PSM
Biological Research

Review Article | 2024 | Volume 9 | Issue 3 | 93-102

Open Access

Article Information

Received: August 25, 2024

Accepted: September 16, 2024

Published: September 30, 2024

Keywords
Glucose homeostasis,
Warburg effect,
Oxidative stress,
Hyperglycemia,
Neurodegenerative diseases.

Authors' Contribution
AJA conceived and designed the study; wrote and revised the paper.

How to cite
Alkhatib, A.J., 2024. Glucose Homeostasis: From Consumption to Complete Metabolic Pathways. PSM Biol. Res., 9(3): 93-102.

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Glucose Homeostasis: From Consumption to Complete Metabolic Pathways

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Abstract:
A complex and precise set of regulatory mechanisms control the concentration of glucose in our blood. This balanced glucose homeostasis is relevant for successful cellular construction, energy provision, and redox balancing. The blood typically contains 5 grams of glucose. To avoid hypoglycemia, cells should have instantaneous access to extra-cellular glucose sources, both due to the secretion of insulin, causing the release of extra glucose, and the glycolysis inhibitor hormone glucagon. This availability of glucose for skeletal muscles, the brain, and cells lacking mitochondrion forms the cornerstone of the evolution of the auxiliary functions of locomotion and warm-bloodedness. But glucose, if prevalent in the extra-cellular environment, might also trigger oxidative stress and, together with it, cell senescence and carcinogenesis. However, the glucose-induced protective response might fail, especially in cells and tissues prone to tumor initiation. Such dysfunctions on the background of active glycolysis bear the hallmarks of the Warburg effect. Hyperglycemia triggered by the modern diet, possibly the main inducer of the Warburg effect, significantly aggravates the risk of many diseases, including cancer and neurodegenerative ones.

INTRODUCTION

Glucose is the primary source of energy for both the brain and red blood cells (Dimitriadis *et al.*, 2021). The latter have a limited capacity to utilize other fuel molecules and the brain works only under aerobic conditions (Cherkas *et al.*, 2020). Consequently, glucose homeostasis is of tremendous importance in providing the appropriate supply of energy for the brain and red blood cells (Alonge *et al.*, 2021). Glucose levels in the blood must be constantly maintained within a tight physiological range to sustain anabolism (Cacciatore *et al.*, 2022). Net postprandial glucose uptake is accomplished through several tissues (Amawi *et al.*, 2019; Kosmachevskaya *et al.*, 2021). The majority of ingested glucose is initially absorbed by enterocytes and transported through the portal vein to the liver (McMahon *et al.*, 2021). The liver may store glucose as glycogen or metabolize it directly or indirectly (by converting it to nonesterified fatty acids) (Alkhatib, 2020a; Maheshwari *et al.*, 2021). Arterialized venous glucose from the liver is delivered to all tissues regardless of their rate of glucose uptake (Nguyen *et al.*, 2022). The more an individual is exposed to a challenging situation, the more pronounced the meal-related glucose metabolism aberrations will be (Nemkov *et al.*, 2024; TeSlaa *et al.*, 2021).

Glucose levels in the blood must be constantly maintained within a tight physiological range, as its utilization is linked to a number of severe complications, a phenomenon defined as glucose homeostasis (Alkhatib, 2019b; Yeo and Sawdon, 2013). The primary hormone linking blood glucose to its homeostasis is insulin (Alkhatib *et al.*, 2020; Norton *et al.*, 2022). Insulin regulates glucose homeostasis via its effects on glucose production from the liver and kidneys and glucose disposal in peripheral tissues, mainly muscle and adipose tissue (Alsarhan *et al.*, 2020; Holst *et al.*, 2021). Immediately after the onset of sleep, the titer of nonesterified fatty acids increases in the plasma (Dimitriadis *et al.*, 2021). This hormonal milieu enhances free fatty acid uptake by muscle and consequently decreases muscle glucose uptake (Erekat *et al.*, 2014; Lewis *et al.*, 2021). Blood levels of glucose are regulated by insulin-mediated rates of glucose production from the liver and removal from muscle; adipose tissue provides nonesterified fatty acids as an alternative fuel for skeletal muscle and liver when blood levels of glucose are depleted (Bizzotto *et al.*, 2021). The latter occurs through inhibiting liver gluconeogenesis or glycogenolysis or by changing the pattern of glucose-directed muscle metabolism (Rahman *et al.*, 2021).

Glucose Consumption and Digestion

Although carbohydrates are not the only sources of glucose, the dietary intake of this monosaccharide and the transport of the monomer is widely accepted as an essential nutrient (Lizák *et al.*, 2019). The human body gets all of its glucose from dietary sources (Hantzidiamantis *et al.*, 2024; Nakrani *et al.*, 2020)*.* Glucose and hexitols released in the small intestine are taken into the blood circulation and distributed to various organs, where their physiological response triggers (Alkhatib, 2019a; Seal *et al.*, 2021). A part of the absorbed glucose/hexitol is transported to the liver through portal veins for elimination (Khalid *et al.*, 2022). In the liver, they will be metabolized by various metabolic pathways, and a part of them is re-distributed to other organs through the reversible operation of the liver by the portal veins (Zavitsanou and Drigas, 2021; Zou *et al.*, 2021).

Major ingested carbohydrates are broken down into absorbable glucose molecules, primarily under the action of various enzymes (Dmour *et al.*, 2020; Iqbal and Ashraf, 2020). For example, starch is hydrolyzed by salivary α-amylase contained in saliva and pancreatic α-amylase in the upper zone of the small intestine to give maltose, maltotriose, and oligosaccharides, which are subsequently digested by digestive α-glucosidase contained in the brush border membrane of the duodenum and jejunum cells to release glucose molecules (Saha and Pathak, 2021). Small amounts of glucose also are formed by hydrolysis of dietary sucrose and lactose on the luminal surface of such digestive tract cells (McQuilken, 2021)*.* The overwhelming majority of glucose finally results from the action of α-glucosidase present as disaccharidized food on the apical membrane of jejunal and duodenal cells (McQuilken, 2024). In glucose absorption from the small intestine, gastric and intestinal phases are differentiated, in addition to the chemical and enzymatic properties of ingested substances, digestibility, rate of gastric emptying and intestinal peristalsis, etc., it stabilizes according to the systemic glucose level (Kobiljonovna, 2022). In the case of the gastric phase, when acid, hypoglycemia occurs after meal, the stomach wall tension and the rate of glucose outflow from the stomach to the duodenum increases (Malik *et al.*, 2023; Monteiro-Alfredo and Matafome, 2022).

Glucose Absorption and Transport

Two main types of glucose transporters have been identified, namely, sodium-glucose linked transporters (SGLTs) and facilitated diffusion glucose transporters (GLUTs) (Navale and Paranjape, 2016). The glucose transporter 4 (GLUT4) has 45% homology with the glucose transporter 1 (GLUT1) protein (Wang *et al.*, 2020). The first model of the solution structure of the cytoplasmic domain of GLUT4 was published in 2002 while a major breakthrough was achieved in 2014 when X-ray-derived three-dimensional structures became available for the full-length and in silico-designed mutant GLUT18 (Chang *et al.*, 2023). The GLUTs do not contain regulatory domains and operate by the alternating exposure of single-line glucose-binding sites on either side of the plasma/cell membrane via a putative "rocker-switch” mechanism of conformational change (Shriwas *et al.*, 2021). Indeed, the molecular mechanisms of glucose transport by the major facilitator superfamily (MFS) of secondary carriers, including GLUTs, are based on their structure and dynamics (Burgos *et al.*, 2024). A significant contribution to the understanding of glucose transport was recently provided by the elucidation of the structures of the bacterial homologs of the human GLUTs (Dai *et al.*, 2024). Each of the six previously reported X-ray-derived structures of the sodium-glucose linked transporters (SGLT1/2) has been solved in a complex with the glucose molecule (Ermini *et al.*, 2021).

The human genome encodes 18 related facilitative glucose transporters, which mediate the selective passive transport of hexoses down a concentration gradient (Głuchowska *et al.*, 2021). Five of these isoforms expressed in human liver cells have been biochemically characterized (Niu *et al.*, 2022). The hepatic GLUTs are dynamically regulated by multiple mechanisms at both transcriptional and post-translational levels (Low *et al.*, 2021). The physiological significance of active glucose uptake relative to passive glucose absorption across the small intestine has been an issue of long-standing debate (Lizák *et al.*, 2019). Nonetheless, it is generally accepted that the bulk of postprandial glucose enters the circulatory system through the basolateral membrane of the Enterocytes (Pliszka and Szablewski, 2021). Enterocyte glucose was extruded by the facilitative glucose transporter 2 (GLUT2), detected in special membrane microdomains including the caveolae as well as in the bulk basolateral, but not in apical plasma lemma (Jiang *et al.*, 2022). Twenty hours after glucose administration, the amount of GSH in both the plasma and liver of untreated rats was unchanged (Dai *et al.*, 2024).

Glucose Metabolism: Glycolysis, Gluconeogenesis, and Glycogenesis

Glucose is the most readily available and malleable carbohydrate used by the human body. All cells need a constant supply for energy production (Zhang *et al.*, 2021). Many different organs, such as the brain, muscles, and kidneys, have their metabolism particularly adapted to glucose consumption (Norton *et al.*, 2022). A lack of glucose in the diet may disrupt energy balance, and cause metabolic dysregulation and pathology (Cherkas *et al.*, 2020). To avoid this, glucose metabolism is tightly regulated at multiple levels (Agbu and Carthew, 2021). As glucose is the most oxidizable metabolite, its consumption is prioritized by the organism and can be promptly modified if the environment changes. In the short term, moderate increases in glucose consumption stimulate its metabolism in many tissues. Yet, in the long term, the decline in glucose availability reduces the costs of its metabolism, particularly in highly efficient tissues such as the brain. The different physiological conditions demand variations in glucose metabolism, and the organism is prepared for each of them. Following ingestion of carbohydrates, most of the glucose enters the bloodstream, and must be metabolized promptly to avoid hyperglycemia. Insulin increases glucose consumption after meals, as it activates the glycolytic machinery and the uptake of glucose by the cell membrane. During physical activity, the muscle consumes great amounts of glucose, which increases proportionally to the exercise intensity (Dimitriadis *et al.*, 2021). In turn, fasting conditions impose the need to rapidly produce glucose by other means, mostly from triacylglycerols in the liver (Mayneris-Perxachs *et al.*, 2022). Then, gluconeogenesis is increased in most tissues, except for the brain and muscle (Morigny *et al.*, 2021). At the same time, glycogen stores can be degraded and used when circulating glucose levels have been fully depleted (Wachsmuth *et al.*, 2022). This situation is usually detected first in the liver and quickly in the muscle and brain (Legouis *et al.*, 2022).

Regulation of Glucose Homeostasis

Endocrine regulation of glucose homeostasis is highly integrated and involves a variety of hormones and other signaling molecules(Alkhatib *et al.*, 2020). The involvement of many chemical signaling pathways and feedback loops enables the body to maintain a stable blood glucose concentration under varying conditions (Zhang *et al.*, 2022). A negative feedback loop in a control system works to maintain a variable at a constant set point, such as wearing a garment that helps maintain body temperature (Ahrorbek *et al.*, 2023). An increase in glucose concentration in plasma, such as after ingesting food (a positive metabolic net balance), induces a strict regulation of hormones to avoid hyperglycemia and hyperinsulinemia (Zhang *et al.*, 2023b).

Hormones play a key role in the control of plasma glucose homeostasis (Rahman *et al.*, 2021). Insulin and glucagon are the principal hormones regulating blood glucose (Zheng *et al.*, 2024). Insulin decreases blood glucose concentration while glucagon increases it (Yeo and Sawdon, 2013). The effect of these hormones results from their action on the storage, synthesis, and breakdown of carbohydrates, fat, and protein. Glucose metabolism is subject to hormonal regulation (Oberoi *et al.*, 2022). Hormones influence metabolic pathways by modulating the activity of enzymes (Banerjee *et al.*, 2024).

The major target of insulin is the liver, but adipose and muscle tissues are also important for maintaining homeostasis (Ahmed *et al.*, 2021). After a meal, insulin primarily stimulates glucose storage as glycogen stimulates the conversion of glucose to fatty acids, and inhibits gluconeogenesis (Li *et al.*, 2022). In contrast, during fasting, glucagon increases glycogenolysis and gluconeogenesis in liver cells, and lipolysis in the adipocytes (Dimitriadis *et al.*, 2021). Recovery of glucose homeostasis occurs within approximately 2-3 hours (Rahman *et al.*, 2021). Strenuous exercise, however, can lead to an elevated post-reservoir need to maintain normal glucose levels (Alkhatib, 2020b; Lee *et al.*, 2022). Stress induces the release of cortisol, epinephrine, and other hormones that increase blood glucose levels (Sylow *et al.*, 2021). This response is especially important in case of concomitant trauma or infection, as it enhances the effectiveness of the immune defense (White and Kahn, 2021).

Future Directions and Concluding Remarks

The essay has taken the reader on a journey from the consumption of glucose through to its complete metabolism, emphasizing control and regulation by the body along the way (Tappy, 2021). This has included an overview of the physiological and metabolic processes involved and of the hormonal systems that control them (Shin and Koo, 2021). The review has placed particular attention on the homeostatic balance and the perturbation in this, outlining the role of glucose as a primary source of fuel and the 'fuel-partitioning' dilemmas of the body (Kieler *et al.*, 2021). It has been discussed how knowledge of glucose metabolism and homeostasis has relevance to both clinical and nutritional practices, including the prevention and management of metabolic and other diseases (Du *et al.*, 2021; Shi *et al.*, 2022).

In recent years, research has made significant advances in understanding the comprehensive pathways of metabolism within the human body (Alkhatib, 2022; Cherkas *et al.*, 2020). This is supported by the listing of detailed and complete metabolic pathways in recent editions of standard textbooks and educational resources in biochemistry. The full description of these research pathways must break the familiar pattern of listing particular compounds (or enzymes) in each part of the Krebs cycle or each step of the 'pay-off' phase of glycolysis. Instead, it must summarize the details of glucose metabolism at each point in a way which can also be used to investigate the complete metabolism of other carbohydrates or intermediate metabolic products, such as glycerol, which may be converted to glucose (Tufail *et al.*, 2024). In turn, the same consideration will be made for the metabolism of fatty acids and amino acids in order to work towards a more holistic view of mammalian metabolism (Zhang *et al.*, 2023a). Further areas for research are outlined, emphasizing the serious, and often detrimental, lifestyle choices that can be made concerning stress, substance misuse, and the improper management of weight, diet, and exercise (Singh *et al.*, 2023). Finally, it is hoped that parallels can be drawn between the increase in popular knowledge and dietary villainization of glucose in recent decades with the earlier stigmatization of fats (Sun *et al.*, 2024).

CONFLICT OF INTEREST

Author hereby declares that he has no conflict of interest.

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