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Main Organs Involved in Glucose Metabolism

Laura Lema-Pérez

Abstract

Sugar, or technically known as glucose, is the main source of energy of all cells in the human body. The glucose homeostasis cycle is the mechanism to maintain blood glucose levels in a healthy threshold. When this natural mechanism is broken, many metabolic disorders appear such as diabetes mellitus, and some substances of interest, like glucose, are out of control. In the mechanism to maintain blood glucose, several organs are involved but the role of most of them has been disregarded in the literature. In this chapter, the main organs involved in such a mechanism and their role in glucose metabolism are described. Specifically, the stomach and small intestine, organs of the gastrointestinal system, are the first to play an important role in the regulatory system, because it is where carbohydrates are digested and absorbed as glucose into the bloodstream. Then glucose as a simple substance goes to the liver to be stored as glycogen. Glucose storage occurs due to the delivery of hormones from the pancreas, which produces, stores, and releases insulin and glucagon, two antagonistic hormones with an important role in glucose metabolism. The kidneys assist the liver in insulin clearance in the postprandial state and gluconeogenesis in the post absorptive state. Physiological aspects and the detailed role of every organ involved in glucose metabolism are described in this chapter.

Keywords: glucose metabolism, homeostasis, diabetes mellitus

1. Introduction

Glucose is contained in foods rich in carbohydrates like bread, potatoes, rice, and fruits. It can be as a simple molecule, sugar, or complex molecules, carbohydrates. Although carbohydrates are more abundant in the diet, they are digested to be converted into glucose molecules to be absorbed in the gut. Previously to be absorbed, stomach and small intestine play an important role in digestion every particle ingested. First, food reaches the stomach after being chewed and swallowed from mouth. The digestion of carbohydrates begins in the mouth with saliva while chewing, but continues in the small intestine because the acidic pH of the stomach inactivates the amylase enzyme that is responsible for breaking them down. In the small intestine, the digestion of carbohydrates ends to be absorbed, through the enterocytes, into the blood. Once the glucose molecules are absorbed into the bloodstream, they reach the liver by traveling through the portal system. In the liver, they are partially stored as glycogen by the action of the insulin previously released in the pancreas. The rest of the glucose continues in the circulation, reaches the heart and all tissues and organs. Insulin concentrations are proportional to glucose concentrations due to this hormone make enter the glucose into the cells. In fact, insulin

concentrations released by the pancreas are usually higher than glucose concentrations in blood. In this sense, the kidneys regulate glucose and insulin concentrations once these molecules reach them. Insulin is clearance in both, liver and kidneys, while glucose is produced from non-carbohydrates precursors in the postprandial state to compensate for the insulin excess in the blood. On the other hand, during a fasting period or a post-absorptive state, glucagon is released into the bloodstream by the pancreas and achieves the liver to dephosphorylate the glycogen into glucose to keep blood glucose levels in the healthy threshold. As can be seen from everything mentioned above, blood glucose levels can be set at the desired threshold thanks to the joint work between all the organs of the human body, where they all play an important role in this regulatory system. Next sections.

2. Importance of glucose in the human body

Cells of the tissues in the human body use glucose, the simplest of the carbohydrates, as the main source of energy to carry out their metabolic processes. Despite this, glucose consumption should be moderate because an excess can trigger multiple metabolic disorders that can even be chronic. Carbohydrates start to be processed immediately they are ingested, i.e., its digestion begins in the mouth with the amylase in the saliva. Then, ingested food travels throughout the esophagus to the stomach. In the stomach, the enzyme amylase is inactivated due to acidic pH, so carbohydrates cannot continue to digest. Other nutrients such as protein and fat are partially digested in the stomach, about 5% and 20%, respectively [1]. Once the ingested food has the appropriate rheological properties, it passes through the pylorus to reach the duodenum, the first part of the small intestine. In the duodenum, the bile produced from and gallbladder, is released to digest fats. The digestion of all nutrients ends in the small intestine by an additional intervention of the pancreas with the release of both pancreatic enzymes such as amylases, lipases, and proteases, and hormones such as insulin and glucagon. The molecules produced during digestion are absorbed by the enterocytes into the bloodstream. The rest of the food that is not absorbed in the small intestine passes into the colon.

Once glucose is in the systemic circulation, insulin hormone helps it to enter into the cells. Inside the cells, glucose is broken down to produce adenosine triphosphate (ATP) molecules by means of glycolysis. ATP are energy-rich molecules that power numerous cellular processes. Therefore, a constant supply of glucose from the blood to the cells must be ensured. Negative feedback systems [2] are responsible to ensure blood glucose concentrations in a normal range of 70 to 110 milligrams of glucose per deciliter of blood (*mg / dL*) [3]. Negative feedback systems are mechanisms that perceive changes in the human body and activate mechanisms that reverse the changes to restore conditions to their normal levels. Furthermore, negative feedback systems are critically important in glucose homeostasis in the maintenance of relatively constant internal conditions. In this regard, negative feedback systems make the pancreas to produce and release more insulin when there is an excess glucose consumption. This fact, maintained over time, can cause disruptions in glucose homeostasis lead to potentially life-threatening such as insulin resistance and diabetes mellitus.

The body also use other sources of energy such as amino acids (building blocks of proteins) and fats. However, despite these alternative energy sources, a minimum level of glucose in the blood must be ensured mainly for the metabolic activities of the brain and nervous system. Glucose is the main source of fuel for the brain and nervous system. Nerve cells and chemical messengers need glucose to process information. On the other hand, the liver and muscles can store the leftover glucose in little bundles

called glycogen once the human body has used all the energy it needs. Glycogen works as a reserve fuel to be used during post-absorptive or fasting periods. Glycogenolysis is the biochemical process for converting glycogen to glucose in the liver. This process, together with the absorption of glucose in the small intestine after an ingested meal and the hepatic and renal gluconeogenesis, are the main factors to increase the levels of glucose in the blood. Sometimes, glucose levels in the blood can also go sky high under stressful conditions. Also, the High-Intensity Interval Training (HIIT) type of exercise is acknowledged to trigger (not completely understood) mechanisms able to rise the blood glucose levels. Contrary, the transport of the glucose into the cells by insulin action, physical exercise, and sometimes glycosuria (a condition characterized by an excess of sugar in the urine occurring under abnormal events when glucose homeostasis is impaired) are the main factors able to decrease blood glucose levels.

Regardless of the condition, the human body is designed to keep the level of glucose in the bloodstream in healthy levels. However, when the glucose homeostasis is broken, diseases such as diabetes mellitus appear and persistent high blood glucose can lead generating acute complications such as diabetic ketoacidosis, retinopathy, diabetic nephropathy, neuropathy, and cardio-cerebrovascular disease. How does the body for regulating glucose levels in the blood? The next section introduces the glucose regulation cycle in detail and the role of every organ that is involved.

3. The glucose regulation cycle

Glucose homeostasis is the mechanism able to maintain the blood glucose levels near the range of 70mg/dl to 110mg/dL by the action of a complex interplay among organs, hormones, metabolic-systems, and neural control mechanisms. As mentioned above, glucose is the main source of energy by allowing essential cellular processes such as respiration, tissue repair, cell multiplication, to be carried out, among others. Production and release of pancreatic hormones, mainly insulin and glucagon, ensures the glucose regulation in the blood [3]. **Figure 1** shows how the human body maintains glucose levels in a specific physiological range. Once carbohydrates nutrients are ingested and enter the digestive tube, several enzymes begin to work to digest macronutrients, e.g., amylases trigger for polysaccharide breakdown. In this way, polysaccharides are converted into monosaccharides, smaller molecules able to be absorbed by enterocytes in the small intestine. Monosaccharides absorption leads to increased blood glucose levels in the bloodstream. Simultaneously to this process, the incretin effect also occurs in which β -cells in the pancreas are stimulated by the action of GIP and GLP-1 hormones. Stimulation of β -cells drives the production and release of insulin, which increases the amount of GLUT4 glucose transporters in the cell membranes of different tissues [3]. Blood glucose concentrations also stimulate insulin production, and the hormones GIP and GLP-1 modulate it. As mentioned before, there are specialized molecules called GLUT to transport glucose from the blood into cells through cell membranes by diffusion. In this way, Excess glucose is eliminated from the blood, decreasing it. This process is represented in the figure with the plus sign. Therefore, glucose is transported within muscle and adipocytes cells, hepatocytes, neurons, etc., to be used as a source of energy. The liver is also answerable to sense blood glucose concentrations coming from the portal system and systemic circulation. In the liver, enzymes known as glucokinase are responsible to sense glucose amount, stimulate its diffusion through the hepatocytes, and simultaneously produce glycogen from glucose excess. Glycogen is a multibranched polysaccharide of glucose used as glucose storage to be used during fasting periods as an energy source in the cells [4].

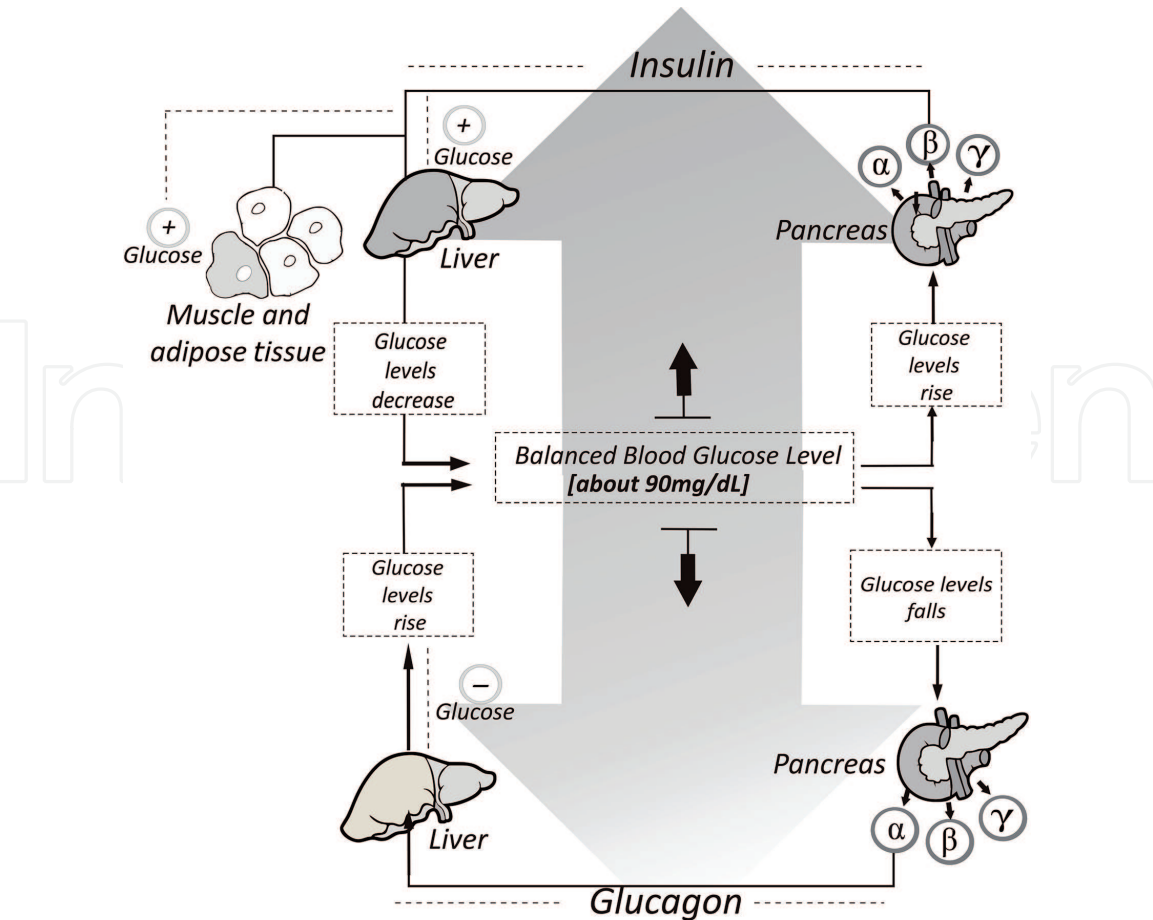


Figure 1.
The glucose homeostasis in the human body.

During fasting periods, glucose levels in the blood decrease causing inhibition of insulin production in the pancreas by the action of hormones known as catecholamines [4]. Consequently, α -cells in the pancreas are stimulated to produce glucagon hormone that acts antagonistically to insulin. Glucagon makes a function on the different hepatocyte receptors triggering both the action of the phosphorylase enzyme and the glycogenolysis process. Glycogenolysis is the process in which glycogen is converted into glucose to increase blood glucose levels and recover the lack of glucose, setting its concentrations in the desired levels [5]. This is symbolized in **Figure 1** by the minus sign.

Diabetes Mellitus is a condition appearing when the glucose homeostasis is broken, that is, plasma glucose levels are no longer maintained at desired levels. This is mainly due to a deficit in the production of insulin from the pancreatic β -cells or from a resistance to the action of the produced insulin.

4. Main organs involved in glucose homeostasis

Although some organs need fatty acids to carry out their metabolic processes, most tissues in the human body use glucose as their main source of energy. Good glucose utilization depends on keeping blood glucose levels within range at all times and on the proper functioning of the glucose homeostatic mechanism. Several complementary physiological processes are involved in the glucose homeostatic mechanism. The gastrointestinal tract is responsible to produce and absorb glucose, the liver carries out biochemical reactions such as glycogenolysis, glycolysis, and gluconeogenesis, the kidneys filter, reabsorb, and in some cases excrete glucose,

and they also produce glucose from non-carbohydrate precursors. The role of the main organs involved in the glucose regulation cycle is described below.

4.1 Pancreas

The pancreas is a special organ because has both endocrine and exocrine functions. Exocrine functions consist of the production and secretion of digestive enzymes whereas endocrine functions include production and secretion of hormones. This chapter is primarily focused in the endocrine function given the crucial role on glucose homeostasis. Endocrine component of the pancreas consists of clustered cells forming the so-called islets of Langerhans. Islets of Langerhans are small island-shaped structures within exocrine pancreatic tissue representing only 1–2% of the entire organ [6]. The pancreatic islet endocrine cells include five different types that produce and release important hormones directly into the bloodstream: α -cells produce glucagon, β -cells produce amylin-, C-peptide, and insulin [7], γ -cells produce pancreatic polypeptide (PP) [8], δ -cells produce somatostatin [7], and ε -cells produce ghrelin [9]. Two of the pancreatic hormones play an essential role in the regulation of the blood glucose levels are insulin, which acts to lower it, and glucagon, which acts to raise it [10]. The balanced antagonistic action between them, maintain the glucose concentrations within the narrow range of 4–6 mM (70 to 110 mg / dL) [6]. However, both hormones are inhibited by somatostatin [11]. Production and secretion of the hormones by pancreatic cells are stimulated by external signals such as nutrients intake, fasting, or stress. Blood glucose levels decrease during periods of rest such as sleep, between meals, or during fasting periods. In these cases, pancreatic α -cells release glucagon to drive glycogenolysis and gluconeogenesis processes. Unlike, in postprandial state, i.e., after a meal ingestion, insulin is released from β -cells in the pancreas to reduce blood glucose levels via glycogenesis [12–14]. Insulin is released on demand but is produced and stored in large, dense-core vesicles that are recruited near the plasma membrane into the β -cells in the islets of Langerhans after stimulation so that insulin is readily available to upcoming stimuli [15]. Glucose is the main signal to release insulin from the pancreas, but free fatty acids and amino acids can increase glucose-induced insulin secretion through the so-called incretin effect. As before mentioned, the incretin effect is originated in the intestinal tract (mainly duodenum) once the food is ingested.

Insulin is a protein made up of 51 amino acids and when produced, it is first synthesized as a single polypeptide known as preproinsulin. Preproinsulin is an insulin gene encoded in 110 amino acids that are then processed into proinsulin. Proinsulin undergoes maturation into active insulin through the action of two different types of cells. One of them cleaves at 2 positions, releasing insulin and a fragment known as C-peptide [16], in an equimolar ratio, into the bloodstream.

Insulin is released from β -cells in the pancreas in two phases, first one is triggered in response to glucose levels and second one is triggered independently of sugar. Glucose and insulin in the bloodstream work together to avoid glucose from going out of range. Thus, Glucose is removed from the circulation thanks to the ability of insulin to cause insulin-dependent tissues to take up glucose [17–19]. Additionally, insulin promotes lipogenesis [20, 21], and the incorporation of amino acids into proteins [22] when it is in high concentrations. Different at low concentrations, which produce lipolysis in adipocytes, releasing free fatty acids by stimulating the use of lipids over glucose to satisfy energy needs at rest [23]. The release of insulin from β -cells is tightly regulated and exactly satisfies the metabolic demand for caloric nutrients in the body [16, 23]. Regarding C-peptide, it has been important to follow some insulin states that are difficult to measure [24].

4.2 Liver

The liver is perhaps considered the main blood glucose regulating organ in the human body because it functions in two different ways: controlling the rate of glucose absorption from the portal system and producing glucose from non-carbohydrate precursors or glycogen. As a curious fact, the liver is the only organ being irrigated by venous and arterial blood simultaneously. Venous irrigation comes from the portal system, provides the 75% of the blood supply, and carries blood rich in nutrients that were absorbed from the small intestine through enterocytes and hormones that were released by the pancreas. On the other hand, 25% of the remaining hepatic blood supply is arterial supply and is oxygen-rich blood coming from the aorta [4]. Blood from terminal branches of the hepatic artery and portal vein at the periphery of lobules is emptied into low-pressure vascular channels called sinusoids. Sinusoids are lined with endothelial cells and flanked circumferentially by plates of parenchymal cells-hepatocytes allowing the exchange of nutrients and oxygen between the blood and the hepatic cells [25]. Millions of sinusoids made up the lobules in the liver. Hepatocytes take up nutrients from blood in the sinusoid and once carry on all metabolic functions, return the substances resulting from the biochemical reactions to the blood via hepatic vein.

As mentioned earlier, the liver is a key organ in maintaining glucose concentrations in the desired range over both post-absorptive and postprandial states¹. In the liver, four biochemical processes regarding glucose metabolism take place: glucose production from glycogen (glycogenolysis) and from non-carbohydrate precursors (gluconeogenesis), glucose consumption during the postprandial state (glycolysis), and glucose storage from the formation of glycogen (glycogenesis). Glucose phosphorylation (formation of glycogen) and dephosphorylation (formation of glucose from glycogen) occurs through the action of insulin and glucagon, respectively. Hepatocytes express dozens of enzymes that alternately turn on and off depending on whether blood glucose levels are rising or falling outside the normal range [26]. In the post-absorptive state, the human body is under fasting and the body must rely initially on stored glycogen to supply with glucose to the central nervous system and simultaneously regulate plasma glucose concentrations. If the fast is prolonged, the glycogen stores end, and the glucose dosage in the liver depends only on gluconeogenesis. On the other hand, after an ingested meal, i.e., in the postprandial state, absorbed nutrients enter the liver first from hepatic portal vein. Consequently, glycogen concentrations in the hepatocytes are restored by taking up a portion of the ingested glucose, minimizing the fluctuations of glycemia. In this case, gluconeogenesis is also occurring at a constant rate but the glucose output generated from glycogenolysis is suppressed. These result in a net switch from hepatic glucose output to hepatic glucose uptake [27].

Hepatic gluconeogenesis occurs by the action of additional groups of enzymes that are activated to start synthesizing glucose out of such precursors as amino acids and non-hexose carbohydrates such as glutamine, alanine, lactate and glycerol. Otherwise, the suppression of the glycogenolysis during the post-absorptive period and the activation of the glycogen synthesis during the postprandial period are mainly driven by stimulation of insulin secretion and suppression of glucagon secretion.

¹ Postprandial state is the time frame after a meal or food intake. Postabsorptive state is the period following absorption of nutrients from the digestive tract, that is, is the time when enterocytes stop providing nutrients to the hepatic portal circulation. Fasting is the willing abstinence or reduction from some or all food, drink, or both, for a long period of time (~ 8 hours).

In addition to being the primary site of glucose utilization during the postprandial period and glucose dosing during the post-absorption period, the liver is the primary site of clearance of insulin in the human body [28, 29]. Although the kidneys are the main site of extrasplanchnic insulin clearance, with additional contributions resulting from uptake and degradation by peripheral insulin-sensitive tissues, i.e., skeletal muscle and adipose tissue, the liver is the main organ responsible for clearance of exogenous and in particular endogenous insulin [30]. Insulin clearance from the liver is a dynamic process that can be modified within a few days under conditions of changing energy and, in particular, carbohydrate intake and before major changes in basal insulin secretion [31]. However, during first-pass transit near to 50% of the portal insulin is removed in the liver [32]. Removal of insulin from circulation does not imply the immediate destruction of the hormone [33]. A significant amount of receptor-bound insulin is released from the cell and reenters the circulation [34].

Hepatic glucose uptake is maximally stimulated by conditions that mimic the postprandial state, such as portal venous hyperglycemia and hyperinsulinemia [35]. Once glucose reaches the hepatocytes, it is phosphorylated to glucose 6-phosphate to synthesize glycogen, among other metabolic pathways. The ability of the liver to store glycogen is limited, and when glycogen concentrations reach maximum capacity, the hepatocytes initiate a process known as lipogenesis. Lipogenesis is the synthesis of excess glucose into fatty acids [36].

In conclusion, during short periods of fasting, glycogenolysis is the predominant source of glucose released into the bloodstream. However, during prolonged periods of fasting, the glycogen store is gradually depleted and glycogenolysis decreases as glycogen stores are depleted. So, gluconeogenesis becomes the predominant source of glucose for the human body. This unique ability of the human liver to store and release glucose is crucial to supporting periods of fasting.

4.3 Kidneys

The kidneys are two bean-shaped organs that are primarily engaged in filtering the blood and excreting waste. Filtration is about cleaning the blood to send it back into circulation, maintaining an overall fluid balance, creating hormones that help make red blood cells, promoting bone health, and regulating blood pressure [37]. Recent studies have demonstrated that kidneys also play a central role in glucose homeostasis through utilization of glucose, glucose production, and glucose filtration and reabsorption via sodium glucose co-transporters (SGLTs) and glucose transporters (GLUT-2). Moreover, the kidneys are an important site of insulin clearance from the systemic circulation, removing approximately 50% of peripheral insulin [34].

The kidneys have a super-specialized microscopic structural and functional unit called the nephron. Nephrons have the ability to distribute all functions in each of their parts. For example, the glomerulus is a network of small blood vessels known as capillaries located within Bowman's capsule. Blood is filtered across the glomerular capillaries into Bowman's space. These capillaries are multiple branches of the afferent arteriole but then converge at the efferent arteriole to exit the glomerulus and surround the renal tubules, including the proximal convoluted tubule, the proximal rectus tubule, the loop of Henle, the distal convoluted tubule, and the collecting ducts. Urine continually forms within the tubules to be excreted with waste products. Reabsorption, secretion, chemical reactions, and excretion also occur within the renal tubules [5].

The release of glucose occurs predominantly in the renal cortex, while the utilization of glucose is limited to the renal medulla. For this reason, the kidneys

can be considered as two separate organs [38–42]. The renal medulla has an appreciable glucose phosphorylation capacity and, therefore, the ability to accumulate glycogen [42]. However, the kidney medulla consumes glucose anaerobically due to its low oxygen tension and low levels of oxidative enzymes, limiting the ability to produce glucose from glycogen. Consequently, lactate is the main metabolic end product of glucose taken up at the renal medulla, unlike carbon dioxide (CO_2) and water that are the end products of glucose uptake of aerobic energy requirements. In contrast, the renal cortex does not have appreciable glycogen stores [43] because has little glucose phosphorylation capacity but has a high level of oxidative enzymes like 6-phosphatase. Consequently, this part of the kidney does not take up and use much glucose, with oxidation of free fatty acids acting as the main source of energy [44]. Therefore, it is likely that glucose release by the normal kidney is primarily due to gluconeogenesis, that is, the synthesis of glucose-6-phosphate from non-carbohydrate precursors such as glutamine, lactate, alanine, glycerol, etc. [45], being glutamine the substrate with more specificity in the kidney but lactate the most abundant.

In addition, to its function both in the use and in the production of glucose, the kidneys contribute to the regulation of glucose in the blood by filtering and reabsorbing glucose. The glomeruli filter glucose once it reaches the kidneys, with other substances such as precursors and insulin, into the proximal tubules, where all the glucose is reabsorbed through the glucose transporting proteins present in the cell membranes within the proximal tubules [46], rendering the urine virtually glucose free. Before being reabsorbed, gluconeogenesis and glucose uptake occur. Glucose production is suppressed by insulin [45] or stimulated by non-carbohydrate precursors [41, 47]. An interesting fact is that GLUT-2 glucose transporters are independent of insulin and for that reason, the kidneys can continue their physiological functions even in states of insulin deficiency [23].

As before mentioned, gluconeogenesis in the human body is mainly carried out by the liver and the kidneys. In the post-absorptive state, both liver and kidneys release glucose into the circulation in comparable amounts [48]. However, in the postprandial state, although overall endogenous glucose release decreases substantially, renal gluconeogenesis increases by approximately twice liver gluconeogenesis. In this sense, the hepatic and renal glucose release into the circulation in the post-absorptive state correspond to the 25–30% and 20–25% of total glucose, respectively, while in postprandial state, hepatic gluconeogenesis is reduced by ~ 80% and the release of glucose molecules generated via this pathway decreases as these molecules are largely directed into the formation of hepatic glycogen. As a consequence of these changes, renal gluconeogenesis increases accounts for ~ 60% of postprandial endogenous glucose release [49].

4.4 Gastrointestinal tract

The gastrointestinal (GI) tract is an organ system, consisting of the mouth, esophagus, stomach, and intestines, where humans ingest food, digest it to extract and absorb energy and nutrients, and expel the remaining waste as feces. However, the literature on glucose homeostasis includes the gastrointestinal tract as a complete organ without taking into account the physiological functions and glucose consumption of the stomach and small intestine as separate organs involved in glucose metabolism.

Meal is ingested through mouth and enters in the stomach to be mixed. The rate at which nutrients pass from the stomach to the duodenum, i.e., crossing the pyloric valve, is known as the gastric emptying rate and is a key determinant of

postprandial glucose flow. In the fed state, glucose homeostasis becomes more complex as the gastrointestinal tract becomes a second source of exogenous glucose. Marked and rapid changes in glucose flux occur as a result of the considerable inflow of meal-derived glucose into the circulation [50]. The delivery of nutrients from the gastrointestinal tract occurs through an important rate limiting mechanical step in the form of gastric emptying rate: the rate at which the pylorus allows small boluses of gastric content to pass into the duodenum for downstream absorption. Importantly, neither insulin nor glucagon has direct effects on gastric emptying and exogenous glucose diffusion from the gastrointestinal tract [51]. However, the influx of glucose is accompanied by secretion of several other regulatory hormones of glucose including amylin from β -cells in the pancreas and glucose-dependent inhibitory peptide (GIP), glucagon-like peptide-1 (GLP-1), and cholecystokinin (CCK) from endocrine cells in the small intestine. Endocrine cells in the small intestine collectively influence glucose homeostasis via several mechanisms of action including regulation of insulin and glucagon responses, as well as the modulation of nutrient passage from the gastrointestinal tract to appropriate tissue stores [52–54].

A key contribution of the GI tract on glucose homeostasis is the incretin effect. This physiological response came from the observation that an oral glucose load results in an increased insulin response compared to the response seen when intravenous glucose administration replicates the same changes in plasma glucose [55, 56]. In other words, when glucose is ingested orally, an augmented β -cell response is observed as a result of a signal passed from the gut. The two hormones responsible for this effect are GIP and GLP-1. Both GIP, secreted from enteroendocrine K-cells in the proximal small bowel, and GLP-1, secreted from enteroendocrine L-cells in the distal ileum and colon, have a strong insulinotropic effect [57]. Additionally, GLP-1 inhibits postprandial glucagon secretion in a glucose-dependent manner, slows gastric emptying, and reduces food intake, contributing to postprandial glucose regulation [58]. Regarding the role of the stomach in the metabolism of glucose, the stomach must consume glucose to generate the energy necessary to mechanically carry out the digestion process. Although the consumption of glucose in the stomach is relatively low, it can affect the concentration of glucose in the bloodstream.

4.5 Brain

The human brain depends on glucose as its main source of energy; neurons have the highest energy demand [59] of all types of cells in the human body, requiring continuous delivery of glucose from blood. Glucose metabolism provides the fuel for physiological brain function through the generation of ATP, the foundation for neuronal and non-neuronal cellular maintenance, as well as the generation of neurotransmitters. Therefore, tight regulation of glucose metabolism is critical to brain physiology. In this sense, the alteration of glucose metabolism in the brain is the basis of several diseases that affect both the brain and the entire organism. Glucose is required in the brain to provide the precursors of neurotransmitter synthesis and ATP to fuel their actions. Additionally, glucose is important for the brain's energy demands unrelated to signaling. Cellular compartmentalization of glucose transport and metabolism are closely related to local regulation of blood flow, and glucose-sensing neurons govern the brain–body nutrient axis. Glucose metabolism is connected to cell death pathways by the glucose-metabolizing enzymes [60]. Thus, disruption glucose delivery pathways and metabolism leads to debilitating brain diseases.

The brain uses about 120 g of glucose per day - 60-70% of the body's total glucose metabolism. The brain has little stored glucose and has no additional sources of stored energy. Brain function begins to become seriously affected when glucose levels fall below $\sim 40 \text{ mg / dL}$. Glucose levels significantly below this can lead to permanent damage and death. The brain cannot use fatty acids for energy (fatty acids do not cross the blood-brain barrier of the neurons), but ketone bodies can enter the brain and be used for energy in hypoglycemic conditions. In this sense, the brain can only use glucose, or, under conditions of starvation, ketone bodies (acetoacetate and hydroxybutyrate) for energy.

5. Conclusions

Glucose, as the main source of energy for the cells of the human body, is regulated by the joint work of several organs. Each organ involved in this glucose regulatory mechanism plays an important role that cannot be disregarded. Metabolic disorders such as diabetes mellitus are supposed to only cause an alteration of the pancreas, but recent studies indicate that when a condition such as diabetes mellitus appears, the rest of the organs are also significantly affected. For this reason, it is important to have a healthy lifestyle both to prevent diseases that cause metabolic disorders if you do not have them or to have better control of blood glucose levels and prevent possible complications that these disorders can cause.

Author details

Laura Lema-Pérez
National University of Colombia, Medellín, Colombia

*Address all correspondence to: llemap@unal.edu.co

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