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Carbohydrate Metabolism in Hypoglycemia

María L. Kennedy and Miguel A. Campuzano-Bublitz

Abstract

Hypoglycemia is generated by mechanisms directly related to an increase in insulin secretion, by metabolic disorders that require increased glucose consumption or by a deficient metabolic production of glucose by the body. Mechanisms include high glucose intake, increased dose of oral hypoglycemic, exogenous administration of insulin, metabolic hepatic conditions that lead to an increase in the production of amino acids, growing tumors, and in diabetic pregnant woman with abnormal increase in glucose and amino acids that end up producing insulin hypersecretion in the newborn. Work that requires high glucose expenditure or reduction of insulin antagonist, such as cortisol and glucagon, ends up in hypoglycemia. Finally, hypoglycemia is generated by metabolic deficit in pathophysiological situations such as defects in enzymatic systems, alcoholic hepatitis, and insufficient nutrition. The most characteristic symptoms include bulimia, fits of sweating, and tremors due to a strong activation of the sympathetic system. Obviously, the CNS is strongly affected by the lack of glucose, which is even more complicated because also hypoglycemia leads to a situation of decreased lipolysis and ketone bodies that finally seriously compromise the supply of energy to the nervous system, producing losses of consciousness, spasms, and even irreversible brain damage.

Keywords: hypoglycemia, increased glucose consumption, hyperinsulinemia, exogenous insulin control, uncontrolled diabetes, high glucose expenditure

1. Introduction

The human body is dependent on a tight control of its blood glucose levels to ensure normal body function. Survival of individuals, the conscious state, the integration of different types of internal and external stimuli, and appropriate responses to these stimuli depend on the proper functioning of the central nervous system, which puts intense activity in their cells. This requires the consumption of oxygen and glucose to obtain the energy that enables the activity of the central nervous system (CNS) and keeps the neurons in constant activity [1].

The lack of oxygen causes, in minutes, serious and irreparable damage to the central nervous system. However, the lack of glucose is tolerated for a longer time because in a deficit situation, the CNS itself makes autonomous adjustments leading to inactivity to other non-vital systems of the body and preserves for more time the availability of glucose for neurons, and ultimately, in multiday starvation states, it substitutes glucose for ketone bodies as a nutrient, which allows life expectancy to be extended during fasting. The availability of glucose in people is vital for a good quality of life, since it allows the lucid and full functioning of the CNS [2, 3].

The rest of the body's cells also obtain energy through oxygen and glucose, thus enabling metabolism and cellular response. The main source of glucose is through

food and specifically depends on the consumption of carbohydrates [4]. The use of this carbohydrate in the body is finely regulated by a hormonal system capable of always maintaining blood glucose (glycemia) in a concentration ranging from 4.0 to 5.4 mmol/L (72 to 99 mg/dL) [5]. The human body is prepared to store excess of glucose (glycogenesis) and use it in the future (glycogenolysis) when this is required and is also able to synthesize glucose from noncarbohydrate precursors (substrates) such as amino acids, lactate, and/or glycerol (gluconeogenesis).

The pancreas is the body in charge, among other functions, of maintaining glycemia at tolerable levels for the organism, through a system of hormones, where insulin is responsible for reducing glycemia in situations of postprandial hyperglycemia, while glucagon is responsible for reversing situations of hypoglycemia [6, 7].

2. Carbohydrate metabolism

The carbohydrates present in foods are primarily as polysaccharides that are digested by various digestive enzymes. Starch is the most common polysaccharide in foods and is metabolized to maltose by the enzyme alpha amylase present in saliva and secreted by the pancreas and this to glucose by the maltases in the microvilli of the duodenum. The lactose present in dairy products is metabolized by lactases in the intestinal villi to glucose and galactose. Sucrose is also metabolized in the intestinal microvilli in glucose and fructose.

The absorption of glucose and galactose is carried out by a secondary active cotransport of Na^+ to the interior of the enterocyte and from there to the portal flow by facilitated diffusion through the GLUT2 glucose transporter (**Figure 1**). Fructose, on the other hand, is only entered into the enterocyte by facilitated diffusion through GLUT5 type transporters located on the apical side, and then they are poured into the portal circulation by the same carrier proteins that are also found on the basal side of the enterocyte.

The duodenum has a very extensive contact surface, in order to take advantage of and absorb as much of these nutrients as possible. The excess, which passes to the jejunum, stimulates the release of the glucose-dependent insulinotropic peptide (GIP) from the K cells and the glucagon-like peptide type 1 (GLP-1) from the L cells. Both stimulate the postprandial release of insulin from the pancreas (**Figure 1**).

Absorbed glucose increases suddenly in the blood, reaching values above 90 mg/dL, and is transported by the GLUT2 carrier protein inside the pancreas where it undergoes glycolysis to generate pyruvate. This is used by the mitochondria for the production of ATP, which is released into the cytoplasm of the beta cells of the pancreas. This excess of ATP desensitizes the ATP-dependent K^+ channels that close and prevent the migration of K^+ ions to the extracellular fluid. With the intracellular increase of K^+ , a depolarization begins; this stimulates the opening of voltage-gated calcium channels, which finally ends with the exocytosis of insulin (**Figure 1**), peptide C, and amylin stored in the vesicles into the bloodstream.

The average life of this circulating insulin is 3–5 minutes; its main action is to stimulate the uptake of glucose from the bloodstream, mainly by the liver and muscle cells. The receptor for insulin in these cells is a tyrosine kinase that, when insulin binds, dimerizes and initiates a signaling cascade that rapidly activates the phosphatidylinositol-3-kinase (PI3K) pathway that translocates GLUT4 carrier to the cell membrane, which allows the massive entry of glucose into the cell. Then the same pathway activates the enzyme glycogen synthetase that converts excess of glucose into glycogen, activates Acetyl CoA carboxylase that stimulates lipogenesis, and finally, in the longer term, activates the pathway of the mitogen-activated kinases (MAP kinases) responsible for the expression of the protein synthesis (**Figure 1**).

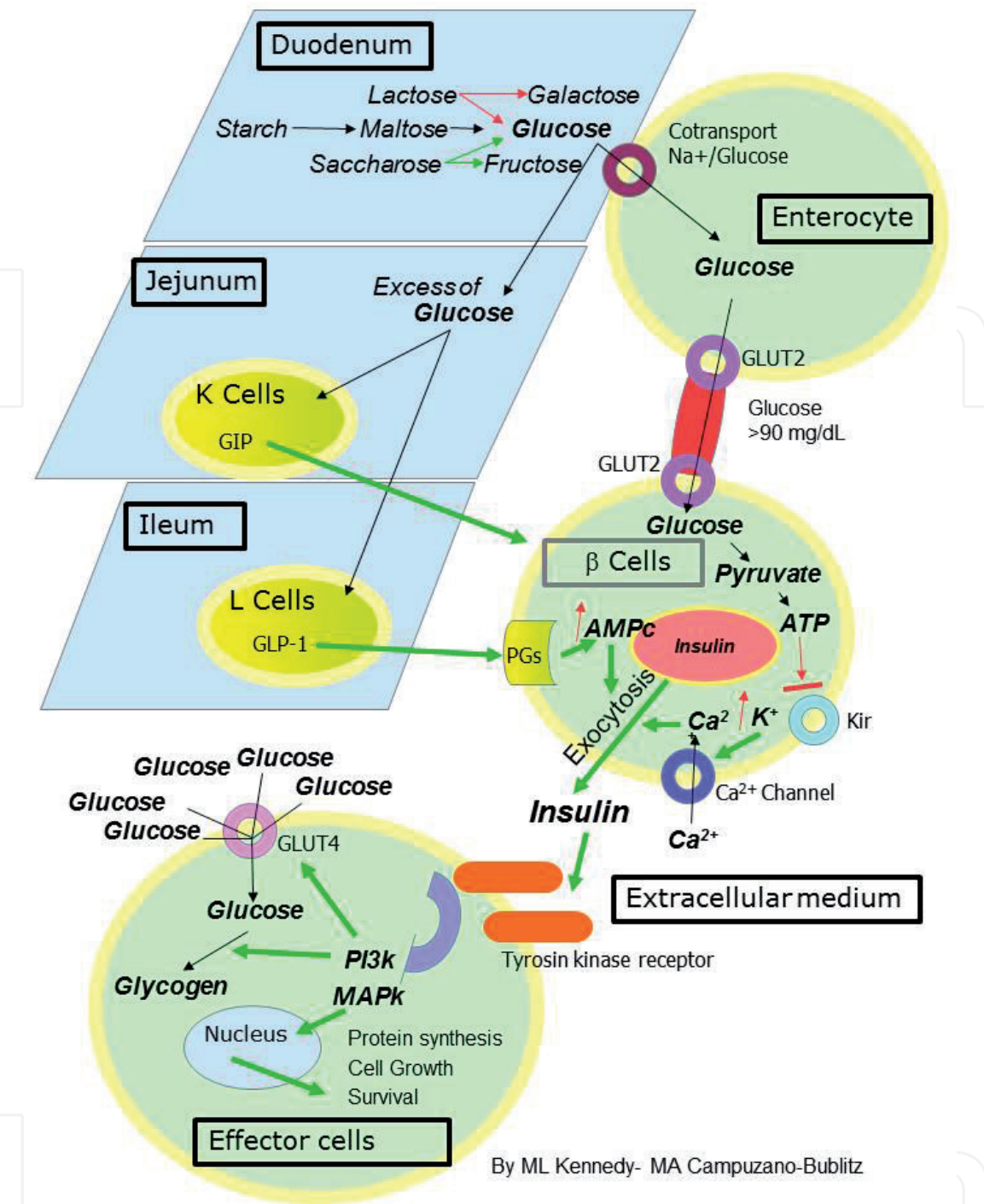


Figure 1.
Carbohydrate metabolism. Polysaccharides in food are digested, by several enzymes. The absorption is mainly in the duodenum. Glucose in the jejunum and ileum stimulates the release of GIP and GLP-1, and postprandial release of insulin is stimulated. Glucose in blood reaches the pancreas and undergoes glycolysis to generate pyruvate and then ATP; ATP closes K⁺ channels, and a depolarization begins. Next, voltage-gated calcium channels are open and exocytosis of insulin occurs. Insulin binds to its tyrosine kinase receptor and initiates a signaling cascade that rapidly produces the massive entry of glucose into the cell.

C peptide is a small molecule that is released when proinsulin is metabolized to insulin; in spite of not knowing the specific physiological role of this molecule, in the clinical environment, it serves to correlate it with the quantity of insulin synthesized by beta cells, because for each molecule of insulin, there is a C peptide, and this remains in the bloodstream for a longer time. Amylin, a peptide hormone produced in the pancreas, and co-secreted with insulin, and in the brain, improves postprandial blood glucose levels by suppressing gastric emptying and glucagon secretion. Amylin also acts centrally as a satiation signal, reducing food intake and body weight.

In this way the glycemia values are usually maintained between 70 and 110 mg/dL; values below this range produce hypoglycemia that stimulates the release of the hormone glucagon from the alpha cells of the pancreas, which promotes anti-insulin effects in such a way to re-raise the glycemia values (Figure 2). To this is added a third pancreatic hormone, somatostatin, of paracrine regulation which collaborates to modulate the release of insulin and glucagon.

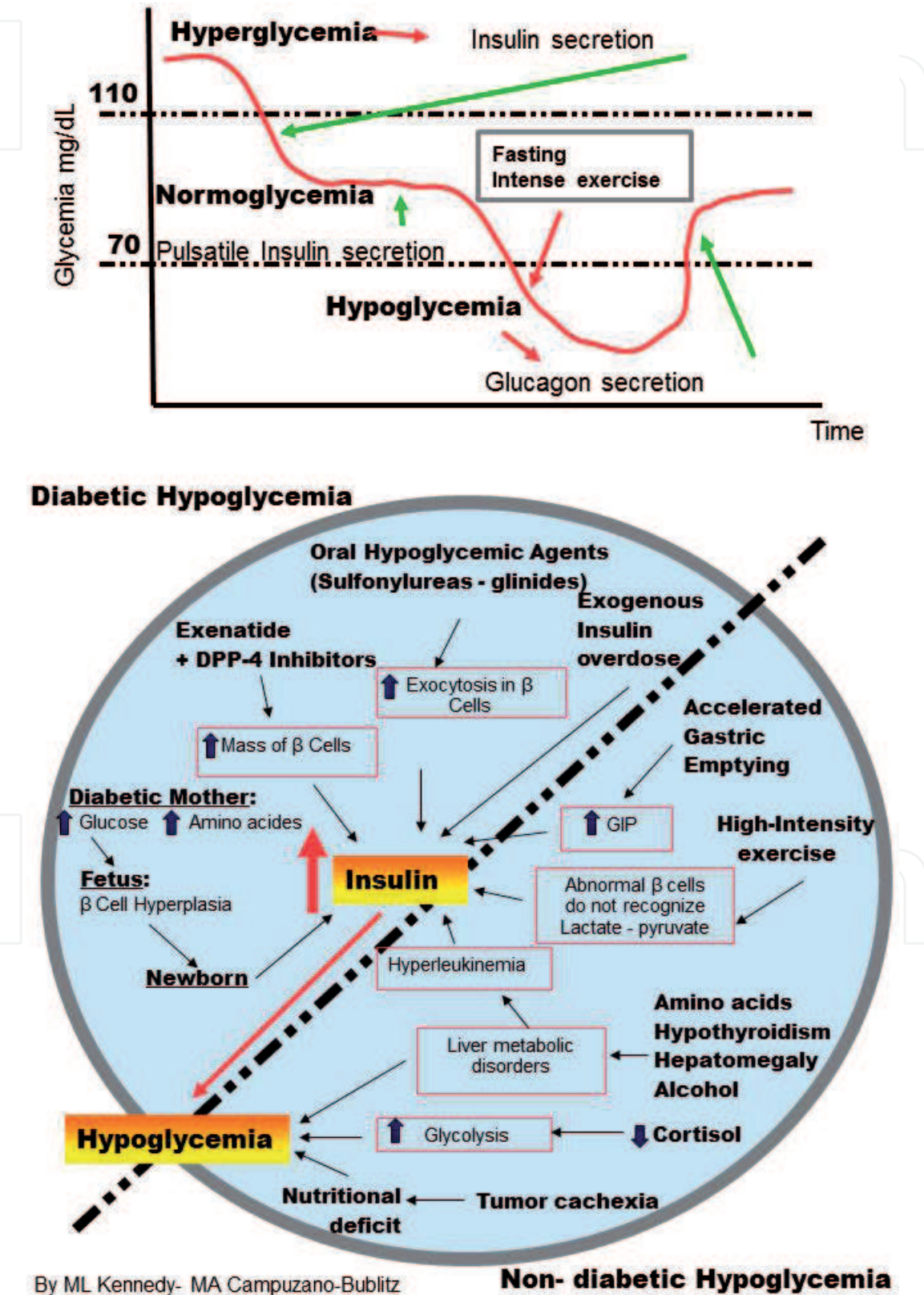


Figure 2. Regulation of plasma glucose level by insulin and glucagon. Hypoglycemia situations related to diabetes and not related to diabetes.

After intense physical activity, the adrenaline released by the stimulus of exercise and the increase of lactate and pyruvate in blood blocks insulin secretion and stimulates glucagon to always make glucose available to the body and avoid reactive hypoglycemia [6, 8, 9].

3. Glucagon

Insulin secretion from the beta cells of the pancreas is a standard response that is directly related to glucose absorbed from food. Thus, if the glycemia increases significantly after an intake, this results in a large insulin secretion, while if the glycemia remains within the normal range, the stimulus decreases and produces a pulsatile insulin secretion that favors the glycemia to remain within the physiological range.

In the case that the glycemia falls below 60 mg/dL, the signal to secrete insulin weakens and eventually becomes blocked. In contrast, this allows the alpha cells of the pancreas to release considerable amounts of glucagon (**Figure 2**). This hormone travels through the portal vein to the liver, where it activates signaling pathways to initiate glycogenolysis, which will cause the formation of glucose in the liver so that it is released into the bloodstream to immediately increase glycemia. Additionally, glucagon increases the recruitment of amino acids to the liver for gluconeogenesis that reinforces the effect of glycogenolysis [10].

4. Nondiabetic hypoglycemia

Hypoglycemia is almost always related to a normal or increased amount of insulin as a direct response to glucose intake in food or other pathophysiological factors that induce an excessive increase in insulin secretion. A balanced intake of carbohydrates, fats, and proteins provides all the nutrients that the body needs for survival, but an inadequate diet, deficient in carbohydrates, leads to a reactive hypoglycemia.

The chronic and excessive intake of alcohol produces metabolic alterations in the liver that lead to decrease the synthesis and release of glucose from the liver to the blood and therefore a decrease in blood sugar (**Figure 2**).

In the case that the gastric emptying is accelerated (dumping syndrome), due for example, to a gastric resection, the digestion and absorption of carbohydrates are much faster than normal and also produce the early release of intestinal hormones, including the GIP, which leads to hyperinsulinemia and then the consequent hypoglycemia (**Figure 2**).

The alteration of various functions of the organism has as one of its consequences the reduction of glycemia to critical values, as occurs in the reduction of glucocorticoid secretion, such as cortisol, which causes an increase in glycolysis and reduced gluconeogenesis from amino acids. This in turn leads to a greater secretion of adrenaline that is contrasted in its effects to insulin. On the other hand, thyroid hormones regulate many cellular metabolic processes, including hepatic metabolism; therefore, in a situation of hypothyroidism, glycogenolysis and gluconeogenesis are drastically reduced (**Figure 2**).

An alteration in the hepatic metabolism of amino acids, either due to liver failure or due to specific enzymatic defects, such as that inducing high leucine level, has an effect on insulin secretion, which is increased producing hypoglycemia (**Figure 2**).

Hepatomegaly is usually caused by an increased hepatic storage of glycogen, known as glycogenosis, due to metabolic alterations produced by defective enzymes such as glucose-6-phosphatase, in Gierke's disease, or a debranching enzyme in Cori

Forbes disease, a phosphorylase in Hers disease, or a phosphoryl kinase in Huijing's disease. This increase in hepatic glycogen deposition produces a marked hypoglycemia throughout the system (**Figure 2**).

Aberrations in the expression of certain genes in beta cells make them unable to relate the increase in lactate and pyruvate with the state of physical activity and therefore induce an increase in insulin secretion that causes significant hypoglycemia in the organism (**Figure 2**).

The development of tumors, of any type, entails an increase in the need for energetic molecules so that cell proliferation is possible. This added to the fact that the formation of tumors produces long-term hormonal disorders that keep oncological patients with hypoglycemia for a long time. This effect is compensated by lipolysis of the adipocytes in order to make more energetic molecules available, and finally the patient develops tumor cachexia [11, 12] (**Figure 2**).

5. Hypoglycemia related to diabetes

One of the most common causes of hypoglycemia in diabetics occurs as a result of the excess administration of insulin or oral hypoglycemic drugs [13, 14]. Patients suffering from diabetes mellitus type 1 and whose treatment is based on the exogenous administration of insulin must previously corroborate the level of glycemia and then adjust the amount of hormone to be administered, considering that 100% of the dose, approximately half, is used to immediately regulate the metabolism of carbohydrates and the other half is to cover the metabolism at night or fasting hours. Therefore, the amount of insulin administered is higher than required, and if the necessary precautions are not taken, there is a high probability that the dose administered will produce a strong hypoglycemia, especially during sleep hours, known as the Somogyi effect. The amount of insulin units to administer considers the actual value of the glycemia, which forces the patient to measure it, compare and extract the difference with the theoretical optimum value of 120 mg/dL of fasting blood glucose, and divide it by the factor 50, since one unit of insulin reduces blood glucose by approximately 50 mg/dL (**Figure 2**).

Even so, the correct amount of insulin to be administered must also be defined by other factors, such as the total amount of carbohydrates ingested with food, the type of insulin to be administered, and the recommendations of the treating medical professional.

Oral hypoglycemic agents, used in the treatment of type 2 diabetes mellitus, can also lead to a strong insulin secretion. The large family of sulfonylureas (chlorpropamide, glibenclamide, gliclazide, glisentide, glipizide, gliquidone, and glimepiride) and the secretagogue glinides (repaglinide and nateglinide) are characterized by the ability to induce hypoglycemia and cause weight gain, due to the decrease in the lipolysis in the patients who use it for their treatment (**Figure 2**).

Another interaction with a high probability of producing hypoglycemia is the concomitant treatment with incretin analogues (exenatide) and inhibitors of dipeptidyl peptidases (vildagliptin) because it significantly increases the pancreatic β cell mass, which leads to greater insulin secretion and even with high risks of producing pancreatitis (**Figure 2**).

Diabetic women during pregnancy have poor control of carbohydrate metabolism and thus coexist with high blood levels of glucose and amino acids; this long-term hyperglycemia is transferred to the fetus and forces hyperplasia in fetal pancreatic beta-cell tissue, which finally predisposes the newborn to a greater secretion of insulin and the consequent hypoglycemia [15–17] (**Figure 2**).

6. Clinical manifestations

The decrease in blood sugar below 60 mg/dL is known as hypoglycemia. In a first phase, this leads to a stimulation of the parasympathetic autonomic nervous system that causes a sensation of hunger and leads the patient to bulimia. In the second phase, the sympathetic autonomic nervous system is stimulated, producing the secretion of important quantities of catecholamines that activate their receptors in important target organs such as the heart, which produces an acceleration of the heartbeat, in sweat glands increases the production of sweat, and in the somatic nervous system causes tremors. It is frequent double vision, difficulty concentrating, loss of ease of speech, and confusion states. A hypoglycemia below 20 mg/dL induces a coma (**Figure 3**).

The most serious effect is a marked cognitive dysfunction, since the supplies of nutrients, glucose, and ketones to the nervous system are markedly diminished; produce loss of consciousness, brain spasms, and epileptic seizures in children; and can potentially lead to irreversible neuronal damage [18, 19].

Glycemia mg/dL	Clinical consequences		Treatment	Precautions
	Mechanism	Patient		
↓ 70	1. Parasympathetic Activation. Activation of the appetite center	Conscious and with bulimia	Ingestion of carbohydrate-rich foods	Follow up of the patient to avoid recidivism
	2. Sympathetic activation. Catecholamines produce tachycardia, sweating, tremor	Conscious, concentration problems, double vision, difficulty in speech, confusion	Administer pharmaceutical preparations containing glucose through a rapid absorption route	Avoid hyperglycemia crisis due to excess glucose, especially in diabetic patients
↓ 20	Energy supply to the S.N.C. is severely compromised, triggering severe cognitive dysfunction	Unconscious with cerebral spasms, epilepsy in children and potential irreversible neuronal damage.	Administration of intravenous glucagon or glucose preparations for rapid recovery of the patient	Verify the recovery of the patient, especially if there is no neuronal damage.

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Figure 3.
A summary of glycemia levels and clinical consequences.

7. Treatment of hypoglycemia

The treatment will depend on the degree of hypoglycemia that the patient develops. That, which does not pass the first phase of the clinical manifestation, requires rapid replacement of glucose from food. The CNS itself is the one that predisposes to this action by triggering bulimia in the patient. Most of the foods available to patients contain abundant amounts of carbohydrates that help to remedy hypoglycemia (**Figure 3**).

In cases where hypoglycemia is more pronounced, it is necessary to administer pharmaceutical preparations containing glucose, but this treatment should be monitored to avoid the opposite effect, i.e., hyperglycemia, especially in diabetic patients who triggered hypoglycemia due to excess insulin.

In patients with severe hypoglycemia crisis, which affects the conscience, it is necessary to act urgently administering parenteral glucagon preparations, or glucose will be administered directly, and the rapid recovery of the patient will be monitored [14, 15, 19–21] (**Figure 3**).

8. Conclusion

Hypoglycemia is generated by mechanisms directly related to an increase in insulin secretion or by metabolic disorders that require increased glucose consumption or by a deficient metabolic production of glucose by the body.

Hyperinsulinemia can be produced by various mechanisms, including high glucose intake in foods, an increased dose of oral hypoglycemic agents, as well as exogenous insulin administration without control, liver metabolic conditions that lead to an increase in the production of amino acids by this organ, tumors in permanent growth, and an abnormal increase in glucose and amino acids in the case of uncontrolled diabetic pregnant women that end up producing insulin hypersecretion in the newborn.

Work that requires high glucose consumption, more than what the body can supply, ends up in situations of hypoglycemia, as well as when there is a decrease in hormone antagonists to insulin, such as cortisol or glucagon. The state of hypoglycemia is generated by metabolic deficit in pathophysiological situations such as defects in enzymatic systems, alcoholic hepatitis, and insufficient diet.

The most characteristic symptoms include bulimia, fits of sweating, and tremors due to a strong activation of the sympathetic system. Primarily, the CNS is strongly affected by the lack of glucose, which is even more complicated because also hypoglycemia leads to a situation of decreased lipolysis and ketone bodies that finally seriously compromise the supply of energy to the central nervous system, producing loss of consciousness, spasms, and even irreversible brain damage.

The treatment of less severe hypoglycemic patients is preferably carried out with the rapid administration of carbohydrate-rich foods. For more serious cases, the use of pharmaceutical products that supply carbohydrates is resorted to, but the glycemia must be monitored to avoid hyperglycemia. Those patients who are much compromised, with loss of consciousness, should receive parenteral glucagon or glucose in an urgent way to recover them.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this chapter.

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References

- [1] Howarth C, Gleeson P, Attwell D. Updated energy budgets for neural computation in the neocortex and cerebellum. *Journal of Cerebral Blood Flow and Metabolism*. 2012;**32**:1222-1232
- [2] Rich L, Brown AM. Glycogen: Multiple roles in the CNS. *The Neuroscientist*. 2017;**23**(4):356-363
- [3] Mergenthaler P, Lindauer U, Dienel G, Meisel A. Sugar for the brain: The role of glucose in physiological and pathological brain function. *Trends in Neurosciences*. 2013;**36**(10):587-597
- [4] Slavin J, Carlson J. American society for nutrition. *Advances in Nutrition*. 2014;**5**:760-761
- [5] Güemes M, Rahman S, Hussain K. What is a normal blood glucose? *Archives of Disease in Childhood*. 2015;**0**:1-6
- [6] Röder P, Wu B, Liu Y, Han W. Pancreatic regulation of glucose homeostasis. *Experimental & Molecular Medicine*. 2016;**48**:e219
- [7] Hill N, Oliver N, Choudhary P, Levy J, Hindmarsh P, Matthews D. Normal reference range for mean tissue glucose and glycemic variability derived from continuous glucose monitoring for subjects without diabetes in different ethnic groups. *Diabetes Technology & Therapeutics*. 2011;**13**(9):921-928
- [8] Dashty M. A quick look at biochemistry: Carbohydrate metabolism. *Clinical Biochemistry*. 2013;**46**:1339-1352
- [9] Slavin J, Carlson J. Carbohydrates. *Advances in Nutrition*. 2014;**5**:760-761
- [10] Briant L, Salehi A, Vergari E, Zhang Q, Rorsman P. Glucagon secretion from pancreatic α -cells. *Upsala Journal of Medical Sciences*. 2016;**121**(2):113-119
- [11] Desimone ME, Weinstock RS. Non-diabetic hypoglycemia. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK355894/> [Accessed: 25-June-2019]
- [12] Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, et al. Evaluation and management of adult hypoglycemic disorders: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*. 2009;**94**:709-728
- [13] Shafiee G, Mohajeri-Tehrani M, Pajouhi M, Larijani B. The importance of hypoglycemia in diabetic patients. *Journal of Diabetes & Metabolic Disorders*. 2012;**11**(1):17
- [14] Malouf R, Brust JC. Hypoglycemia: Causes, neurological manifestations, and outcome. *Annals of Neurology*. 1985;**17**:421-430
- [15] Heller S, Damm P, Mersebach H, Vang Skjøth T, Kaaja R, Hod M, et al. Hypoglycemia in type 1 diabetic pregnancy: Role of preconception insulin aspart treatment in a randomized study. *Diabetes Care*. 2010;**33**:473-477
- [16] Evers IM, ter Braak EW, de Valk HW, van Der Schoot B, Janssen N, Visser GH. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. *Diabetes Care*. 2002;**25**:554-559
- [17] <https://www.healthline.com/health/pregnancy/hypoglycemic-and-pregnant> [Accessed: 25-June-2019]
- [18] The diabetes control and complications trial research group. Adverse events and their association with treatment regimens in the diabetes control and complications trial. *Diabetes Care*. 1995;**18**:1415-1427

[19] <http://www.diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/hypoglycemia-low-blood.html> [Accessed: 25-June-2019]

[20] Nielsen L, Pedersen-Bjergaard U, Thorsteinsson B, Johansen M, Damm P, Mathiesen E. Hypoglycemia in pregnant women with type 1 diabetes. Predictors and role of metabolic control. *Diabetes Care*. 2008;**31**(1):9-14

[21] Farrar D. Hyperglycemia in pregnancy: Prevalence, impact, and management challenges. *International Journal of Women's Health*. 2016;**8**:519-527