspective, in each day, the kidneys produce 15–55 g glucose via gluconeogenesis and metabolize 25–35 g glucose. Therefore, in terms of glucose economy, renal reabsorption is the primary mechanism by which the kidney influences glucose homeostasis. Alterations in renal tubular glucose reabsorption may therefore be expected to have a considerable impact on glucose homeostasis.

Reabsorption of glucose from glomerular filtrate occurs by means of sodium–glucose co-transporters (SGLTs) in the proximal convoluted tubule. SGLT2 is a high-capacity, low-affinity glucose transporter (GLUT) located in the early convoluted segment (S1) of the proximal tubule, where luminal glucose is abundant. The SGLT2 transporter mediates 90% of renal glucose reabsorption by coupling glucose transport to the electrochemical sodium gradient.

First, sodium is absorbed across the luminal cell membrane, creating an energy gradient that permits glucose to passively enter the cell. Then, an adenosine triphosphatase (ATPase)-mediated sodium–potassium pump returns the sodium to the bloodstream. This exchange alters the concentration gradient within the cell, and glucose diffuses to the basolateral GLUT2, through which it passes back into the bloodstream

The other 10% of renal glucose reabsorption occurs through SGLT1, a high-affinity, low-capacity transport protein that is found in the more distal, straight section of the proximal tubule (S3), where there is less luminal glucose. SGLT1 also resides in the intestine, where it is responsible for absorption of dietary glucose and galactose. Because SGLT1 resides in intestinal as well as renal tissues, and because it is not specific for glucose alone, it is not considered a viable target for therapeutic intervention. Inhibition of this transporter has the potential to cause osmotic diarrhoea and malabsorption. However, if clinically significant gastrointestinal side effects are not observed, combined SGLT2/SGLT1 inhibition remains a therapeutic option.

In the kidney, the amount of glucose reabsorbed through the SGLT1 and SGLT2 transporters is equal to the amount of glucose that is filtered by the glomerulus. Glucose reabsorption by the proximal tubule increases linearly with increasing glucose concentration, up to a theoretical threshold of approximately 11 mmol/l. At this concentration, the glucose transport system becomes saturated and all the filtered glucose in excess of this threshold is excreted in the urine. This threshold varies from nephron to nephron, because of both anatomical and physiologic heterogeneity between nephrons, and this results in slight differences in glucose reabsorption levels between individual renal tubules. Thus, the actual threshold at which glucose starts to appear in the urine is slightly below the maximum of 11 mmol/l and occurs gradually in a curvilinear slope that begins at approximately 10 mmol/l. The difference between the actual and theoretical thresholds is known as ‘splay’ in the glucose titration curve. The maximal transport rate for glucose (TmG) varies among individuals, but it has an average value of approximately 375 mg/min for healthy subjects. Like the glucose excretion threshold, the actual TmG occurs, not at a precise cut point, but in a curvilinear manner that mirrors the excretion threshold

2) PROCESS OF MICTURITION

Micturition or urination is the process of emptying urine from the storage organ, namely, the urinary bladder. It is a reflex process. However, in grown up children and adults, it can be controlled voluntarily to some extent. 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 detrusor is the smooth or involuntary muscle of the bladder wall. The urethral muscles consist of the external and internal sphincter. The internal sphincter and detrusor muscle are both under autonomic control. The external sphincter, however, is a voluntary muscle under the control of voluntary nerves.

<u>Stages of Micturition</u>

The urinary bladder has two distinct stages or phases:

- Resting or filling stage
- Emptying 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 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.

Emptying stage

When the bladder is filled with urine, the nerves in it are triggered, which in turn stimulates the need to urinate. The brain signals urinary bladder to contract. The receptors of the urinary bladder send a signal to the central nervous system, in response to which the nervous system sends a signal that incites the contraction of the urinary bladder. Through the urinary opening at the urethra, the urine is eliminated, and the process is called micturition. The neural mechanism involved is called the **micturition reflex**.

MICTURITION REFLEX

Micturition reflex is the reflex by which micturition occurs. This reflex is elicited by the stimulation of stretch receptors situated on the wall of urinary bladder and urethra. When about 300 to 400 mL of urine is collected in the bladder, intravesical pressure increases. This stretches the wall of bladder resulting in stimulation of stretch receptors and generation of sensory impulses.

Sensory signals from the bladder stretch receptors are conducted to the sacral segments of the cord through the pelvic nerves. Motor (efferent) impulses produced in spinal cord, travel through motor fibres of pelvic nerve towards bladder and internal sphincter. Motor impulses cause contraction of detrusor muscle and relaxation of internal sphincter so that, urine enters the urethra from the bladder. Once urine enters urethra, the stretch receptors in the urethra are stimulated and send afferent impulses to spinal cord via pelvic nerve fibers. Now the impulses generated from spinal centers inhibit pudendal nerve. So, the external sphincter relaxes, and micturition occurs.

Once a micturition reflex begins, it is self-regenerative, i.e. the initial contraction of bladder further activates the receptors to cause still further increase in sensory impulses from the bladder and urethra. These impulses, in turn cause further increase in reflex contraction of bladder. The cycle continues repeatedly until the force of contraction of bladder reaches the maximum and the urine is voided out completely. During micturition, the flow of urine is

facilitated by the increase in the abdominal pressure due to the voluntary contraction of abdominal muscles.

Spinal centers for micturition are present in sacral and lumbar segments. But, these spinal centers are regulated by higher centers. The higher centers, which control micturition are of two types, inhibitory centers and facilitatory centers. Centers in midbrain and cerebral cortex inhibit the micturition by suppressing spinal micturition centers. Centers in pons facilitate micturition via spinal centers. Some centers in cerebral cortex also facilitate micturition.

3) JUXTAGLOMERULAR APPARATUS

The juxtaglomerular apparatus is a specialized structure formed by the distal convoluted tubule and the glomerular afferent arteriole. It is located near the vascular pole of the glomerulus. Juxtaglomerular apparatus is formed by three different structures:

a) Macula densa:

The macula densa is a collection of specialized epithelial cells in the distal convoluted tubule that detect sodium concentration of the fluid in the tubule. In response to elevated sodium, the macula densa cells trigger contraction of the afferent arteriole, reducing flow of blood to the glomerulus and the glomerular filtration rate.

b) Extraglomerular mesangial cells

Extraglomerular mesangial 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. These cells have a contractile property like vascular smooth muscles and thus play a role in “regulating GFR” by altering the vessel diameter. Renin is also found in these cells. They also secrete prostaglandin and cytokines.

c) Juxtaglomerular cells.

Juxtaglomerular cells 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.

The juxtaglomerular cells secrete renin, and as specialised smooth muscle cells surrounding the afferent arteriole also have the capacity to affect the perfusion of the glomerulus. Although they are activated by prostaglandins released from the macula densa cells, they can also release renin independently of the macula densa. Baroreceptors found in the arterioles trigger renin secretion if there is a fall in blood pressure in the arterioles. Activation of the sympathetic nervous system can also stimulate renin release through activation of beta-1 receptors. Renin is a protease enzyme that catalyses the conversion of angiotensinogen to angiotensin I. Angiotensin I is converted into the active vasoconstrictor angiotensin II by Angiotensin Converting Enzyme (ACE) found in the kidney and largely in the lung.

4) ROLE OF KIDNEY IN BLOOD PRESSURE REGULATION

The kidney plays a central role in the regulation of long-term arterial blood pressure. The kidneys regulate blood pressure by:

a) Regulation of the ECF 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.

b) Through renin-angiotensin mechanism.

Specialized cells called macula densa 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 cells 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-2 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

The kidney is the central organ for calcium homeostasis through fine regulation of renal calcium excretion. Calcium is both filtered and reabsorbed in the kidneys but not secreted. Only about 60 percent of the plasma calcium can be filtered at the glomerulus. More than 98% of filtered calcium is reabsorbed along the renal tubules. About 50% of plasma calcium (ionized and complexed form; ultra-filterable fraction, excluding the protein bound form) is freely filtered through the renal glomerulus, and 99% of the filtered calcium is reabsorbed along renal. About 65 percent of the filtered calcium is reabsorbed in the proximal tubule, 25 to 30 percent is reabsorbed in the loop of Henle, and 4 to 9 percent is reabsorbed in the distal and collecting 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.

One of the primary controllers of renal tubular calcium reabsorption is PTH. Increased levels of PTH stimulate 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 and is independent of PTH. 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. Increased 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 alkalosis and inhibited by metabolic acidosis. Thus, acidosis tends to increase calcium excretion, whereas alkalosis tends to reduce calcium excretion. Most of the effect of hydrogen ion concentration on calcium excretion results from changes in calcium reabsorption in the distal tubule.

Kidneys play a role in the regulation of blood calcium level by also activating 1,25 dihydroxycholecalciferols into vitamin D. Vitamin D is necessary for the absorption of calcium from intestine.