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Question
Assignment

Q1. Discuss the role of kidney in glucose homeostasis?

The kidneys' contributions to maintaining glucose homeostasis are significant and include such functions as release of glucose into the circulation via, uptake of glucose from the circulation to satisfy their energy needs, and reabsorption of glucose at the level of the proximal tubule. Renal release of glucose into the circulation is the result of glycogenolysis and gluconeogenesis, respectively involving the breaking down and formation of glucose-6-phosphate from precursors (eg, lactate, glycerol, amino acids). With regard to renal reabsorption of glucose, the kidneys normally 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. The process of renal glucose reabsorption is mediated by active (sodium-coupled glucose cotransporters) and passive (glucose transporters) transporters.

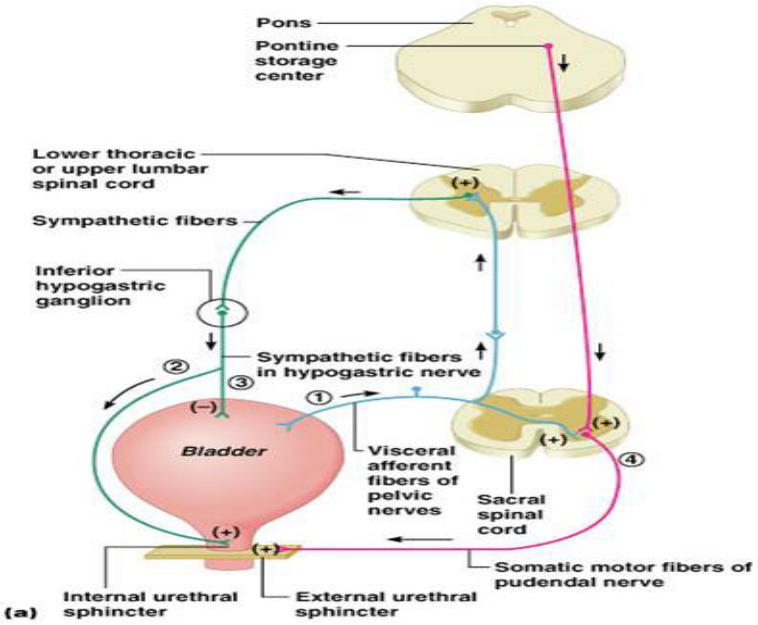
CLINICAL SIGNIFICANCE

In hyperglycemia, the kidneys may play an exacerbating role by reabsorbing excess glucose, ultimately contributing to chronic hyperglycemia, which in turn contributes to chronic glycemic burden and the risk of microvascular consequences.

Q2. 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 process of micturition is regulated by the nervous system and the muscles of the bladder and urethra. At its most basic level, micturition is a simple reflex which is displayed by infants who are not toilet-trained and aged individuals who have lost voluntary control of the process.

When the volume of urine in the bladder reaches about 250ml in children and about 350ml in adults, stretch receptors in the bladder walls are stimulated and excite sensory parasympathetic fibres which relay information to the sacral area of the spine. This information is integrated in the spine and relayed to two different sets of neurones. Parasympathetic motor neurones are excited and act to contract the detrusor muscles in the bladder so that bladder pressure increases and the internal sphincter opens. At the same time, somatic motor neurones supplying the external sphincter via the pudendal nerve are inhibited, allowing the external sphincter to open and urine to flow out, assisted by gravity.



Control of micturition

Children and adults have considerable control over when and where they pass urine. They can also increase or decrease the rate of flow and even stop and start again, so micturition is clearly more than just a simple reflex. This control is learnt in infancy and involves other sensory fibres in the bladder wall. These fibres convey information on the degree of bladder fullness via the spine to the higher centres of the brain, the thalamus and cerebral cortex.

The brain is able to override the micturition reflex by inhibiting the parasympathetic motor nerve fibres to the bladder and reinforcing contraction of the external sphincter. The internal sphincter will not open until the external sphincter does.

The increase in bladder volume increases stretch receptor and nerve activity, making the sensation of pressure more acute. When it is convenient, the brain centres remove the inhibition and permit micturition under our conscious control. When the bladder contains about 500ml, pressure may force open the internal sphincter; this in turn forces open the external sphincter and urination occurs whether it is convenient or not.

We can increase the rate of urine flow by contraction of the abdominal muscles and by the performance of Valsalva's manoeuvre (forced expiration against a closed glottis). Contraction of the strong pelvic floor muscles can stop urine in mid-flow. The sound of running water also encourages micturition

After micturition, less than 10ml of urine remains in the bladder and the cycle begins again.

CLINICAL SIGNIFICANCE

-Urinary incontinence- Loss of bladder control, varying from a slight loss of urine after sneezing, coughing or laughing, to complete inability to control urination.

Q3. Explain juxtaglomerular apparatus?

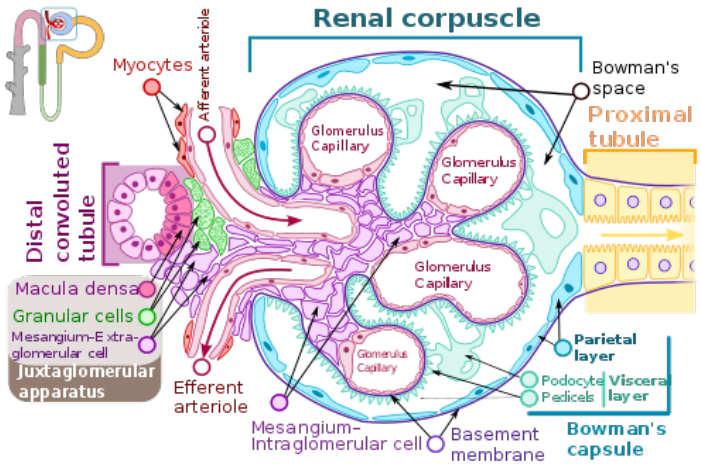
The juxtaglomerular apparatus (also known as the juxtaglomerular complex) is a structure in the kidney that regulates the function of each nephron, the functional units of the kidney. The juxtaglomerular apparatus is part of the kidney nephron, next to the glomerulus. It is found between afferent arteriole and the distal convoluted tubule of the same nephron. This location is critical to its function in regulating renal blood flow and glomerular filtration rate.

The juxtaglomerular apparatus consists of three types of cells:

-the macula densa, a part of the distal convoluted tubule of the same nephron

-juxtaglomerular cells, (also known as granular cells) which secrete renin

-extraglomerular mesangial cells



JUXTAGLOMERULAR CELLS

Renin is produced by juxtaglomerular cells. These cells are similar to epithelium and are located in the tunica media of the afferent arterioles as they enter the glomeruli. The juxtaglomerular cells secrete renin in response to:

-Stimulation of the beta-1 adrenergic receptor
-Decrease in renal perfusion pressure (detected directly by the granular cells)
-Decrease in NaCl concentration at the macula densa, often due to a decrease in glomerular filtration rate

EXTRAGLOMERULAR MESANGIAL CELLS

Extraglomerular mesangial cells are located in the junction between the afferent and efferent arterioles. These cells have a contractile property similar to vascular smooth muscles and thus play a role in “regulating GFR” by altering the vessel diameter.

MACULA DENSA

At the point where the afferent arterioles enter the glomerulus and the efferent arteriole leaves it, the tubule of the nephron touches the arterioles of the glomerulus from which it rose. At this location, in the wall of the distal convoluted tubule, there is a modified region of tubular epithelium called the macula densa. Cells in the macula densa respond to changes in the sodium chloride levels in the distal tubule of the nephron via the tubuloglomerular feedback (TGF) loop.

The macula densa's detection of elevated sodium chloride, which leads to an increase in GFR, is based on the concept of purinergic signaling. An increase in the salt concentration causes several cell signals to eventually cause the adjacent afferent arteriole to constrict. This decreases the amount of blood coming from the afferent arterioles to the glomerular capillaries, and therefore decreases the amount of fluid that goes from the glomerular capillaries into the Bowman's space (the glomerular filtration rate (GFR)).

When there is a decrease in the sodium concentration, less sodium is reabsorbed in the macular densa cells. The cells increase the production of nitric oxide and Prostaglandins to vasodilate the afferent arterioles and increase renin release.

CLINICAL SIGNIFICANCE

Excess secretion of renin by the juxtaglomerular cells can lead to excess activity of the renin–angiotensin system, hypertension and an increase in blood volume.

Q4 Discuss the 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 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-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.

CLINICAL SIGNIFICANCE

If the renin-angiotensin-aldosterone system is too active, blood pressure will be too high and would result to hypertension.

Q5. Discuss the role of Kidney in Calcium homeostasis?

The kidney has been known as the central organ for calcium homeostasis through fine regulation of renal calcium excretion.

The ionized calcium is tightly regulated by hormones like parathyroid hormone (PTH), 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), calcitonin, and calcium itself. The kidney, intestine, and bone are the main target organs of these regulators, and the kidney plays a key role in the fine regulation of calcium excretion.

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. 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.

1. 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 versa,
3. Diuretics like thiazide and furosemide also alter calcium absorption in the renal tubules; thiazide promotes calcium reabsorption and furosemide inhibits it,
4. 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 favorable for Ca2+ passage, i.e., a positive voltage in the lumen;
   II. concentration difference should be favorable 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 favorable for Ca2+ reabsorption. Each renal tubular segment has a different Ca2+ concentration difference or voltage environment for its unique mechanism for calcium reabsorption.

   CLINICAL SIGNIFICANCE

-Hypocalcemia is defined as a total serum calcium concentration < 8.8 mg/dL (< 2.20 mmol/L) in the presence of normal plasma protein concentrations.
-If urine calcium levels are too high or too low, it's a sign of a medical condition, such as kidney disease or kidney stones. Kidney stones are hard, pebble-like substances that can form in one or both kidneys when calcium or other minerals build up in the urine. Most kidney stones are formed from calcium.