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Question 1) Discuss the role of kidney in glucose homeostasis?

The kidneys are essentially designed to filter large quantities of plasma, reabsorb substances that the body must conserve and secrete substances that must be eliminated. These basic functions are critical to regulation of fluid and electrolyte balance, body fluid osmolality, acid-based balance, excretion of metabolic waste and foreign chemicals, arterial pressure, hormone secretion and most relevant to this discussion, glucose balance.

The kidneys' contribution to maintaining glucose homeostasis are significant and include such functions as release of glucose into the circulation. 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.

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 the cell membranes within the proximal convoluted tubules. If the capacity of the glucose is exceeded, glucose appears in the urine. The process of renal glucose reabsorption is mediated by active and passive transporters.

MECHANISM OF GLUCOSE HOMEOSTASIS IN THE KIDNEYS.

With respect to renal involvement in glucose homeostasis, the primary mechanisms include release of glucose into the circulation by gluconeogenesis,

uptake of glucose from the circulation to satisfy the kidneys' energy needs and reabsorption of glucose at the level of the proximal tubule.

1) Glycogenolysis and Gluconeogenesis:

Renal release of glucose into the circulation is the result of glycogenolysis and gluconeogenesis. GLYCOGENLOSIS involves the breakdown of glycogen to glucose-6-phosphate from precursors (examples; lactate, glycerol, amino acids) and its subsequent hydrolysis to free glucose. Conversely, GLUCONEOGENSIS involves the formation of glucose-6-phosphate from those same precursors and subsequent conversion to free Glucose.

Glucose release is limited to the renal cortex and so, the cells possess gluconeogenic enzymes (including glucose-6-phosphatase), and therefore can make and release glucose into the circulation. These cells also have little phosphorylating capacity, they cannot synthesize glycogen.

The magnitude of renal glucose release in humans is somewhat unclear, with inconclusive evidence regarding the contribution of the kidneys to total body gluconeogenesis. Based on the assumption that gluconeogenesis accounts for approximately half of all circulatory glucose release during fasting state, renal gluconeogenesis is projected, although not conclusively proven to potentially be responsible for approximately 40% of all gluconeogenesis.

2) Glucose Reabsorption

In addition to their important role in gluconeogenesis, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. Under normal conditions, the kidneys 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.

The maximum capacity, known as the tubular maximum for glucose ranges from 260 to 360mg/min/1.73m2 in healthy adults and children and corresponds to a plasma glucose level approximately 200mg/dL. If the capacity of these transporters is exceeded, glucose appears in the urine (glucosuria).

Glucosuria may also occur at lower plasma glucose concentrations in certain conditions of hyper-filtration (eg; pregnancy), but as a consequence of hyper-filtration rather that significant hyperglycemia.

3) Renal Glucose Transporter

The transport of glucose into and across cells is dependent on specialized carrier proteins in 2 gene families:

- The facilitated glucose transporters (GLUT)and
- Sodium-coupled glucose co-transporters (SGLTs).

These transporters control glucose transport and reabsorption in several tissue types, including the proximal renal tubule, small intestine, blood-brain barrier and peripheral tissue. GLUTs are involved in the passive transport of glucose across cell membranes, facilitating its downhill movement as it equilibrates across a membrane.

SGLTs on the hand, mediate active transport of glucose against a concentration gradient by means of cotransport with sodium. Of the various SGLT proteins expressed in the kidney, SGLT2 I is responsible for reabsorbing 90% of the glucose filtered at the glomerulus. Also, of the various GLUT proteins expressed in the kidneys, GLUT2 is the major transporter, releasing into circulation the glucose reabsorbed by the SGLTs in the proximal tubular cells.

GLUT2 is a widely distributed facilitative glucose transporter that has a key role in glucose homeostasis through its involvement in intestinal glucose uptake, renal reabsorption of glucose, glucosensing in the pancreas and hepatic uptake and release of glucose.

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 process of micturition is regulated by the nervous system and 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 phase
- Voiding stage

Resting or Filling stage: It is in this phase of the bladder that the urine is transported from the kidneys through the ureters into the bladder. The ureters are thin muscular tubes that arise from each of the kidneys and extends 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 ureter. 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 sphincter is a skeletal muscle. Both these sphincters are in a contacted state during the filling state.

When the volume of urine in the bladder reaches about 250ml, stretch receptors in the bladder walls are stimulated and excite sensory parasympathetic fibers which relay information to the sacral area of the spine. His information is integrated in the spine and relayed to two different sets of neurons.

Parasympathetic motor neurons 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 neurons supplying the external sphincter through the pudendal nerve are inhibited, allowing the external sphincter to open and urine to flow out, assisted by gravity.

Urinary incontinence is referred to as the leakage of urine when one do not mean to urinate. It is a common condition with many causes and is particularly common in people with neurological condition. Neurological conditions affect the body's nervous system, involving damage to the brain, spinal cord or other nerves. Examples of some neurological disorders include stroke, Alzheimer's disease etc.

The neurotransmitter acetylcholine (ACh) is involved in the relaying of nerve signals in micturition. Ach can be blocked with a drug atropine, so the detrusor muscle will not contract and retention of urine will occur.

Question 3) Explain Juxtaglomerular apparatus?

The juxtaglomerular apparatus (JG apparatus) is a structure in the kidney that regulates the function of each nephron (the functional units of each kidney). The juxtaglomerular apparatus consists of three types of cells:

- The macula densa, a part of the distal convoluted tubule of the same nephron.
- The juxtaglomerular cell (JG cell)
- The mesangial cells
- The extraglomerular mesangial cells.

Macula Densa: Macula densa cells 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.

Characteristic features of macula densa cells are:

a) They are not well adapted for reabsorption.

b) They are not innervated.

c) These cells are in direct contact with the mesangial cells and in close contact with the Juxtaglomerular cells.

d) They act as chemoreceptors and are stimulated by decreased NaCl concentration and thereby causing increased renin release.

Juxtaglomerular cell (JG cell): juxtaglomerular cells are specialised myoepithelial (modified vascular smooth muscle) cells located in the media of the afferent arteriole in the region of JG apparatus.

Characteristic features of JG cells are:

a) They have well-developed Golgi apparatus and endoplasmic reticulum, abundant mitochondria and ribosomes.

b) They synthesize, store and release an enzyme called renin. Renin is stored in the secretory granules of JG cells and, therefore, these are also called granular cells.

c) They act as baroreceptors (tension receptors) and respond to changes in the transmural pressure gradient between the afferent arterioles and the interstitium.

d) They are densely innervated by the sympathetic nerve fibers and release their renin content in response to the sympathetic discharge.

e) As these cells act as vascular volume receptors, they monitor renal perfusion pressure and are stimulated by hypovolaemia or decreased renal perfusion pressure.

Mesengial cells: Mesangial cells or lacis cells are the interstitial cells of the JG apparatus.

Characteristic features of these cells are:

a) They are in contact with both the macula densa cells (on one side) and JG cells (on the other side).

b) Functionally, these cells possibly relay the signals from macula densa to the granular cells after modulating the signals. In this way, a decreased intraluminal Na^+ load, Cl^- load, or both in the region of macula densa stimulates the JG cells to secrete renin.

c) They also show granulation to secrete renin in conditions of extreme hyperactivity.

d) They also secrete various substances and take up immune complexes.

Extraglomerular mesengial cells: These 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 glomerular filtration rate by altering the vessel diameter. Renin is also found in these cells.

Question 4) Discuss the role of kidney in regulation of blood pressure?

The kidneys play a central role in the regulation of arterial blood pressure. A key modulator of blood viscosity is the renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system, a hormone system that regulates blood pressure and water balance.

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 convoluted 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 vessel contract and 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 increase blood pressure. If the renin-angiotensin-aldosterone system is too active, blood pressure will be too high.

How the kidneys increase circulating blood volume

Angiotensin-2 also stimulates the adrenal gland to secrete a hormone called Aldosterone. Aldosterone stimulates more Na reabsorption in the distal tubule and water gets reabsorbed along with the Na. The increased Na and water reabsorption from the distal tubule reduces urine output and increases the circulating blood volume. The increased blood volume helps stretch the heart muscle and causes it to generate more pressure with each beat, thereby increasing the blood pressure.

The actions taken by the kidney to regulate blood pressure are especially important during traumatic injury, when they are necessary to maintain blood pressure and conserve the loss of fluids.

Question 5) Discuss the role of kidney in Calcium homeostasis?

The maintenance of calcium homeostasis is very important because calcium is the main component of bony skeleton and serves as the intracellular and extracellular messenger in numerous essential cellular events such as neuronal network, immune response, muscle contraction and hormone secretion. About 50% of plasma calcium is freely filtered through the renal glomerulus and 99% of the filtered calcium is actually reabsorbed along renal tubules.

In humans who have a glomerular filtration rate of about 180 liters per 24 hours, roughly 10 grams of calcium is filtered per day. The excreted calcium in the final urine is about 100-200mg per day. Hence, 98% to 99% of the filtered load of calcium is reabsorbed by the renal tubules.

The reabsorption of calcium in the proximal convoluted tubule occurs mainly by passive diffusion or solvent drag. The passive paracellular pathways account for approximately 80% of calcium reabsorption in this segment of the nephron. Calcium is also reabsorbed by active transport and it is mainly regulated by parathyroid hormone and calcitonin. In the thick ascending limb of the loop of

henle, 20% of the filtered calcium is reabsorbed largely by the cortical thick ascending limb, through both transcellular and paracellular pathway. The distal convoluted tubule absorbs 5%-10% of the filtered calcium. Calcium absorption in this segment is active because it proceeds against a chemical and an electrical gradient.