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MBBS 300LVL

PHYSIOLOGY ASSIGNMENT

QUESTION 1: Discuss the role of the kidney in glucose homeostasis

The kidney has an important role in ensuring the energy needs during fasting periods. This organ has a vital role in absorbing the entire quantity of the filtered glucose. Having a glomerular filtration rate of 180 litres per day, it filters approximately 180 grams of glucose per day, bringing its contribution in maintaining normal fasting plasma glucose (FPG) levels. The reabsorption of glucose is ensured by the sodium-glucose transporter (SGLT) 2, responsible for the reabsorption of 90% of glucose, and SGLT1, that reabsorbs the remaining glucose.

The plasma glucose concentration is determined by the amount of glucose synthesized, and the one removed from the circulation and metabolized. This concentration must be maintained within a relatively narrow range despite the wide daily fluctuations in glucose ingestion and glucose demands in various tissues. Other substrates such as free fatty acids (FFAs), glycerol, lactate and ketone bodies have greater daily fluctuations. This can be explained by the need of the body to protect himself against hyper- and hypoglycaemia. Hyperglycaemia is associated with both chronic effects (such as nephropathy, retinopathy, neuropathy and premature atherosclerosis) and also acute complications (including diabetic ketoacidosis and hyperosmolar hyperglycaemic state that are associated with higher morbidity and mortality). Hypoglycaemia is also harmful because it can cause neurological events (including coma, seizures), cardiac arrhythmias and death.

The kidneys play an important role in glucose homeostasis. It helps to maintain glucose homeostasis by at least two mechanisms.

- Under normal circumstances, the kidney filters and reabsorbs 100% of glucose, approximately 180 g (1 mole) of glucose each day. The glucose transporters expressed in the renal proximal tubule ensure that less than 0.5 g/day (range 0.03-0.3 g/d) is excreted in the urine of healthy adults. More water than glucose is reabsorbed resulting in an increase in the glucose concentration in the urine along the tubule. Consequently the affinity of the transporters for glucose along the tubule increases to allow for complete reabsorption of glucose from the urine.
- It produces glucose by gluconeogenesis. The key enzymes of gluconeogenesis are phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase (G6Pase). These are expressed in the renal proximal tubule only and not the renal medulla. The kidneys produce between 2.0-2.5umol of glucose/kg/min thereby contributing about 20-25% of circulating glucose.

QUESTION 2 : Discuss the process of micturition

Micturition is a process where urine is expelled from the body. Animals and humans have a specialised system of organs known as the excretory system to eliminate the waste products from the body. In other words, the process of expelling urine from the body is called micturition. It is brought about by reflex contraction of a special muscle called the detrusor muscle after voluntary relaxation of the sphincter muscle. The human excretory system consists of a pair of kidneys and ureters, a urinary bladder, and a urethra. The kidneys play a major role in the process of urine formation and its excretion. The urine formed is stored in the urinary bladder.

Micturition is also known as voiding phase of bladder control and lasts for a short time. As the bladder becomes full, the stretch receptors increase their firing rate. This increase the urge to urinate and causes micturition reflex. It sometimes even causes involuntary urination.

Micturition Process

Micturition process consists of two phases:

- Storage phase
- Voiding phase

Storage Phase

The urinary bladder is a balloon-shaped, hollow, muscular, organ that acts as the storage organ for urine. The urinary bladder in a healthy urinary system can store up to 16 ounces of urine for 2 to 5 hours easily. The circular sphincter muscles prevent leakage of urine. They close tightly around the opening of the bladder into the tube (urethra) that allows the passage of urine outside the body.

Voiding Phase

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.

Bladder Emptying and the 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.

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.

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 (pontine micturition Centre) 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.

Problems Associated With Micturition

There are several factors which affect the process of micturition. Some of these can be due to physical trauma or disease; others are psychological in nature. Following are a few disorders that affect micturition:

- Detrusor Instability – This is a condition where the detrusor muscle contracts without any apparent reason. This muscle is responsible for contracting the bladder and help with the micturition process. As a result, detrusor instability results in urinary incontinence.
- Urinary Retention – This condition is characterized by the inability to empty the bladder completely. The onset may be gradual or sudden. The causes can range from a blockage in the urethra, nerve problems and weak bladder muscles.
- Spinal Cord Trauma – Injuries to the spinal cord, specifically the tenth thoracic vertebra (T10) can cause the bladder to be overactive or cause urinary incontinence.

QUESTION 3: Explain the 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 and its main function is to regulate blood pressure and the filtration rate of the glomerulus. The cells of the JGA include:

- macula densa
- juxtaglomerular cells
- extra glomerular mesangial cells

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.

The juxtaglomerular cells, derived from smooth muscle cells, of the afferent arteriole secrete renin when blood pressure in the arteriole falls. Renin increases blood pressure via the renin-angiotensin-aldosterone system.

Lacis cells, also called extraglomerular mesangial cells, are flat and elongated cells located near the macula densa. Their function remains unclear.

QUESTION 4: Discuss the role of the 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 pressure natriuresis, and influences the activity of various vasoactive systems such as the renin–angiotensin–aldosterone (RAS) system. Along with vessel morphology, blood viscosity is one of the key factors influencing resistance and hence blood pressure. A key modulator of blood viscosity is the renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS), 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 ventricles 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 constrict-- 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

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-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.

QUESTION 5: Discuss the role of the kidney in calcium homeostasis

The kidney is critically important in calcium homeostasis. Under normal blood calcium concentrations, almost all of the calcium that enters glomerular filtrate is reabsorbed from the tubular system back into blood, which preserves blood calcium levels. If tubular reabsorption of calcium decreases, calcium is lost by excretion into urine.

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 actually reabsorbed along renal 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. PTH and activated vitamin D

enhance calcium reabsorption in the thick ascending limb (TAL), distal convoluted tubule (DCT) and/or connecting tubule (CNT), and oestrogen promotes calcium absorption in the DCT/CNT1, 2). Acidosis contributes to hypercalciuria by reducing calcium reabsorption in the proximal tubule (PT) and DCT, and alkalosis vice versa3).

Diuretics like thiazide and furosemide also alter calcium absorption in the renal tubules; thiazide promotes calcium reabsorption and furosemide inhibits it. Plasma calcium itself also controls renal calcium absorption through altered PTH secretion as well as via binding to the calcium sensing receptor (CaSR) in the TAL. To facilitate Ca2+ reabsorption along renal tubules;

(I) Voltage difference between the lumen and blood compartment should be favourable for Ca2+ passage, i.e., a positive voltage in the lumen

(ii) Concentration difference should be favourable for Ca2+ passage with a higher Ca2+ concentration in the lumen

(iii) An active transporter should exist if the voltage or concentration difference is not favourable for Ca2+ reabsorption.

Each renal tubular segment has a different Ca2+ concentration difference or voltage environment for its unique mechanism for calcium reabsorption.