Name: Law-Adepoju Inumidun Adejumoke

Matric no: 17/mhs01/175

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Assignment

1. Role of kidney in glucose homeostasis

The kidneys are involved in maintaining glucose homeostasis through three different mechanisms: gluconeogenesis; glucose uptake from the blood for its own energy requests and reabsorption into the general circulation of glucose from glomerular filtrate in order to preserve energy.

Renal gluconeogenesis

From the point of view of glucose utilization, the kidney is considered as 2 separate organs; the renal medulla is characterized mainly by glucose utilization and the renal cortex is responsible for glucose release. The separation of these activities represents the consequence of differences in the distribution of numerous enzymes along the nephron. The cells in the renal medulla can use only glucose for their needs (like the brain) and they have enzymes capable of glucose-phosphorylation and glycolysis. They can therefore phosphorylate important amounts of glucose and accumulate glycogen but, because these cells do not have glucose-6-phosphatase or any other gluconeogenic enzymes, they are unable to release glucose into the bloodstream. Moreover, the cells in the renal cortex have gluconeogenic enzymes and they can produce and release glucose into the circulation. However these cells cannot synthesize glycogen because they have little phosphorylating capacity. After a 16-h overnight fast, approximately 10 µmol ⁄ (kg /min) of glucose is released into the circulation. Almost 50% of this is the result of glycogenolysis from the liver stocks and the other half is produced by liver and kidney gluconeogenesis. The renal cortex (like the liver) contains gluconeogenic enzymes and it can synthesize glucose-6-phosphate from precursors (lactate, glutamine, glycerol and alanine). Because it contains glucose-6-phosphatase, it is able to release glucose into the blood stream and the human liver and kidneys are the only organs that can perform gluconeogenesis. Therefore, after an overnight fast, the liver produces 75–80% of glucose released into the circulation and the remaining 20–25% is derived from the kidneys. 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.

A new concept of hepatorenal glucose reciprocity emerged from the differences observed in regulation and interchange between renal and hepatic glucose release. This concept refers to the facts that a pathological or physiological reduction in glucose release by kidney or liver determines a compensatory increase in glucose release of the other one (liver or kidney) in order to avoid hypoglycaemia. This situation occurs in the anhepatic phase during liver transplantation, prolonged fasting, meal ingestion, acidosis and insulin overdoses in diabetes mellitus.

Glycogenolysis

Glycogenolysis is the breakdown of glycogen to glucose-6-phosphate and a hydrolysis reaction (using glucose-6-phosphatase) in order to free glucose. The liver is the only organ that contains glucose-6-phosphatase. So, the cleavage of hepatic glycogen releases glucose, while the cleavage of glycogen from other sources can release only lactate. Lactate, that is generated via glycolysis, is often absorbed by other organs and helps regenerating glucose.

Glucose reabsorption

Apart from the important role in gluconeogenesis and the role of renal cortex in glucose uptake, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. In normal conditions, the kidneys can reabsorb as much glucose as possible, the result being a virtually glucose free urine. Approximately 180 grams of glucose are filtered by the glomeruli from plasma, daily but all of this quantity is reabsorbed through glucose transporters that are present in cell membranes located in the proximal tubules.

These glucose transporters have a limited capacity of reabsorption. If this capacity is exceeded, glucose usually appears in the urine. The tubular maximum for glucose (TmG), the term used for the maximum capacity, can vary from 260 to 350 mg/min/1.73 m2 in healthy subjects. It corresponds to blood glucose levels of 180-200 mg/dL. When the blood glucose is very high and the TmG is reached, the transporters cannot reabsorb all the glucose and glucosuria occurs. Nevertheless, there can be slight differences between the nephrons and the inaccurate nature of biological systems may potentially lead to the development of glucosuria when blood glucose is below TmG. Glucosuria may occur at lower plasma glucose levels in certain conditions of hyperfiltration (eg. pregnancy), but as a consequence of hyperfiltration and not of significant hyperglycemia.

In a given day, the kidneys can produce, via gluconeogenesis, 15–55g glucose and it can metabolize 25–35g glucose. Regarding the glucose metabolic pathways, it is obvious that renal reabsorption represents the main mechanism by which the kidney is involved in glucose homeostasis. Therefore, the change in tubular glucose reabsorption may have a considerable impact on glucose homeostasis.

3.3.1. Renal glucose transporters

Glucose is a polar compound with positive and negative charged areas; therefore it is soluble in water. Its transport into and across cells is dependent on two specialized carrier protein families: the GLUTs (facilitated glucose transporters) and the SGLTs (sodium-coupled glucose cotransporters). These transporters are responsible for glucose passage and reabsorption in several tissue types, including the proximal renal tubule, blood-brain barrier, small intestine. GLUTs are responsible for the passive transport of glucose across cell membranes, in order to equilibrate its concentrations across a membrane. SGLTs, on the other hand, are involved in active transport of glucose against a concentration gradient by means of sodium-glucose cotransport.

There are six members of the SGLT family indicated in

| Co-transporter | Substrate | Tissue distribution |
| --- | --- | --- |
| SGLT1 | Glucose, galactose | Intestine, kidney, heart, trachea, brain, testis, prostate |
| SGLT2 | Glucose | Kidney, brain, liver, muscle, heart |
| SGLT4 | Glucose, mannose | Intestine, kidney, uterus, pancreas, liver, brain, lung, trachea |
| SGLT5 | Unknown | Kidney |
| SGLT6 | Glucose, myoinositol | Brain, kidney, intestine |
| SMIT1 | Glucose, myoinositol | Brain, heart, lung, kidney |

The sodium glucose co-transporter

SGLT2 is considered the most important because, based on animal studies, it is responsible for the reabsorption of 90% of the glucose filtered at the glomerulus. The other 10% of glucose reabsorbed in the proximal tubule is ensured by SGLT1. Of the family of GLUT proteins expressed in the kidneys, GLUT2 is the major transporter and it releases into circulation the glucose reabsorbed by SGLTs in the proximal tubular cells.

1. Process of micturition

Micturition is the process by which urinary bladder empties when filled. The main physiological events in the process of micturition are:

Filling of urinary bladder and

Emptying of urinary bladder.

FILLING OF URINARY BLADDER

Transport of urine into urinary bladder through ureters

As urine collects in the renal pelvis, the pressure in the pelvis increases and initiates a peristaltic contraction beginning in the pelvis and spreading along the ureter to force urine towards the bladder.

Capacity of the bladder

Physiological capacity of the bladder varies with age, being 20–50 mL at birth, about 200 mL at 1 year, and can be as high as 600 mL in young adult males. In all cases, the physiological capacity is about twice that at which the first desire to void is felt.

Volume and pressure changes in bladder during filling

The normal bladder is completely empty at the end of micturition and the intravesical pressure is equal to the intraabdominal pressure. As the bladder is filled up, it adjusts its tone and a fairly large volume of urine can be accommodated with minimal alterations in the intravesical pressure. This is possible because of the phenomenon of adaptation. The adaptation occurs because of the inherent property of plasticity, the smooth muscles of detrusor and because of law of Laplace.

EMPTYING OF THE BLADDER

Emptying of the bladder is basically a reflex action called the micturition reflex, which is controlled by supraspinal centres and is assisted by contraction of perineal and abdominal muscles. Therefore, emptying of the urinary bladder focuses on:

Micturition reflex, Voluntary control of micturition and Role of perineal and abdominal muscles in micturition.

Micturition reflex

Initiation. Micturition reflex is initiated by the stimulation of the stretch receptors located in the wall of urinary bladder.

Stimulus. Filling of bladder by 300–400 mL of urine in adults constitutes the adequate stimulus for the micturition reflex to occur.

Afferents. The afferents from the stretch receptors in the detrusor muscle and urethra travel along the pelvic splanchnic nerves and enter the spinal cord through dorsal roots to S2, S3 and S4 segments to reach the sacral micturition centre

Sacral micturition centre is formed by the sacral detrusor nucleus and sacral pudendal nucleus.

Efferents. Efferents arising from the sacral detrusor nucleus are the preganglionic parasympathetic fibres, which relay in the ganglia near or within bladder and urethra.The post-ganglionic parasympathetic fibres are excitatory to the detrusor muscle and inhibitory to the internal sphincter.

Response. Once micturition reflex is initiated, it is self regenerative, i.e. initial contraction of the bladder wall gurther activates the receptors to increase the sensory impulses (afferents) from the bladder and urethra which cause further increase in the reflex contraction of detrusor muscle of the bladder. The cycle thus keeps on repeating itself again and again until the bladder has reached a strong degree of contraction.

Once the micturition reflex becomes powerful enough, this causes another reflex which passes through pudendal nerves to external sphincter to cause its inhibition. If this inhibition is more potent than the voluntary constrictor signals from brain, then urination will not occur. If not so, urination will not occur unless the bladder fills still more and micturition reflex becomes more powerful.

Voluntary control of micturition

Role of supraspinal centres

The micturition reflex is fundamentally a spinal reflex facilitated and inhibited by higher brain centres (supraspinal centres) and, like defaecation, is subjected to voluntary facilitation and inhibition. In infants and young children, micturition is purely a reflex action. Voluntary control is gradually acquired as a learned ability of the toilet training.

Once voluntary control is acquired, the supraspinal control centres exert final control of micturition by following means:

The higher centres keep the micturition reflex partially inhibited all the time except when it is desired to micturate.

When the convenient time to urinate present, the higher centres facilitate the sacral micturition centre (SMC) to initiate a micturition reflex and inhibit the external urinary sphincter so that urination can occur.

Supraspinal control centres which control the micturition reflex (a completely automatic cord reflex) include the pontine micturition centre (PMC) and suprapontine centres.

Pontine micturition centre, corresponds to the locus ceruleus of the rostral pons. Neurons from PMC descend in the reticulospinal tract and exert control over the SMC and thoracolumbar sympathetics. Function of PMC is coordination of detrusor contraction and sphincter relaxation, which is important for proper micturition.

Suprapontine centres which relay their influence on the sacral micturition centre through the PMC are:

Cerebral cortex

Basal ganglion

Limbic system

Role of perineal and abdominal muscles in micturition

Certain muscular movements, which aid the emptying of bladder, but are not the essential component of micturition process are:

At the onset of micturition, the levator ani and perineal muscles are relaxed, thereby shortening the post-urethra and decreasing the urethral resistance.The diaphragm descends and the abdominal muscles contract, accelerating the flow of urine by raising intra-abdominal pressure which in turn secondarily increase the intravesical pressure thereby increasing the flow of urine. A voiding contraction, once initiated, is normally maintained until all the urine has been discharged from the urinary bladder. This is a function of facilitating impulses from the higher centres. However, if required so, the micturition can be voluntarily stopped in between by inhibitory impulses from the higher centres. The bladder contracts in all directions like a toy balloon deflating from its neck.

After urination, the female urethra empties by gravity, whereas the urine remaining in the urethra of male is expelled by several contractions of bulbospongiosus muscle. In the urinary bladder dysfunction, bladder contractions are insufficient to completely empty the bladder, therefore, some urine is left in the urinary bladder called residual urine.

1. 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 named because it is next to (juxta) the glomerulus. The juxtaglomerular apparatus consists of three types of cells:

the macular densa, a part of the distal convoluted tubule of the same nephron

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

extraglomerular mesengial cells

The juxtaglomerular apparatus is part of the kidney nephron, next to the glomerulus . It is found between different arterioles 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.

Juxtaglomerular cells

The renin angiotensin system . It is activated when juxtaglomerular cells are poorly perfused.

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 mesengial 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. renin is also found in these cells.

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, the distal convoluted tubule, there is a modified region of tubular epithelium called the macular densa. Cells in the macula densa respond to changes in the sodium chloride levels in the distal tubule of the nephron via the tubuloglomerulelar 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 signalling . 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)

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. This is not responsive to the usual treatment for essential hypertension, namely medications and lifestyle modification.

One cause of this can be increased renin production due to narrowing of the renal artery, or a tumour of juxtaglomerular cells that produces renin. These will lead to secondary hyperaldosteronism , which will cause hypertension, high blood sodium, low blood potassium, and metabolic alkalosis.

1. 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-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.

1. Role of kidney in calcium homeostasis

Hormonal Control Systems

Maintaining normal blood calcium and phosphorus concentrations is managed through the concerted action of three hormones that control fluxes of calcium in and out of blood and extracellular fluid:

Parathyroid hormone: serves to increase blood concentrations of calcium. Mechanistically, parathyroid hormone preserves blood calcium by several major effects:

Stimulates production of the biologically-active form of vitamin D within the kidney.

Facilitates mobilization of calcium and phosphate from bone. To prevent detrimental increases in phosphate, parathyroid hormone also has a potent effect on the kidney to eliminate phosphate (phosphaturic effect).

Maximizes tubular reabsorption of calcium within the kidney. This activity results in minimal losses of calcium in urine.

Vitamin D acts also to increase blood concentrations of calcium. It is generated through the activity of parathyroid hormone within the kidney. Far and away the most important effect of vitamin D is to facilitate absorption of calcium from the small intestine. In concert with parathyroid hormone, vitamin D also enhances fluxes of calcium out of bone.

Calcitonin  is a hormone that functions to reduce blood calcium levels. It is secreted in response to hypercalcemia and has at least two effects:

Suppression of renal tubular reabsorption of calcium. In other words, calcitonin enhances excretion of calcium into urine.

Inhibition of bone resorption, which would minimize fluxes of calcium from bone into blood.

Although calcitonin has significant calcium-lowing effects in some species, it appears to have a minimal influence on blood calcium levels in humans.