Physiology

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Question 1

Discuss the role of kidney in glucose homeostasis.

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.

The human liver and kidneys release approximately equal amounts of glucose via gluconeogenesis in the post-absorptive state. In the postprandial state, although overall endogenous glucose release decreases substantially, renal gluconeogenesis increases by approximately twofold. Glucose utilization by the kidneys after an overnight fast accounts for ~ 10% of glucose utilized by the body. Following a meal, glucose utilization by the kidney increases. Normally each day, ~ 180 g of glucose is filtered by the kidneys; almost all of this is reabsorbed by means of sodium–glucose co-transporter 2 (SGLT2), expressed in the proximal tubules. However, the capacity of SGLT2 to reabsorb glucose from the renal tubules is finite and, when plasma glucose concentrations exceed a threshold, glucose appears in the urine. Handling of glucose by the kidney is altered in Type 2 diabetes mellitus (T2DM): renal gluconeogenesis and renal glucose uptake are increased in both the post-absorptive and postprandial states, and renal glucose reabsorption is increased. Specific SGLT2 inhibitors are being developed as a novel means of controlling hyperglycaemia in T2DM.

Question 2

Discuss 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. 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.

Stages of Micturition

The urinary bladder has two distinct stages or phases:

Resting or filling stage

Voiding 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 oblique placement of the ureters in the bladder wall serves a very important function. The opening of the ureter into the urinary bladder is not guarded by any sphincter or muscle. Therefore, this oblique nature of opening prevents the urine from re-entering the ureters. At the same time, the main muscle of the urinary bladder, the detrusor muscle, is relaxing allowing the bladder to distend and accommodate more urine.

Voiding Stage

During this stage, both the urinary bladder and the urethra come into play together. The detrusor muscle of the urinary bladder which was relaxing so far starts to contract once the bladder's storage capacity is reached.

The urethra is controlled by two sets of muscles: The internal and external urethral sphincters. The internal sphincter is a smooth muscle whereas the external one is skeletal. Both these sphincters are in a contracted state during the filling stage.

Physiology of Micturition

As mentioned earlier, the process of micturition is governed by both the nervous and muscular systems. Within the nervous system, the process is governed by the autonomous nervous system and the somatic system. Once the urinary bladder reaches its maximum capacity, the stretch receptors in the walls of the bladder send an impulse via the pelvic nerve to the brain via the spinal cord.

The micturition reflex is ultimately generated from the level of the spinal cord after it receives reflexes from the pontine region in the brain. Once the bladder and the urethra receive the signals to empty the bladder, the two sphincters relax and the detrusor muscle causes the contractions of the bladder.

Along with these muscles, the muscles of the abdomen also play a role by putting pressure on the bladder wall. This leads to complete emptying of the bladder.

Question 3

Discuss the juxtaglomerular apparatus

The juxtaglomerular apparatus of the kidney serves as a intrarenal baroreceptor that is composed of four basic elements: the terminal portion of the afferent arteriole, the macula densa (a segment of the distal tubule), the extraglomerular mesangial region, and the efferent arteriole at the glomerulus.

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

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.

Because of its location in the nephron, it is highly sensitive to changes in volume as induced by various diuretic classes, and thus it is sensitive to changes in kidney perfusion pressure. The juxtaglomerular apparatus is also known to be adrenergically innervated, and has β-1 adrenoreceptors.

Sympathetic stimulation or decreases in volume or perfusion pressure can all stimulate the juxtaglomerular apparatus response to release renin into the afferent arteriole. Renin then converts angiotensinogen, which is formed in the liver, to angiotensin I. Angiotensin-converting enzyme converts angiotensin I to angiotensin II, which is a potent vasoconstrictor and stimulates secretion of aldosterone from the adrenal cortex. Most beta-blockers used clinically can cause adverse hemodynamic alterations in the kidney, including a decline in kidney blood flow and GFR, and a reduction of renin release with a subsequent antinatriuretic response, most prominently with upright posture. However, neither nebivolol nor carvedilol appears to have adverse effects on renal hemodynamics.

Question 4

Discuss the role of kidney in the regulation of blood pressure.

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 kidney in calcium homeostasis

About 50% of plasma calcium (ionized and complexed form; ultrafilterable 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 (Table 1). 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 estrogen 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 it4, 5). 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 Ca^{2+} reabsorption along renal tubules; (i) voltage difference between the lumen and blood compartment should be favorable for Ca^{2+} passage, i.e., a positive voltage in the lumen; (ii) concentration difference should be favorable for Ca^{2+} passage with a higher Ca^{2+} concentration in the lumen; (iii) an active transporter should exist if the voltage or concentration difference is not favorable for Ca^{2+} reabsorption. Each renal tubular segment has a different Ca^{2+} concentration difference or voltage environment for its unique mechanism for calcium reabsorption.