NAME: ALFA UNEKWU-OJO MICHELLE

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ASSIGNMENT

1. ROLE OF KIDNEY IN GLUCOSE HOMEOSTASIS

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 itself 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 regulation of endogenous production of glucose is determined by hormonal and neural factors. In the acute phase, glucoregulatory mechanisms involve insulin, glucagon and catecholamines and they can effect changes in plasma glucose levels in a matter of minutes. Insulin is able to suppress glucose release in both the kidney and liver by direct enzyme activation⁄deactivation and by reducing the availability of gluconeogenic substrates. Glucagon has no effect on the kidneys, but it stimulates glycogenolysis and gluconeogenesis in the liver. Catecholamines also have multiple acute actions. They can stimulate renal glucose release and glucagon secretion and inhibit insulin secretion.

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.

Several studies have indicated that human kidneys and liver provide approximately the same amounts of glucose through gluconeogenesis in postabsorptive period. If the duration of fasting is increased, the glycogen stores are depleted and gluconeogenesis produces all the glucose released into circulation.

An important aspect is that kidney and liver use different gluconeogenic precursors and several hormones have different effects on their release of glucose. Lactate represents the predominant gluconeogenic precursor in both organs, but regarding the amino acids, the kidney prefers to use glutamine, whereas the liver preferentially uses alanine. Insulin can suppress glucose release in both organs with almost comparable efficacy, whereas glucagon stimulates hepatic glucose release only. Catecholamines normally have a direct effect only on renal glucose release, but their effect on both hepatic and renal glucose release may be indirect by increasing the quantity of gluconeogenic substrates available and by suppressing insulin secretion. Other hormones, such as growth hormone, cortisol and thyroid hormones can stimulate hepatic glucose release over a great period of time. Their effects on the kidneys regarding glucose release in humans are not completely deciphered.

In the postprandial state the situation changes significantly. Postprandial glucose levels in the plasma are determined by insulin and glucagon levels. After glucose ingestion, plasma glucose levels reach the peak in 60–90 minutes and they return to post-absorptive levels in almost 3–4 h. The plasma insulin increases four times and the plasma glucagon levels decrease by 50% indicated that endogenous glucose release is reduced by almost 60% and hepatic glycogenolysis drops to zero in the 4- to 6-h period after meal ingestion.This is happening because this period determines the refilling of hepatic glycogen stores and inhibition of endogenous glucose release is able to limit postprandial hyperglycaemia. There is also a reduction in hepatic gluconeogenesis by 82% and glucose molecules generated through hepatic gluconeogenesis are also directed into hepatic glycogen, not only released in the circulation.

Renal gluconeogenesis can increase by approximately two-fold 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 ahepatic 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 (e.g. pregnancy), but as a consequence of hyperfiltration and not of significant hyperglycemia.

1. PROCESS OF MICTURITION

Urine flow through the ureters to the bladder is propelled by contractions of the ureter wall smooth muscle. The urine is stored in the bladder and intermittently ejected during urination or **micturition.**

The bladder is a balloon-like chamber with walls of smooth muscle collectively termed the **detrusor muscle.** The contraction of the detrusor muscle squeezes on the urine in the bladder lumen to produce urination. That part of the detrusor muscle at the base (or “neck”) of the bladder where the urethra begins functions as the **internal urethral sphincter.** Just below the internal urethral sphincter, a ring of skeletal muscle surrounds the urethra. This is the **external urethral sphincter,** the contraction of which can prevent urination even when the detrusor muscle contracts strongly. The neural controls and influence bladder structures during the phases of filling and micturition. While the bladder is filling, the parasympathetic input to the detrusor muscle is minimal, and, as a result, the muscle is relaxed. Because of the arrangement of the smooth muscle fibers, when the detrusor muscle is relaxed, the internal urethral sphincter is passively closed. Additionally, there is strong sympathetic input to the internal urethral sphincter and strong input by the somatic motor neurons to the external urethral sphincter. Therefore, the detrusor muscle is relaxed and both the internal and external sphincters are closed during the filling phase.

What happens during Micturition? As the bladder fills with urine, the pressure within it increases, which stimulates stretch receptors in the bladder wall. The afferent neurons from these receptors enter the spinal cord and stimulate the parasympathetic neurons, which then cause the detrusor muscle to contract. When the detrusor muscle contracts, the change in shape of the bladder pulls open the internal urethral sphincter. Simultaneously, the afferent input from the stretch receptors reflexively inhibits the sympathetic neurons to the internal urethral sphincter, which further contributes to its opening. In addition, the afferent input also reflexively inhibits the somatic motor neurons to the external urethral sphincter, causing it to relax. Both sphincters are now open, and the contraction of the detrusor muscle can produce urination.

Thus far micturition has being described as a local spinal reflex, but descending pathways from the brain can also profoundly influence this reflex, determining the ability to prevent or initiate micturition voluntarily. Loss of these descending pathways as a result of spinal cord damage eliminates the ability to voluntarily control micturition. As the bladder distends, the input from the bladder stretch receptors causes, via ascending pathways to the brain, a sense of bladder fullness and the urge to urinate. But in response to this, urination can be voluntarily prevented by activating descending pathways that stimulate both the sympathetic nerves to the internal urethral sphincter and the somatic motor nerves to the external urethral sphincter. In contrast, urination can be voluntarily initiated via the descending pathways to the appropriate neurons. Complex interactions in different areas in the brain control micturition. Briefly, there are areas in the brainstem that can both facilitate and inhibit voiding. Furthermore, an area of the midbrain can inhibit voiding, and an area of the posterior hypothalamus can facilitate voiding. Finally, strong inhibitory input from the cerebral cortex, learned during toilet training in early childhood, prevents involuntary urination.

1. JUXTAGLOMERULAR APPARATUS

There are two types of nephrons. About 15% of the nephrons are **juxtamedullary,** which means that the renal corpuscle lies in the part of the cortex closest to the cortical–medullary junction. The Henle’s loops of these nephrons plunge deep into the medulla and are responsible for generating an osmotic gradient in the medulla responsible for the reabsorption of water. In close proximity to the juxtamedullary nephrons are long capillaries known as the **vasa recta,** which also loop deeply into the medulla and then return to the cortical– medullary junction. The majority of nephrons are **cortical,** meaning their renal corpuscles are located in the outer cortex and their Henle’s loops do not penetrate deep into the medulla. In fact, some cortical nephrons do not have a Henle’s loop at all; they are involved in reabsorption and secretion but do not contribute to the hypertonic medullary interstitium.

One additional anatomical detail involving both the tubule and the arterioles is important. Near its end, the ascending limb of each loop of Henle passes between the afferent and efferent arterioles of that loop’s own nephron. At this point, there is a patch of cells in the wall of the ascending limb as it

becomes the distal convoluted tubule called the **macula densa,** and the wall of the afferent arteriole contains secretory cells known as **juxtaglomerular** (**JG**) **cells.** The combination of macula densa and juxtaglomerular cells is known as the **juxtaglomerular apparatus** (**JGA**). As described later, the JGA has important functions in the regulation of ion and water balance, and the production of factors that control blood pressure.

1. ROLE OF KIDNEY IN REGULATION OF BLOOD PRESSURE

Evidence that the kidneys play a key role in blood pressure regulation comes from the fact that chronic abnormalities of blood pressure control, such as hypertension, almost always begin with some abnormality of renal function. For example, Goldblatt hypertension begins with stenosis of one or both of the renal arteries; mineralocorticoid hypertension begins with increased renal tubular sodium reabsorption; and hypertension caused by infusion of vasoconstrictors such as angiotensin III or norepinephrine may be associated with increased tubular reabsorption as well as renal vasoconstriction. As hypertension develops, many of these initial changes in renal function are obscured in various compensatory mechanisms that act to restore renal excretory function toward normal. Secondary to increased arterial pressure, a cascade of circulatory alterations occurs that in many instances is much more striking than the disturbance of renal function, even though the original abnormality was in the kidney. For this reason, the importance of changes in renal function in causing hypertension has often been underestimated. Several connections between the kidney and blood pressure regulation have been postulated:

(a) the kidneys secrete renin and therefore control formation of angiotensin which can act directly as a vasoconstrictor, on the central nervous system to stimulate thirst and perhaps increase sympathetic nerve activity, on the adrenal cortex to stimulate aldosterone secretion, and directly on the kidneys to cause sodium and water retention;

(b) the kidneys produce vasodilator substances, including prostaglandins, kallikrein, renal medullary lipids, and perhaps other substances that may act on peripheral blood vessels or influence renal excretion of sodium and water;

(c) the kidneys are believed to stimulate reflex pathways via afferent nerve fibers connected to the sympathetic nervous system which, in turn, may influence the peripheral circulation and heart, as well as the kidney;

(d) the kidneys control arterial pressure by regulating excretion of water and electrolytes and therefore extracellular fluid volume, a control mechanism that has often been referred to as the renal-body fluid feedback system; this function of the kidney is closely interrelated with some of the neurohumoral control mechanisms, especially the renin-angiotensin system (RAS), that regulate renal excretion. Some of these mechanisms are mainly short-term controllers of blood pressure. For example, the vasoconstrictor effect of all on peripheral arterioles provides a rapidly acting and powerful means of preventing large decreases in arterial pressure during acute disturbances such as hemorrhage. However, long-term regulation of arterial pressure by the RAS and other renal control systems is closely intertwined with their effects on sodium and water excretion and volume homeostasis. Renal-body fluid feedback system and the RAS play dominant roles in chronic blood pressure regulation.

1. ROLE OF KIDNEY IN CALCIUM HOMEOSTASIS

Calcium and phosphate balance are controlled primarily by parathyroid hormone and 1,25-(OH)2D. Approximately 60% of plasma calcium is available for filtration in the kidney. The remaining plasma calcium is protein-bound or complexed with anions. Because calcium is so important in the function of every cell in the body, the kidneys have very effective mechanisms to reabsorb calcium ion from the tubular fluid. More than 60% of calcium ion reabsorption is not under hormonal control and occurs in the proximal tubule. The hormonal control of calcium ion reabsorption occurs mainly in the distal convoluted tubule and early in the cortical collecting duct. When plasma calcium is low, the secretion of parathyroid hormone (PTH) from the parathyroid glands increases. PTH stimulates the opening of calcium channels in these parts of the nephron, thereby increasing calcium ion reabsorption. Another important action of PTH in the kidneys is to increase the activity of the 1-hydroxylase enzyme, thus activating 25(OH)-D to 1,25-(OH)2D, which then goes on to increase calcium and phosphate ion absorption in the gastrointestinal tract.

About half of the plasma phosphate is ionized and is filterable. Like calcium, most of the phosphate ion that is filtered is reabsorbed in the proximal tubule. Unlike calcium ion, phosphate ion reabsorption is decreased by PTH, thereby increasing the excretion of phosphate ion. Therefore, when plasma calcium is low, and PTH and calcium ion reabsorption are increased as a result, phosphate ion excretion is increased.