Seung-Hoon Lee
Dong-Wan Kang *Editors*

Stroke Revisited: Diabetes in Stroke

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Stroke Revisited

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Preface

Professor Seung-Hoon Lee, my mentor and teacher, served as a principal editor for the *Stroke Revisited* series. I thankfully had the opportunity to write two chapters as a coauthor with Professor Lee, including "Diabetes management after stroke" in Vol. 1—*Diagnosis and Treatment of Ischemic Stroke*." Vol. 1 was written to quickly understand a specific topic by simply looking up the textbook in practice. The chapter "Diabetes management after stroke" was also written from that point of view.

However, as soon as Vol. 1 was published in 2017, the diabetes guidelines have been significantly updated based on the numerous clinical trials of the emerging antidiabetic medications. In particular, the effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP1-RA) in atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease have been published, resulting in tectonic shift of the guidelines.

Vol. 6—Diabetes in Stroke is made into a comprehensive textbook covering (1) basic science of glucose metabolism and diabetes, (2) general treatment principles for diabetes, and (3) effects of diabetes on cerebro-cardiovascular disease and practice in stroke patients. As Professor Lee made the overall composition of this book, he has given me an insight of concepts of diabetes in relation to stroke. The physicians who manage patients with stroke should keep pace with the rapidly changing diabetes guidelines, and have knowledge that encompasses the basic science of diabetes and practice. I wish to express my deep and sincere gratitude for all the authors who have participated.

As a physician and a researcher, our ultimate goal is to help the patients live better lives. I hope this book will guide the physicians to better understand diabetes in relation to stroke and give prompt management to the patients.

Seoul, Republic of Korea
March 2021

Dong-Wan Kang

Preface

The *Stroke Revisited* series now presents its final publications. As a principal editor, since Vol. 1:—*Diagnosis and Treatment of Ischemic Stroke* published in 2017, I sequentially presented Vol. 2:—*Hemorrhagic Stroke*, Vol. 3—*Vascular Cognitive Impairment*, and Vol. 4—*Pathophysiology of Stroke: From Bench to Bedside*. Finally, the contract with Springer Nature to publish six volumes of the *Stroke Revisited* series is now completed together with the current books: Vol. 5—*Dyslipidemia in Stroke* and Vol. 6—*Diabetes in Stroke*. Writing and editing these series in approximately five years, I have done my best to create a complete series, not to leave any scratch on the honor of the publisher and me. Looking back over the years, there are some regrets that it would have been a better book series if I had invested a little more energy. However, working concurrently as a clinical professor at Seoul National University Hospital, chair of the Korean Cerebrovascular Research Institute (KCRI), and CEO of a bio-venture company, Cenyx Biotech Inc., I am comforting myself with this level of achievement. Of course, while continuing to monitor the contents of the books, I commit to maintain the latest level of knowledge by revising, reinforcing, or replacing chapters that have become knowledge of the past. Vols. 1, 2, and 4 are books I put much effort into as the sole principal editor, whereas for Vols. 3, 5, and 6, I am very grateful for the efforts of the coeditors. In the initial contract, Vols. 5 and 6 were planned to have titles of "Small vessel disease" and "Large artery atherosclerosis," respectively. Writing Vol. 4, *Pathophysiology of Stroke*, I realized that I put a considerable amount of content prepared for Vols. 5 and 6 into Vol. 4. Therefore, I was exceedingly worried about the necessity of proceeding with the original series. Meanwhile, a new era began with the introduction of various new drugs and biologics for the treatment of dyslipidemia and diabetes. Considering the changed circumstances, I thought it would be better to make books that reflect the development of new drugs in these fields. Since the publisher generously agreed with my idea, Vols. 5 and 6 were presented to you with new themes: dyslipidemia and diabetes in stroke.

Vol. 6—Stroke Revisited: Diabetes in Stroke is another comprehensive book that deals with the effects of diabetes mellitus in relation to stroke, basic knowledge, and clinical aspects. Physicians involved in the management of stroke have not been interested in diabetes because it has been studied in the field of endocrine medicine, and antidiabetic drugs have critical side effects such as hypoglycemia. As the number of patients with diabetes worldwide is rapidly increasing, and new diabetes drugs that are effective while significantly

lowering the side effects are emerging, physicians managing stroke also feel a need to accept the current knowledge on diabetes. Notably, new antidiabetic drugs such as sodium-glucose co-transporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have a superior ability to suppress the occurrence of vascular diseases, including stroke, compared to other classes of drugs. They are now being recommended as first-line therapy in patients with stroke and diabetes. In this book, I invited experts to comprehensively explain the latest findings from the basics of diabetes to clinical practice in relation to stroke. With few clinical studies on the preventive effect of diabetes on stroke, I am confident that this book will be a good guide for clinicians dealing with stroke or diabetes.

The six-volume *Stroke Revisited* series is now completed. I would like to express my deep gratitude to Springer Nature for providing me with this great opportunity. While producing six books up to this point, the KCRI has provided great support for writing these books, and my colleagues have provided valuable help in various ways. I profoundly appreciate it all. In the future, whenever new information is released regarding the contents of the series, partial or full revisions will be made to offer cutting-edge knowledge as much as possible. When I was studying stroke in my youth, I had hard times because of difficulties finding optimal books in the clinical aspects of stroke. The fact that I have produced some books that will help clinicians worldwide is quite rewarding for the rest of my life.

Seoul, Republic of Korea Seung-Hoon Lee
March 2021

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Part I

Basic Science: Diabetes and Stroke

Glucose Metabolism

1

Obin Kwon

Abstract

- Insulin, the glucose-lowering hormone, is the key hormone in glucose regulation. In response to each meal intake, insulin is secreted from pancreatic β-cells, where its proper function is essential for glucose homeostasis. Long-term body energy imbalance (such as obesity) can change insulin level and sensitivity. Counterregulatory hormones include glucagon, epinephrine, and cortisol which prevent hypoglycemia.
- Blood glucose concentration is normally maintained within a narrow range. Glucose, the main outcome of carbohydrate digestion, is a major source of cellular energy. Blood glucose can be transported into cells by cell type-specific glucose transporters and utilized to produce ATP. Intracellular glucose can also be converted into other metabolites linked with lipid and protein metabolism. To provide glucose in the fasted state, the liver can synthesize glucose.
- The brain is a "consumer" and also a "modulator" in glucose metabolism at the same time. Glucose is the primary fuel for the brain in normal states. During prolonged fasting, increased ketone body can replace the main fuel for the brain. The brain can detect glucose levels, interpret related signals through hormones, and continuously tune the body mechanisms to maintain blood glucose within a predetermined range.

1.1 Pancreatic β-Cell Function

1.1.1 Pancreas

The pancreas is a digestive and endocrine organ located in the abdomen. As a digestive organ, the pancreas synthesizes and secretes pancreatic juice, which contains a variety of digestive enzymes, including trypsinogen, lipase, and amylase. These enzymes are produced in exocrine glands consisting of acinar cells, which make up more than 85% of the whole pancreas volume. On the other hand, pancreatic hormones are produced in scattered endocrine glands: these regions containing endocrine cells are called islets of Langerhans. [Note: The word "insulin" is from the Latin word *insula,* meaning "island."] Several subsets of hormone-producing cells are distributed in the islet, and each type of cell secretes a distinct hormone. Table 1.1 shows the characteristics of each cell type and the hormones they produce. In glucose metabolism, insulin released from pancreatic β-cells lowers blood glucose levels, and glucagon from pancreatic

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Table 1.1 Types and characteristics of endocrine cells in pancreatic islets

Cell type	Hormone and its action on glucose metabolism	Proportion(%) in human	Histological distribution in the islet
Alpha (α) cell	Glucagon: increase blood glucose level as a counterregulatory hormone of insulin	20~35[a]	Periphery in rodents
Beta (β) cell	Insulin: decrease blood glucose level by stimulation of cellular uptake	50~70[b]	Central in rodents
Delta (δ) cell	Somatostatin: inhibit glucagon and insulin release	5~10[a]	Periphery in rodents; central in human

Relatively [a]lower and [b]higher proportion in rodents compared to humans

α-cells raises them. These islets make up only about 1~2% of the total pancreas cells but receive 10~15% of their blood flow. This anatomical structure makes it suitable for the islet to release relevant hormones in response to changes in blood content.

The composition and structure of the islet vary among species. Compared with rodents, islets of humans and other primates are more heterogeneous in cellular composition and more prominently vascularized [1]. Rodents have relatively higher proportions of β-cells while humans have higher proportions of α- and δ-cells [2]. Rodent islets are organized into a mantle of α- and δ-cells surrounding centrally clustered β-cells [3]. These differences may be the reason behind poor translation across species in the pancreatic regulation of glucose metabolism [4].

1.1.2 Insulin

Insulin is the most important hormone regulating the use of energy sources (fuels) by tissues. It is an anabolic hormone in metabolism: it stimulates the synthesis of glycogen, triacylglycerol, and protein. In human disease, insulin is the key treatment for patients with type 1 diabetes or type 2 diabetes with β-cell failure.

1.1.2.1 Synthesis

Insulin is a 51-amino acid polypeptide hormone composed of two amino acid chains linked together by two disulfide bonds. The human insulin gene is located on the short arm of chromosome 11 at position 15.5 (11p15.5) [5]. The synthesis, processing, and intracellular transport of insulin are shown in the upper part of Fig. 1.1. After transcription of the insulin gene inside the nucleus, the mRNA is translated by cytosolic ribosomes. Initial translation results in the formation of an N-terminal signal sequence, which aids the transport of the mRNA-ribosome complex to the rough endoplasmic reticulum (RER). The translated peptide penetrates the RER membrane and is further elongated in its lumen to form preproinsulin (an inactive precursor). Proinsulin is formed from preproinsulin by cleavage of the signal sequence and the formation of two disulfide bonds between the chains. Proinsulin is transported to the Golgi, where it is cleaved into insulin and C-peptide (connecting peptide). Insulin is precipitated with Zn^{2+} and packaged with the C-peptide into secretory granules stored in the β-cell. The C-peptide level is a good indicator of endogenous insulin production and secretion, because it has a longer half-life compared to insulin and does not exist as a constituent of currently available exogenous insulin analogs [6].

1.1.2.2 Secretion

Insulin is stored in vesicles (cytosolic granules) until released by exocytosis in response to proper stimuli. The lower part of Fig. 1.1 briefly describes the pathway to insulin release upon stimulation by glucose. Glucose enters the β-cell via specific glucose transporter proteins, glucose transporter 2 (GLUT2, see Sect. 1.2.2.1. and Table 1.2 below). Intracellular glucose is utilized to increase adenosine triphosphate (ATP) levels within the β-cell, resulting in the inhibition

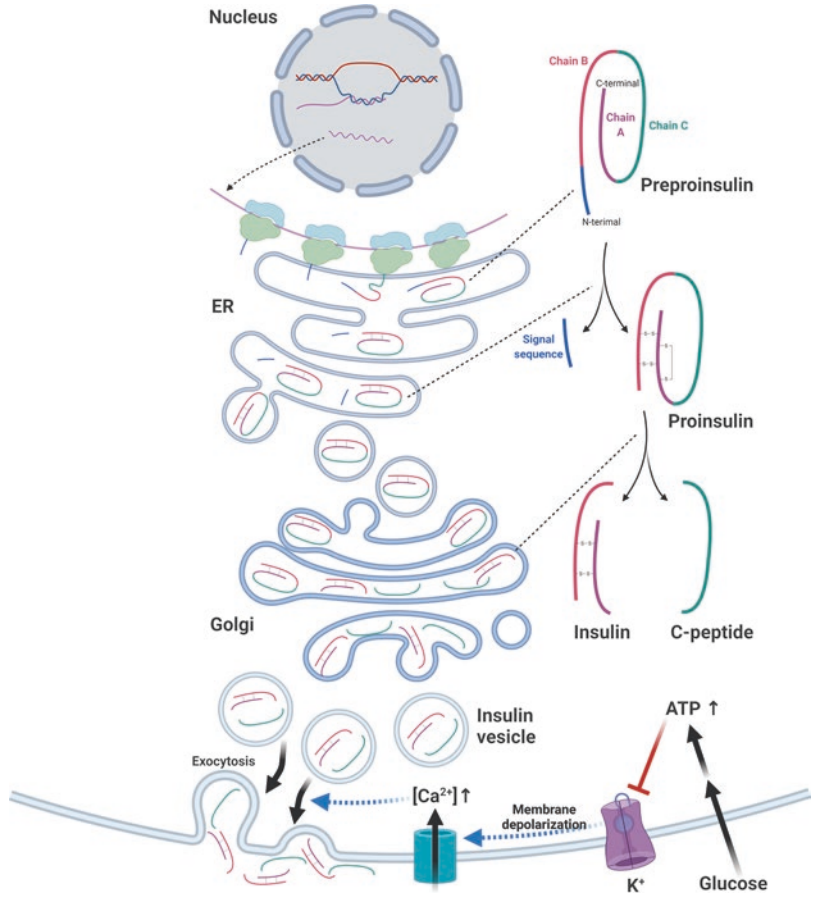

Fig. 1.1 Synthesis, processing, intracellular transport, and release of insulin in pancreatic β-cell. *ATP* adenosine triphosphate, *ER* endoplasmic reticulum (made in ©BioRender—biorender.com)

Table 1.2 Properties of the major isoforms of the glucose transport proteins

Isoform	Tissue distribution	Characteristics
GLUT1	Cell types with barrier functions (including blood-brain barrier) Human erythrocyte Expressed to some degree in most tissue	– Provides a low, constant level of glucose transport necessary for basal cellular processes – Postnatal switch from GLUT1 to GLUT4 in mice – High affinity to glucose
GLUT2	Liver Kidney Pancreatic β-cell Intestinal luminal surface	– Glucose sensor in pancreatic β-cells and intestinal epithelial cells absorbing glucose – High capacity, low affinity to glucose
GLUT3	Brain (neurons)	– Major transporter in the central nervous system – Transports glucose into neurons (with GLUT1) – High affinity to glucose
GLUT4	Adipose tissue Heart muscle Skeletal muscle	– Insulin-dependent expression: sequestered in intracellular vesicles under basal conditions and mobilized to cell surface in the presence of insulin – High affinity to glucose
GLUT5	Intestinal luminal surface Spermatozoa	– Transports fructose

GLUT glucose transporter

(closing) of ATP-dependent K^+ channels (K^+_{ATP}) on the plasma membrane. This leads to membrane depolarization, which activates voltage-gated Ca^{2+} channels allowing Ca^{2+} to enter the β-cell. Elevated intracellular Ca^{2+} stimulates the fusion of insulin-containing vesicles, and insulin is released. First-phase secretion, in which the "readily releasable" pool below the plasma membrane is depleted, usually occurs within 10 min of glucose stimulation. Second-phase secretion is less robust but more gradual and long lasting [7, 8].

1.1.2.3 Regulation of β-Cell Function

As β-cell function is critical for glucose homeostasis, insulin secretion is finely regulated by multiple mechanisms. In humans, food intake usually occurs regularly at multiple (usually three or two) times throughout the day. Insulin is secreted in response to each meal: this is a typical example of how insulin secretion is regulated in the short term. Different nutrients have distinct effects on the release of metabolic hormones. Glucose stimulates insulin release and inhibits glucagon release, whereas amino acids stimulate the secretion of both insulin and glucagon. Therefore, the relative amounts of insulin and glucagon in the blood (and thus their final composite effect) after a mixed meal depend on its composition. Other short-term regulation mechanisms related to body energy status will be further described in Sect. 1.2. Normal glucose metabolism.

The function of the β-cell is also controlled in a long-term manner. After prolonged starvation, insulin stores decrease markedly [9]. On the other hand, obesity due to chronic overnutrition is associated with insulin resistance and higher demand for insulin. Initially, the body can adapt by increasing β-cell mass, since a small number of β-cells can still proliferate. If continued, however, β-cells gradually become dysfunctional and ultimately fail to compensate sufficiently. This process is found in the natural history of type 2 diabetes, which will be described in detail in the next chapter ("Pathophysiology of diabetes").

1.1.3 Glucagon and Other Counterregulatory Hormones

In the regulation of blood glucose, insulin is the dominant hormone lowering blood sugar, whereas several counterregulatory hormones increase it. Such a system is advantageous for survival because prolonged and marked hypoglycemia due to energy depletion can be a threat to life. These counterregulatory hormones include glucagon, epinephrine, and cortisol.

Glucagon is a polypeptide hormone consisting of 29 amino acids arranged in a single polypeptide chain. It counters many of the actions of insulin. Most importantly, glucagon mobilizes fuel to maintain blood glucose levels. This is achieved by promoting glycogenolysis and gluconeogenesis in the liver and fatty acid release from adipose tissue. Similar to insulin biosynthesis, preproglucagon, a large precursor molecule, is first synthesized and converted to glucagon by proteolytic cleavages. Interestingly, preproglucagon can be processed into different products according to tissue type: in intestinal L cells, glucagon-like peptide-1 (GLP-1) is produced from preproglucagon and works as an insulin secretagogue [10, 11].

Epinephrine is released during periods of stress (such as hypoglycemia) to signal an immediate need for increased fuel availability. When the adrenal medulla is activated by the sympathetic nervous system, epinephrine levels rise rapidly, triggering the fight-or-flight response. It stimulates glucose production by glycogenolysis in muscle and liver and fatty acid release from adipose tissue. Its role during hypoglycemia can be critical if the action of glucagon is impaired [12].

Cortisol is a glucocorticoid released by the adrenal cortex in response to fasting. [Note: in rodents, corticosterone is the primary adrenal corticosteroid.] It stimulates amino acid mobilization from muscle protein to meet changing requirements during periods of stress. Cortisol also promotes hepatic gluconeogenesis and fatty acid release from adipose tissue. Cortisol and

growth hormone (from the anterior pituitary gland) are involved in the prevention or correction of hypoglycemia, but their role is not critical compared with glucagon or epinephrine.

1.2 Normal Glucose Metabolism

1.2.1 Homeostasis (at the Level of an Organism)

Homeostasis is the steady state of conditions for the optimal function of an organism, including humans. Many variables in the body need to be maintained within a narrow range: these include body temperature, acid-base balance, blood oxygen, blood pressure, concentrations of various ions, osmolality, etc. In fact, homeostasis is not a passive state but rather a dynamic equilibrium actively regulated by complex systems with multiple feedback mechanisms.

In humans, plasma glucose concentration is also normally maintained within a narrow range, about 72–144 mg/dL (4–8 mmol/L). This range is achieved by a fine balance between glucose influx and efflux. Glucose influx can be either exogenous glucose intake or endogenous glucose production by gluconeogenesis or glycogenolysis. Glucose efflux mainly occurs as glucose utilization in the peripheral tissues and brain. [Note: glucose efflux can also occur as glycosuria (excretion of glucose into the urine) in diabetic patients or by the sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor, a "glycosuric" antidiabetic drug [13].]

1.2.1.1 Glucose in Fed (Absorptive) State

Figure 1.2 shows glucose homeostasis in fed and fasting states. Carbohydrates provide a significant proportion of dietary calories for most organisms. Human meals are usually a mix of various polysaccharides, oligosaccharides, and disaccharides. Digestion of dietary carbohydrates occurs mainly in the mouth and intestinal lumen. Amylase (salivary and pancreatic) and various glycosidases in the brush border of the intestine sequentially hydrolyze glycosidic bonds in carbohydrates. Mastication (chewing) and peristalsis of the gut mechanically help digestion. Monosaccharides (glucose, galactose, and fructose), the final products of digested carbohydrates, are absorbed by enterocytes (intestinal epithelial cells) of the small intestine. Enterocytes express hexose transporters on their luminal surface: sodium-dependent glucose cotransporter 1 (SGLT1) for glucose and galactose and/or GLUT5 for fructose uptake, respectively [14, 15]. These monosaccharides are released into the portal circulation by GLUT2: so, the liver is the first tissue that absorbed glucose passes through.

Elevated blood glucose levels after meal intake induce insulin release from pancreas β-cells. Within the pancreatic islet, insulin from β-cells can affect nearby α-cells directly and/or indirectly [16, 17]. Therefore, secreted insulin can locally inhibit glucagon release first, efficiently lowering blood glucose, especially after meal intake. [Note: current insulin treatment (exogenous insulin injection/infusion) for diabetic patients does not recapitulate this paracrine effect of endogenous insulin.]

In healthy individuals, oral glucose induces similar levels of glycemia but greater insulin secretion compared to intravenous glucose; this is called the incretin effect [18, 19]. A portion of the glucose that enters the liver is extracted from circulation. Some are oxidized to generate ATP, and the remainder is converted to glycogen and triacylglycerol or used in other biosynthetic pathways. These anabolic mechanisms are promoted by insulin secreted in the fed state.

Glucose from portal circulation that is not metabolized by the liver moves to peripheral tissues. All tissues can utilize glucose as metabolic fuel. Many tissues have small stores of glycogen, while muscle has relatively larger ones. Insulin stimulates glucose uptake by muscle and adipose tissue, two types of tissue that occupy the largest mass in the body. As a result, 2-h postprandial blood glucose is normally controlled under 140 mg/dL (7.8 mmol/L).

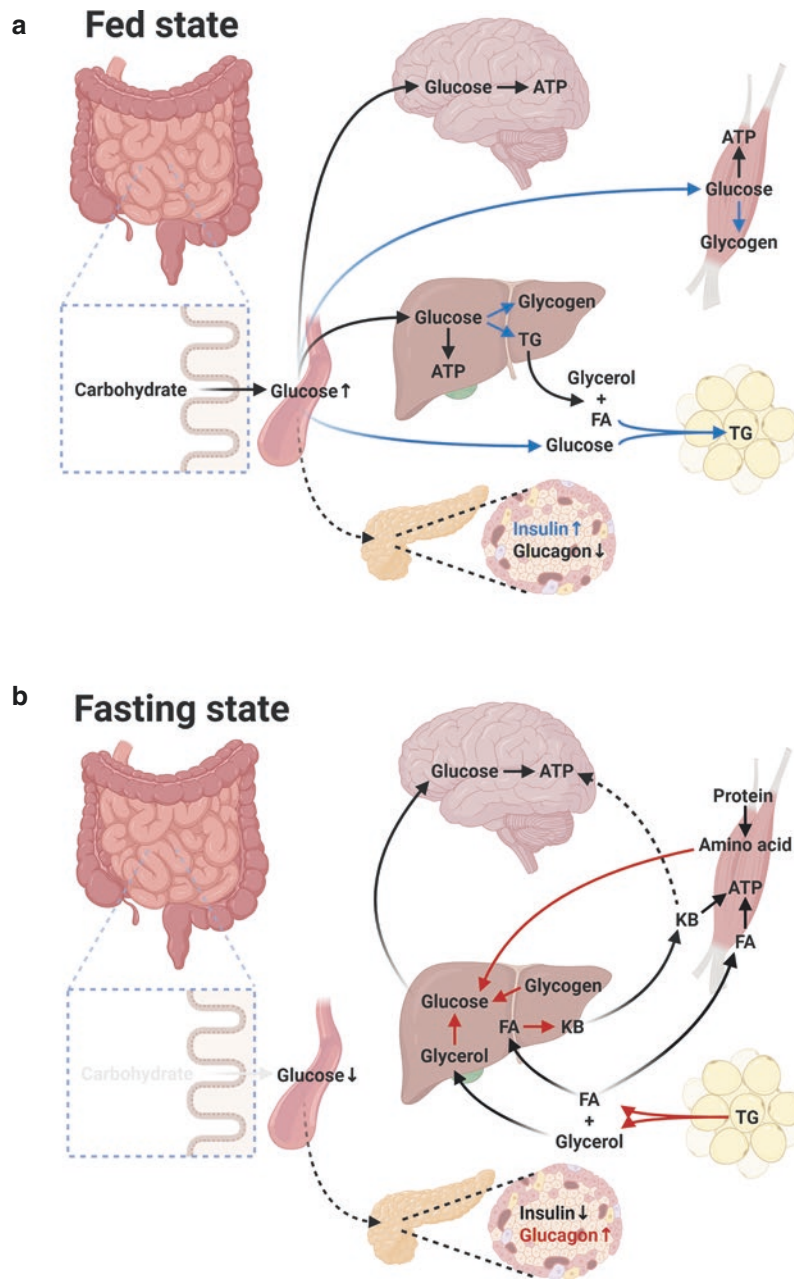

Fig. 1.2 Glucose homeostasis in fed vs. fasting state. (**a**) Interorgan relationships in the fed state; (**b**) interorgan relationships in the fasting state. *Blue* and *red arrows* indicate pathways stimulated by increased insulin and glucagon, respectively, in each state. *ATP* adenosine triphosphate, *FA* fatty acid, *KB* ketone body, *TG* triacylglycerol (made in ©BioRender—biorender.com)

1.2.1.2 Glucose in Fasting (Postabsorptive) State

What happens when we continue to fast for a 12-h period, as in the case of overnight fasting (no food since the previous dinner)? No glucose has been provided from the intestine, and plasma levels of energy sources (including glucose, amino acids and triacylglycerol) fall. Peripheral tissues need to provide glucose to maintain blood glucose homeostasis, so serum insulin levels are low, and glucagon is rising at this point. Initially, stored fuels are used to produce energy, especially by the liver. It maintains blood glucose levels first by glycogenolysis then by gluconeogenesis using other carbon sources (such as lactate, glycerol, and amino acids). [Note:

Proteolysis in the muscle provides amino acids.] Lipolysis in adipose tissue releases fatty acids, which serve as the major fuel for most organs during fasting. The liver converts most of its fatty acids into ketone bodies through partial oxidation. These are released into circulation; thus, blood levels of fatty acids and ketone bodies increase at the beginning of fasting. Muscle utilizes fatty acids, ketone bodies and (when exercising and available) glucose from glycogenolysis of muscle glycogen. Most other tissues use fatty acids or ketone bodies. However, red blood cells, the brain, and other neural tissues are mainly dependent on glucose.

During prolonged fasting, when we continue to fast for longer than a 24-h period, we are in a starved state. Muscle continues to oxidize fatty acids but decreases the use of ketone bodies. The resulting rise in blood ketone body concentration allows the brain to oxidize them for energy. The brain's demand for glucose decreases, so the rate of gluconeogenesis in the liver declines. This spares the protein in muscle and other tissues from being degraded to supply amino acids for gluconeogenesis. As a result, vital functions can be preserved for as long as possible. These changes in the fuel use patterns of various tissues enable humans to survive extended periods of fasting.

1.2.2 Glucose Uptake in Cellular Level

The inside of the cell is physically and chemically separated from the outside environment by the cell membrane. This barrier is primarily composed of a phospholipid bilayer with the hydrophobic tails facing the interior. As glucose is hydrophilic, specific transporters are needed to facilitate the uptake of glucose across the plasma membrane.

1.2.2.1 Glucose Transporter (GLUT)

Glucose transporters are facilitative transport proteins located in the cell membrane that binds to glucose and carry it across the lipid bilayer. The human genome encodes 14 GLUTs [20]. Table 1.2 describes the major GLUTs found in mammals; each isoform is expressed in a tissue-specific manner. In the brain, GLUT1 and GLUT3 transport glucose across the blood-brain barrier and into neurons, respectively. GLUT2 acts as a glucose sensor in pancreatic β-cells. In liver and kidney cells, it is involved both in glucose uptake when blood glucose levels are high and glucose release into circulation when blood glucose levels are low (for example, during fasting). GLUT4 is the major isoform regulated by insulin: upon hormonal stimulation, GLUT4 in intracellular membrane compartments are mobilized to the cell surface, where they function to transport glucose into the cell. This is important for the uptake of increased blood glucose by adipose tissue and skeletal muscle in the fed state.

1.2.2.2 Glycolysis

Glycolysis is the intracellular metabolic pathway that converts glucose into pyruvate. In all tissues, glucose is oxidized through the glycolytic pathway to produce energy (as ATP) and other metabolic intermediates.

Glucose transported into the cytosol can be phosphorylated by hexokinase, which inhibits sugar molecules from readily penetrating the cell membrane. Thus, glucose-6-phosphate is effectively trapped in the cytosol and becomes committed to further metabolism in the cell. The next step is the conversion to fructose 6-phosphate catalyzed by phosphoglucose isomerase, which can be competitively inhibited by 2-deoxy-$_{D}$-glucose (2DG) [21]. [Note: this chemical has thus been largely used to mimic a glucose-deprived state or to block glycolysis in experimental settings.] The next reaction is the rate-limiting step of glycolysis: phosphorylation into fructose 1,6-bisphosphate catalyzed by phosphofructokinase-1. Through several further steps, glucose is finally converted into two pyruvate molecules, yielding a net gain of two ATP molecules (from ADP) and two reduced NADH (from NAD^+).

If cells are deprived of oxygen (i.e., in a hypoxic state) or lack mitochondria (ex. erythrocytes), NAD^+ is regenerated by oxidation of NADH as pyruvate is reduced to lactate. This

process is called anaerobic glycolysis. Otherwise, with an adequate supply of oxygen, pyruvate can be oxidized in mitochondria to acetyl-CoA, a major fuel of the next step, the tricarboxylic acid (TCA) cycle.

1.2.2.3 TCA Cycle and Oxidative Phosphorylation

Most of the ATP generated from glucose oxidation is produced in these steps. Breakdown of glucose and other fuels (including fatty acids, amino acids, and ketone bodies) can provide acetyl coenzyme A (acetyl-CoA), the substrate for the TCA cycle. One acetyl-CoA molecule can be oxidized into two molecules of CO_2, and energy is transferred to three molecules of reduced nicotinamide adenine dinucleotide ($NADH+H^+$), one flavin adenine dinucleotide ($FADH_2$), and one guanosine triphosphate (GTP). $NADH+H^+$ and $FADH_2$ subsequently donate electrons to O_2 via the electron-transport chain, which is coupled to ATP production by oxidative phosphorylation. Thus, the TCA cycle has a central part in generating energy via cellular respiration. Remnant energy can be transformed into heat, which helps maintain body temperature.

1.2.2.4 Gluconeogenesis and Other Related Pathways

Synthesis of glucose from compounds other than carbohydrates, called gluconeogenesis, occurs primarily in the liver. [Note: The Greek word "*neo*s" means "new."] The liver produces glucose to maintain blood glucose levels, especially during fasting. In humans, the major substrates of gluconeogenesis are lactate, glycerol, and amino acids, particularly alanine. Except for three key reactions, gluconeogenesis is mostly a reversal of the glycolytic pathway. The sequences that do not use glycolytic enzymes correspond to the irreversible, regulated steps of glycolysis. These three sequences are the conversion of (1) pyruvate to phosphoenolpyruvate (PEP), (2) fructose 1,6-bisphosphate to fructose 6-phosphate and (3) glucose 6-phosphate to glucose.

Intracellular metabolic pathways involving glucose are also closely linked to lipid and protein metabolism. Several metabolites of glycolysis are connected with the pentose phosphate pathway, which generates sugars, ribose 5-phosphate (a precursor for nucleotide synthesis), and nicotinamide adenine dinucleotide phosphate (NADPH). Synthesis and degradation pathways of triacylglycerol are connected with acetyl-CoA and some other metabolites. Components of the TCA cycle are connected with the urea cycle, which plays an important role in eliminating toxic ammonia derived from the catabolism of amino acids. Thus, the metabolism of all nutrients is tightly intertwined and regulated within an organism.

1.3 Glucose Metabolism in Brain

1.3.1 Brain Glucose Use

The brain is both a "consumer" and a "modulator" in glucose metabolism. This section will describe the respective mechanisms by which the brain uses and controls blood glucose.

The brain and other neural tissues (and also red blood cells) are very dependent on glucose for their energy needs as they cannot synthesize glucose on their own. Although it represents only 2% of the total body mass, the brain accounts for some 60% (120~150 g/day) of the glucose used by the body in the resting state. This is equivalent to approximately 5.6 mg glucose consumed per 100 g human brain tissue per minute [22]. The brain is given exclusive priority for fuel because of its vital role in orchestrating the functions of all the body organs. Substrates must cross the blood-brain barrier (BBB), including the endothelial cells that form the inner lining of blood vessels, to be metabolized in the brain [23]. One structural component of the BBB is the foot process of astrocytes, where glucose is taken up and catabolized to pyruvate by the glycolytic pathway. Pyruvate is preferentially reduced to lactate in astrocytes, then transported into neurons and converted back to pyruvate [24]. [Note: normal levels of glucose in the cerebrospinal fluid (CSF) are 50~80 mg/dL, lower than blood glucose.]

Neurons in the brain contain no significant storage of glycogen or triacylglycerol, which necessitates complete dependency on the availability of blood glucose. Circulating fatty acids also contribute little to brain energy production during the fed state. Meanwhile, glycogen is stored mainly in astrocytes, but their involvement in brain energetics needs further investigation.

In terms of cellular respiration, the brain accounts for about 20% of the body's basal O_2 consumption [25]. The cerebral metabolic rate of oxygen can increase by two- or threefold under certain circumstances in the healthy brain [26]. In aerobic conditions, most of the glucose is oxidized and used to produce ATP through oxidative phosphorylation. However, in the human brain, glucose is also catabolized by aerobic glycolysis, the nonoxidative metabolism of glucose even with adequate oxygen supply [27, 28]. This mechanism is especially upregulated during brain activation to help provide precursors for the biosynthesis of glucose-derived neurotransmitters (such as glutamate and acetylcholine) [29] (also check Sect. 1.2.2.4 above). It also has an important role in providing ATP, albeit occurring heterogeneously in different brain areas and contexts.

During the initial stages of fasting, the brain continues to use glucose as the main fuel. As described above, blood glucose in the fasted state is maintained mainly by hepatic gluconeogenesis. In prolonged fasting (for more than 2 weeks), however, plasma ketone body levels significantly increase and surpass glucose as the brain's primary fuel. Even after several days of starvation, more than 30% of the body's energy requirements (based on oxygen consumption) can be provided by ketone body oxidation. As the brain and other nervous tissues begin to use ketone bodies, their glucose consumption decreases, using roughly one-third of the glucose (~40 g/day) required under normal dietary conditions. [Note: As fasting continues from days to weeks, blood glucose levels initially drop to 65–75 mg/dl, where they are maintained at a steady low level.] These metabolic changes during fasting, which are included in Fig. 1.2, help provide adequate energy supply to all the organs in the body.

1.3.2 Central Regulation of Blood Glucose Levels

The brain serves as the regulating center for body homeostasis. It detects glucose levels, interprets related signals through hormones, and continuously tunes body mechanisms to maintain blood glucose within a predetermined range.

Some neurons can respond to extracellular glucose levels, i.e., glucose-sensing neurons. Two such groups of neurons exist glucose-excited (GE) neurons vs. glucose-inhibited (GI) neurons. These functionally opposing neurons are found intermingled in many hypothalamic regions, including the arcuate nucleus, ventromedial nucleus, paraventricular nucleus, and lateral hypothalamus [30]. Glucose sensing in the brain is modulated by hormonal status, which reflects body energy homeostasis. The "satiety" hormones leptin (from adipose tissue) and insulin, as well as the incretin GLP-1 (from the small intestine), are released after meal intake. In contrast, the "hunger" hormone ghrelin is secreted from the stomach in the fasting state. These hormones can activate or inhibit relevant glucose-sensing neurons by binding onto their specific receptors.

Mounting evidence suggests that hypothalamic glial cells also play an important role in glucose sensing. These cells include astrocytes and tanycytes, specialized ependymal cells lining the lower part of the third ventricle [31, 32]. Notably, the median eminence of the third ventricle has BBB-free areas, which is favorable for glucose transport from the peripheral blood to the nearby arcuate nucleus [33]. The nucleus of the solitary tract in the hindbrain is another brain region containing glucose-sensing cells [34]. This area is a viscerosensory center that collects metabolic signals from the body, especially from the gastrointestinal tract, via vagal afferents.

When the body is deprived of glucose, GE neurons are inhibited, and GI neurons are activated, which increases hepatic glucose production while lowering glucose disposal and energy expenditure. Altered neuronal activities also result in higher wakefulness and locomotor activity, which help trigger food-seeking behaviors for glucose replenishment. By coordinating these

various mechanisms, the brain can simultaneously monitor and control glucose levels.

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