Chapter

Hypoglycemia and Brain: The Effect of Energy Loss on Neurons

Daniel Arturo Martínez-Piña, Gustavo Alexis Alvarado-Fernández, Edith González-Guevara, Carlos Castillo-Pérez, Gerardo Romero-Luna and Jorge Alejandro Torres-Ríos

Abstract

Glucose provides the necessary fuel to cover the physiological functions of the organism. In the brain, glucose represents the main energy supply through the generation of adenosine triphosphate, with oxygen and glucose being the main components involved. The imbalance in glucose levels in the central nervous system produces substantial changes in metabolism. Hypoglycemia, or decreased blood glucose levels below 50 mg/dl, is accompanied by symptoms such as decreased performance of cognitive tasks such as verbal fluency, reaction time, arithmetic ability, verbal memory and visual, in addition to excitotoxicity, oxidative stress, neuroinflammation and apoptosis. Hyperglycemia participates in some cardiovascular diseases, neuropathy, nephropathy, retinopathy. Changes in glucose metabolism must be regulated and considered in order to obtain the best treatment for different pathologies, such as infections, non-infections, traumatic, primary or acquired.

Keywords: hyperglycemia, hypoglycemia, neuroglycopenia, neuroinflammation, oxidative stress

1. Introduction

The human brain requires a high and continuous input of energy, which is obtained mainly from glucose, due to its high metabolic rate. Some interesting facts about the brain are that it accounts for only 2% of body weight, but it also requires 15% of cardiac output, 20% of total body oxygen and 25% of serum glucose, which means that the human brain uses up between 5 and 10 g of glucose per hour or 140 g per day on average [1]. Under normal conditions, serum glucose is around 80–90 mg/dl and may increase up to 200 mg/dl after meals. On the other hand, serum glucose may decrease up to 54 mg/dl during prolonged fasting. The concept of hypoglycemia refers to a clinical situation in which patients have a serum glucose value below 50 mg/dl matching with neuroglycopenic symptoms or serum glucose values below 40 mg/dl without any symptoms [1]. The high energy requirements of the human brain employ such complex metabolic strategies to manage energy sources. Glucose enters the central nervous

system through the Blood-Brain Barrier (BBB), a process that requires a transport protein located in the cell membrane [2, 3]. There are two systems of glucose and other monosaccharide transporter proteins: sodium-glucose transporters, also known as SGLTs (sodium-dependent glucose transport), and glucose transporters, also known as GLUTs (glucose transporters). There are several types of GLUT transporters in the human body, but in the central nervous system, there are only two types: GLUT1, which is found in the BBB, and GLUT3, which is found in neurons. Glucose enters cells via GLUT transporters in a process composed of four steps; (1) first, glucose binds to the transporter protein on the outer face of the cell membrane; (2) the transporter protein changes its conformation and glucose enters into the cell membrane; (3) glucose is released into the cytoplasm by the transporter; (4) the transporter returns to its original conformation and its glucose binding site is exteriorized again (**Figure 1**) [4, 5].

The human brain requires a lot of energy to carry out all its functions, this energy comes from different pathways in which glucose and oxygen work together to develop adenosine triphosphate (ATP). The bonds of the ATP molecule are then broken to obtain stored energy, and most of this energy is used for information processing. For example, in the human brain, there are about 10 billion neuronal cells communicated by more than 50 trillion synapses through neurotransmitters that are synthesized in the cerebral cortex in a process that requires about 3.8 × 1012 molecules of ATP [5, 6].

Neuronal and glial cells have distinct functions and are metabolically different from each other [6]. In fact, the gray matter of the human brain uses 10 times more glucose than any other organ in the body. With the known stoichiometry of glucose oxidation ($C_6H_{12}O_6 + 6O_2$ $6CO_2 + 6H_2O$) and its coupled reactions, it is possible to obtain an estimated flux at different points in the metabolic chain. This allows us to know how glucose enters into glycolysis and the Krebs cycle, leading to the release of energy that is then split into small components such as ATP, increasing its molar flux to 31 molecules of ATP for each molecule of glucose [7].

Oxidation of glucose molecules through the tricarboxylic acid cycle develops small amounts of lactate, which plays an important role as a precursor to the process of

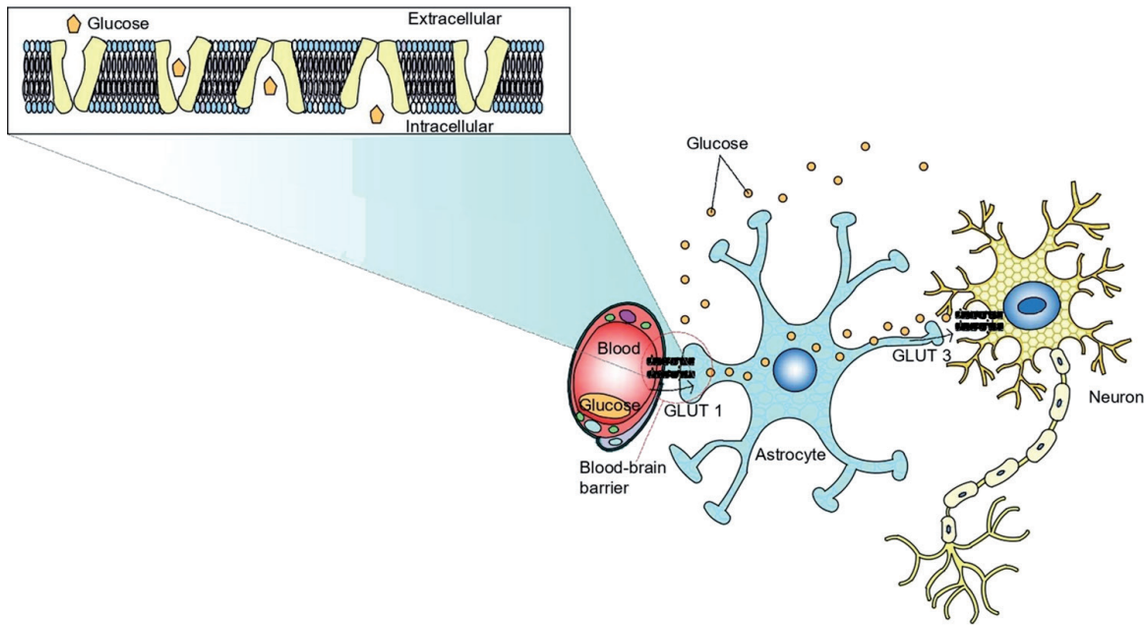

Figure 1.
Glucose transport from blood vessels to neuronal cells. GLUT (glucose transporters). Modified from Iatreia: 2002;15(3).

gluconeogenesis in the nervous system. Lactate becomes an energetic compound for the nervous system, which is demonstrated in neuronal and glial uptake, improving ATP synthesis in neurons. Such articles suggest that glucose is stored by the astrocytes and then released as glucose or lactate, to be used by neurons, when energetic requirements increase [8].

2. Cellular and molecular facts of glucose

Glucose is absorbed by GLUT1 protein transporters and can be stored as glycogen (the most important storage of glycogen is located on astrocytes) or go into glycolysis (**Figure 2**) [9].

2.1 Neurons

Glucose represents the main source of energy and its metabolic regulation is so important for normal nerve cell functions, including ATP synthesis, regulation of oxidative stress, synthesis of neurotransmitters and neuromodulatory molecules and many processes such as memory, learning and sensitivity and motor functions [10, 11]. The overall performance of neurons, astrocytes and endothelial cells is very important during the transit of energy supplements in the nervous system necessary to cover cellular functions [12]. As mentioned above, neuronal cells require a high amount of energy which is obtained from glucose; also glucose can be obtained directly by neurons or indirectly from astrocytes that converted lactate into glucose previously [13, 14]. In normal conditions, neurons obtain energy from glucose, but

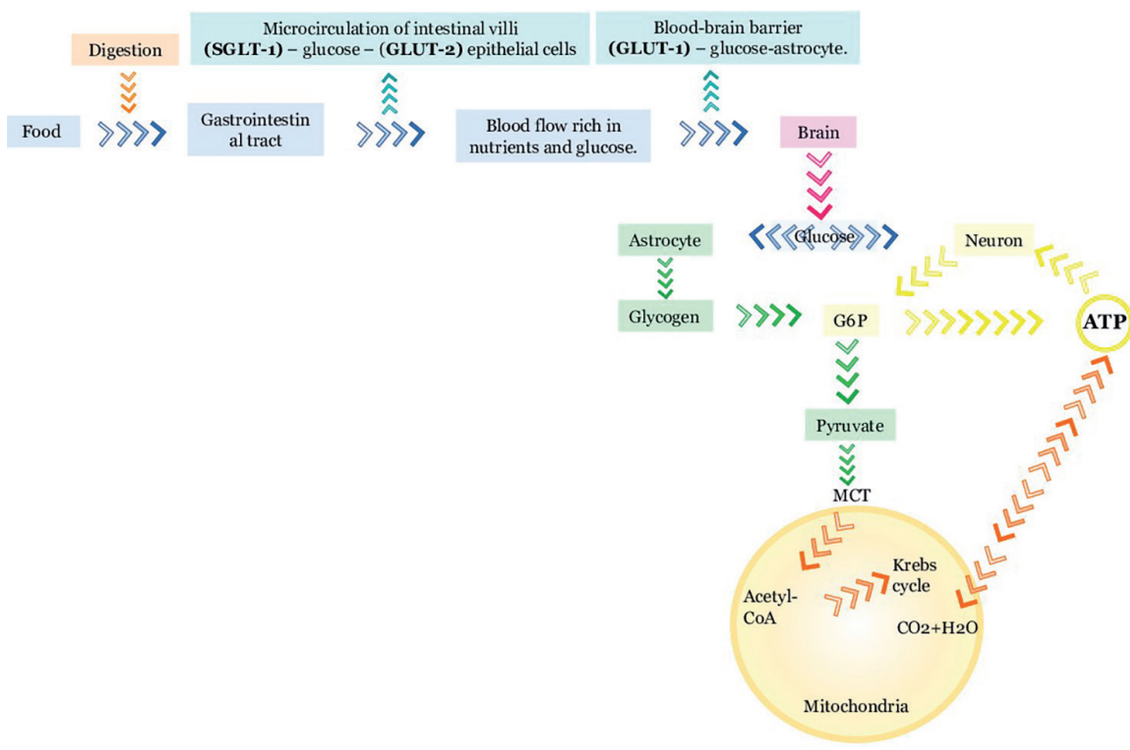

Figure 2.
Pathway of glucose from food to ATP in the neuron. The blue color is the area outside the blood-brain barrier, the green color represents only processes in the astrocyte, the yellow color processes in the neuron, and the orange color represents the intramitochondrial pathways.

during the synaptic activity, they mainly consume lactate as a product of glucose metabolism. In both cases, the overall net brain consumption would be sustained by glucose. Under conditions of glutamatergic synaptic activity, glutamate stimulates GLUT-1-mediated glucose incorporation and glycolysis in astrocytes, followed by the release of lactate into the extracellular space and its capture in neurons, the neuron uptake of glucose is made via the GLUT-3 transporter [9, 15–17].

2.2 Astrocytes

Astrocytes also need the energy to carry out their functions, these cells play such an important role in brain metabolism by providing lactate as a metabolic substrate when neuronal energy requirements increase. In astrocyte cells, the GLUT-1 transport protein is the main glucose uptake protein. Once glucose enters the astrocyte, it is converted to glucose-6-phosphate (G6P) to undergo glycolysis or be converted to glycogen. Glucogenic enzymes involved in glycogen metabolism, such as glycogen synthase, store backup glycogen. Glycogen phosphorylase and the debranching enzyme metabolize glycogen into G6P to undergo glycolysis when the astrocyte, or near neurons, require energy sources (**Figure 3**) [18, 19].

2.3 Hypoglycemia in neurons and astrocytes

It has been described that hypoglycemia actively causes neuronal death. When glucose concentration decreases below 1 mM (18 mg/dl), causes energy deficit, the release of excitatory amino acids (aspartate and glutamate) induces the expression of

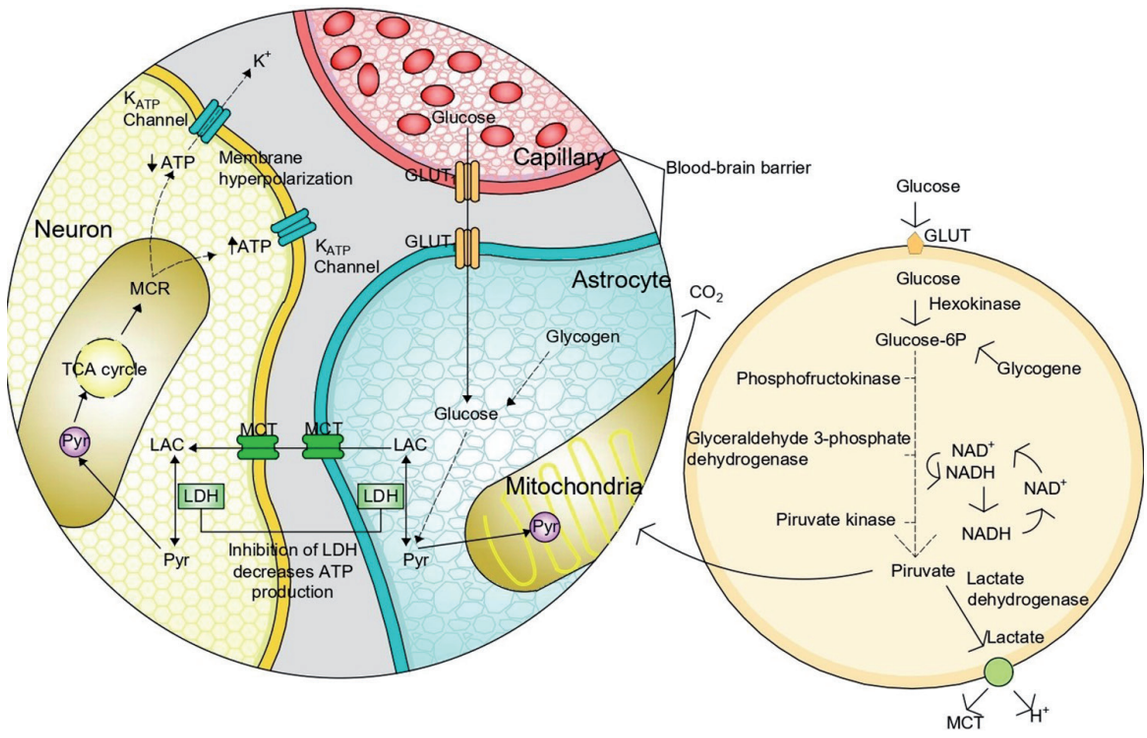

Figure 3.
Glucose metabolism and energy synthesis in astrocytes and neurons. LDH (lactate dehydrogenase), MCT (medium-chain triglycerides), LAC (lactate), ATP (adenosine triphosphate), NAD+ (nicotinamide adenine dinucleotide oxidized), NADH (nicotinamide adenine dinucleotide reduced), H+ (hydrogen), Pyr (pyruvate). Modified from N Engl J Med 2015; 373:187–189.

excitatory receptors located in neuronal dendrites that produce calcium fluxes, inducing neuronal necrosis. Hypoglycemia constitutes a metabolic brain injury [20, 21].

During hypoglycemia or periods of intense brain activity, glycogen can be used to generate lactate, which is translocated to nearby neuronal cells. Thus, glycogen within astrocytes functions as a backup system in case of hypoglycemia, ensuring neuronal functions and survival during glucose deprivation [22, 23]. In cases of brain ischemia, astrocytes have shown a high resistance, a situation that is explained by its glycogen store. Astrocytes also keep glucose synthesis for longer time periods compared with neuronal cells. Besides, astrocytes lead glycogen to turn into lactate which is moved within neurons when these cells have increased energy requirements or during lack of glucose. However, the amount of mitochondria within astrocyte cells is smaller than the amount of mitochondria within neuronal cells. A single molecule of lactate can generate 10 mM ATP, which is equivalent to 17 molecules of ATP [7, 23]. Several papers suggest that glucose molecules are stored mainly in astrocyte cells and can be released as glucose or lactate to contribute to neuronal metabolism when energy needs increase [8, 22, 23]. Other studies, recently published, suggest that other substrates such as pyruvate, glycogen, ketone bodies, glutamate, glutamine and aspartate can be metabolized by neuronal cells in case of glucose deprivation, supporting neuronal functions and delaying ATP depletion during hypoglycemia [24]. Astrocytes can release purines made of adenine, specifically adenosine (which plays an important role as a neuroprotective molecule) and guanosine which can lead to cell repair after a brain injury (**Figure 3**) [25].

In situations of low glycogen levels, glycogen can modulate some neurotransmitters and also serum glucose levels. These facts are explained by the fact that, during periods of hypoglycemia, glycogen is converted into lactate and reaches nearby neurons and axons where it is used as an energy source, leading to protection against hypoglycemia-induced brain injury and ensuring that neuronal functions supplying energy demands [26].

3. Cellular and molecular neuroglycopenia

3.1 Calcium and hypoglycemic damage

As mentioned above, intracellular calcium accumulation promotes lipolysis, increasing the amount of free fatty acids due to phospholipids metabolism, including arachidonic acid, activated by cyclooxygenase enzyme and promoting oxygen reactive species releasing, platelet aggregation and neutrophil chemotaxis, leading to inflammation and direct/indirect cell damage. Calcium accumulation can also activate regulatory mechanisms to keep adequate levels of this ion, such as calsequestrin and chelation promoted by the endoplasmic reticulum and mitochondria [27]. When these mechanisms fail, an ionic overcharge takes place in the mitochondria and the cell membrane polarity is dropped. When the membrane potential is dispelled, the ATP synthase works upside down, metabolizing ATP. Also, it is impossible to generate ATP by Krebs cycle or oxidative phosphorylation. Serum calcium levels decrease during isoelectric periods and return to normal levels after glucose administration. This fact correlates to an increase in intracellular calcium levels and neuronal injury. Besides, proapoptotic factors are released as cytochrome C, caspase 3 and apoptosis-inducing factors. A persistent state of oxidative stress

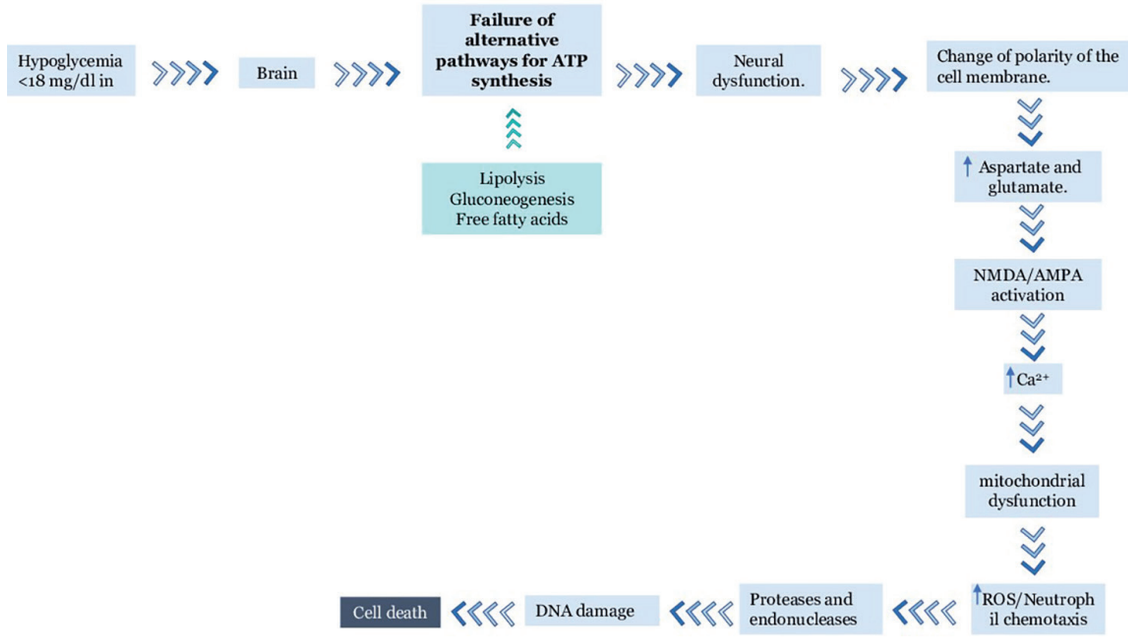

Figure 4.
Example of severe hypoglycemia in the brain.

is induced by a failure in the I and IV complex of the electron transport chain and release of reactive oxygen species (**Figure 4**) [28].

3.2 Reactive oxygen species and oxidative stress

Oxygen ions, free radicals and peroxides are very small molecules, which appear as a result of oxygen metabolism, and play an important role in the oxidation-reduction process, activating genes, exchanging ions when their values need to be regulated. The regulating mechanisms to avoid over synthesis of these small molecules include important enzymes groups such as catalase and superoxide dismutase. There are also antioxidant molecules, for example, ascorbic acid, uric acid and glutathione. Oxidative stress can be defined as a metabolic status with overproduction of oxygen reactive species and exceeding the antioxidant molecules' capacity to offset this process. Some important molecules that can be affected by this situation are cell membrane lipids, deoxyribonucleic acid (DNA) and proteins. An increase in catalase and superoxides dismutase enzymes indicate, indirectly, the presence of peroxides and superoxide, respectively. That is because these enzymes are considered important indirect markers of oxidative stress [29].

The glutathione tripeptide functions as a chemical synthesis buffer during oxidation-reduction reactions carried out by the mitochondria. This chemical buffer is made of glycine, glutamate and cysteine. Another chemical buffer that appears in cases of oxidative stress is glutathione in its oxidized form, which is formed by two glutathione molecules linked by a disulfide bond. There is also an increase in nitric oxide synthase, subsequently, nitric oxide becomes reactive when it is combined with superoxides, forming peroxynitrite, a highly reactive molecule with a short half-life, which in addition to oxidizing nearby molecules, can be transformed into nitrotyrosine when reacting with tyrosine residues, increasing immunoreactivity. The neuronal cells located on the Ammon's horn 1 region (CA1), in the hippocampus, promote an increase in zinc levels during long times of hypoglycemia. The glucose reintroduction

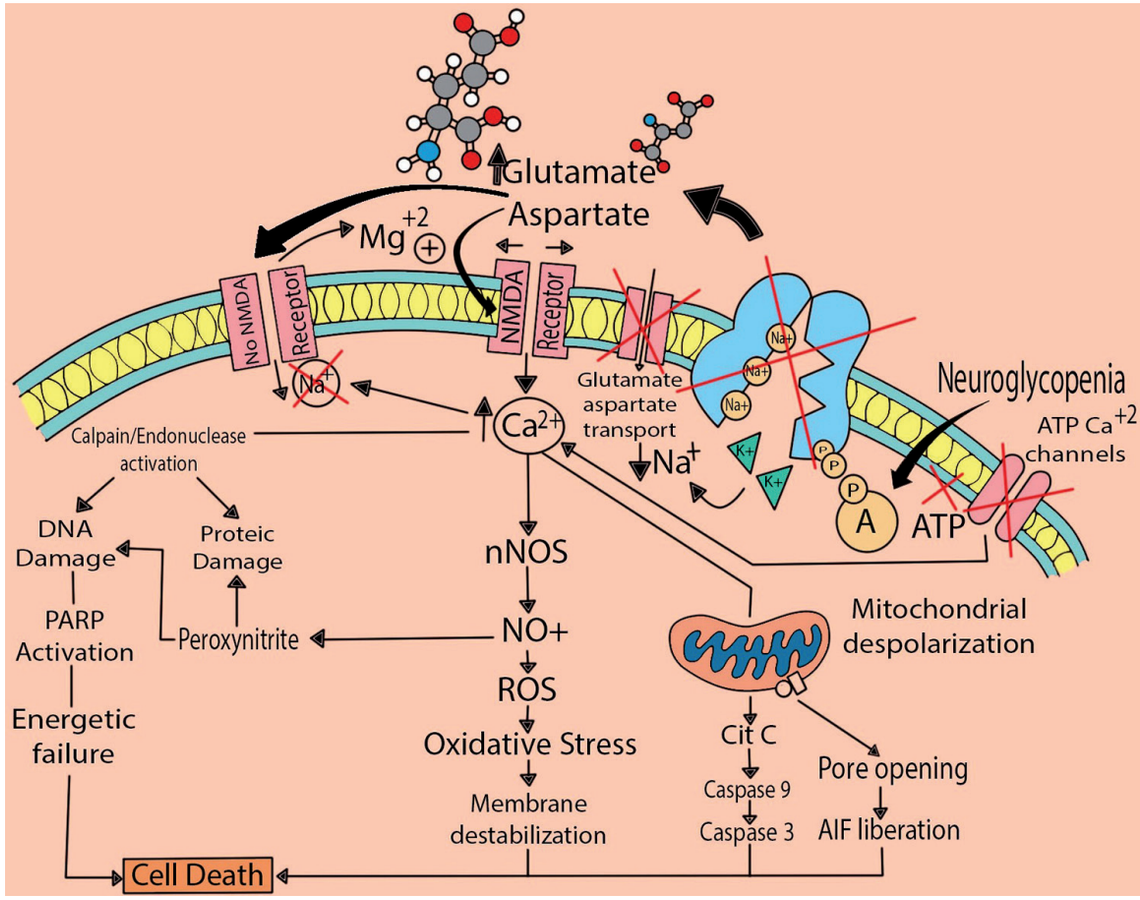

Figure 5.
Cell death in neuroglycopenia. DNA (deoxyribonucleic acid), PARP (poly-ADPribose), NMDA (N-methyl-D-aspartate), Mg^{2} (magnesium), $Ca2^{+}$ (calcium), Na^{+} (sodium), K^{+} (potassium), nNOS (neuronal nitric oxide synthase), NO+ (derived from oxygen species), ROS (reactive oxygen species), Cit C (cytochrome C), AIF (apoptosis inducing factor).

to the system promotes zinc vesicles and nitric oxide synthesis that trigger neuronal damage. Zinc activates the NADPH enzyme oxidase (NOX) and poly-ADP ribose (PARP-1) after being translocated to postsynaptic neurons, leading to the production of reactive oxygen species (ROS), depletion of oxidized nicotinamide adenine dinucleotide (NAD+) and lead to neuronal death. The production of ROS by NOS and NOX induces DNA damage and consequent activation of PARP-1, which consumes the NAD+ which is required for glucose oxidation through the glycolytic pathway, as well as activating programmed cell death pathways such as calpain [30]. During hypoglycemia, PARP-1 activation is an important factor involved in neuronal death (it leads to increased nitrotyrosine and products of this polymerase). On the other hand, PARP-1 inhibitors can rescue neurons that would otherwise die after severe hypoglycemia (**Figures 4** and **5**) [31, 32].

3.3 Apoptosis and inflammatory response

Apoptosis is a type of cell death that depends on energy and various cellular functions in which the membrane retains its integrity. For its activation, specific proteins are required to avoid inflammatory responses, which are divided into intrinsic and extrinsic pathways. The intrinsic activation pathway consists of caspases and calpain. Caspases are classified as initiators, such as caspase 9 and executors, including

caspase 3. The intrinsic pathway starts with the release of cytochrome C from the mitochondrial inner membrane, which increases its concentration in the cytosol and binds APAF1 (apoptotic protease-activating factor 1) protein, dATP and procaspase 9 zymogen [29, 32]. Once bound, this complex becomes an active initiator form of the pathway, caspase 9, which consequently causes the activation of the executioner pathway, procaspases 3 and 7, responsible for promoting apoptosis.

It has been postulated recently that an inflammatory response also participates in hypoglycemic cell damage, this is known due to a study that demonstrates microglial reactivity in the rat of hippocampus 1–7 days after 30 minutes of hypoglycemic isoelectric, with activation of calpain, xanthine oxidase and phospholipase A2.

Tkacs and cols., demonstrated that three hypoglycemic episodes related to 30–35 mg/dl glucose blood levels increased the number of positive cells to TUNEL (apoptosis marker in the arcuate nucleus of the hypothalamus). Subsequently, other authors reported positive degenerative cells to the neuronal death marker Fluoro-Jade B (FJB) after only 1 week of a single hypoglycemia event, particularly in the cerebral cortex, although some were also observed in the hippocampus and striatum [33].

In 1880, blood glucose levels were measured for the first time, which made it possible to understand the different clinical neurological manifestations and their association with low blood glucose levels [34]. It was in 1938, when the surgeon Allen Whipple proposed a triad characterized by hypoglycemia symptoms, decreased venous glucose concentration and the disappearance of these symptoms after the correction of glycemia. Although this description was proposed as criteria to perform or not the insulinomas resection, this triad became widely generalized among the medical community in the face of hypoglycemia events due to any cause. Reversibility of the clinical syndrome is frequent when treatment is initiated, although there are also less fortunate scenarios in which sustained damage to the nervous system is produced, which will depend on the degree of hypoglycemia when treatment is not timely. This situation is directly related to functional prognosis and mortality [34, 35].

The physician must be able to identify the clinical signs of hypoglycemia since the first organ to suffer the consequences is the brain, and we must avoid unfavorable outcomes, such as neuronal damage and death (neuroglycopenia). When the arterial glucose supply is interrupted and the protective mechanisms are overcome, the previously described alterations occur at the level of ionic gradients, neurotransmitter release and reuptake, and oxidative stress, culminating in mitochondrial and cellular dysfunction [36].

There are usually very effective endogenous mechanisms to prevent neuroglycopenia. The first line of defense against falling blood glucose levels is to decrease endogenous insulin production, increasing hepatic glucose production and decreasing its utilization by other peripheral tissues such as muscle and fat tissue [37]. If glucose levels remain low, there will be glucagon secretion, followed by an increase in adrenaline. These counterregulatory mechanisms will be as intense as hypoglycemia severity, resulting in mobilization of glycogen stores, gluconeogenesis and decreased glucose utilization at the peripheral level [38].

A very particular characteristic of the brain is the high consumption of glucose and oxygen, with a high tolerance to periods of transient deficit of these substrates, however, when glucose decreases below 20 mg/dl, there is a cessation of brain electrical activity (hypoglycemic coma). Blood glucose concentrations may decrease to 30% of the normal value, but this supply must be constant, as neuronal glycogen stores are limited and depleted in less than 2 minutes. From this point on, the extent of neuronal damage is directly related to the time the isoelectric period is maintained. Neuronal

death occurs after a period of approximately 15 minutes of inactivity. Repeated episodes of hypoglycemia cause irreversible damage, causing the irreversible cognitive deficit, which correlates to various brain structures, the most sensitive to the damage being the cortex, hippocampus and striatum [39].

3.4 Excitatory amino acids in hypoglycemic damage

Excitotoxicity refers to the ability of some amino acids (glutamate) to cause neurodegeneration secondary to prolonged stimulation of postsynaptic receptors. This type of toxicity was first described in cerebral vascular disease; later evidence was found in severe hypoglycemia. The mechanism of damage is as follows: extracellular concentrations of glutamate are regulated by reuptake into the synaptic space by specific transporters located in astrocytes and neurons. This reuptake is mediated by sodium, regulated by the electrochemical gradient of ATP-dependent Na/K+ pumps. These ionotropic receptors are classified according to their specific agonist: the N-methyl D-aspartate (NMDA) receptor, permeable to calcium and sodium. The non-NMDA receptors (kainate receptor and a-amino-3-hydroxy-methyloxazole-4propionic acid (AMPA) are sensitive to sodium [40].

Under resting conditions, the NMDA receptor ion channel is blocked by magnesium, which is released during depolarization mediated by non-NMDA aspartate receptor-dependent ion channels, allowing calcium to enter the intracellular space. Both glutamate and aspartate have been shown to be associated with neuronal damage in hypoglycemia, being released in large amounts during the isoelectric trace [41]. In this situation glutamate is used as a metabolic substrate, favoring the release of aspartate by altering the electrochemical gradient of Na+/K+, promoting the accumulation of intracellular calcium and with it, the release of vesicles by exocytosis with excitatory neurotransmitters. Even with the accumulation of excitatory neurotransmitters, the inhibition of their transporters can limit neurological damage; however, when there is an absence of energetic substrates, neuronal death is induced. As mentioned, neuronal death and cognitive impairment caused by hypoglycemia suggest that they are involved in excitotoxicity and DNA damage.

4. Neuroglycopenia secondary to hypoglycemia

To avoid neuronal death during a period of hypoglycemia, the brain sets in motion two main regulatory mechanisms: increased cerebral blood flow and the use of alternative substrate pools to glucose [39, 41]. During hypoglycemia, oxygen consumption remains constant, giving rise to the theory that these alternative pools are able to compensate for the lack of glucose, allowing adequate cellular function during relatively short periods of hypoglycemia. The brain can use other substrates for energy, such as lactate, pyruvate and ketone bodies, although the primary substrate in the first instance appears to be glycogen, which seems to be depleted in more than 5 minutes after the onset of the isoelectric period [42].

The nervous system is very susceptible to changes when serum glycemia value is low, which leads to protective mechanisms; on the other hand, when there is hyperglycemia it has a better regulation. The endocrine counterregulatory response mechanisms that are activated when glucose drops below 70 mg/dl, at the level of the pancreatic b-cells the first response is initiated, which consists in the cessation of insulin release and when the glucose level reaches 66 mg/dl, growth hormone and

cortisol are released, which stimulate lipolysis in adipose tissue, ketogenesis and gluconeogenesis in the liver. Below 54 mg/dl, glucagon (a hormone produced in pancreatic cells, which stimulates hepatic glucose production through glycogenolysis and gluconeogenesis) and epinephrine are secreted. Epinephrine secreted by the adrenal glands increases glycogenolysis and gluconeogenesis in the liver, stimulates lipolysis and decreases insulin secretion while elevating glucagon release (**Table 1**) [38, 39, 42].

The first modulatory process in hypoglycemia is decreased insulin synthesis. This is followed by an increase in other involved hormones such as GH, ACTH, glucagon, and epinephrine, resulting in the activation of metabolic regulatory pathways such as lipolysis, ketogenesis, and gluconeogenesis.

Recurrent hypoglycemia can cause the loss of these counterregulatory mechanisms and create a vicious cycle increases the risk of severe hypoglycemia with each event. Recurrent hypoglycemia reduces the glucose levels necessary to trigger the autonomic counterregulatory response during a subsequent hypoglycemic period, leading to patients being unable to recognize sympathoadrenal symptoms, leading to the onset of neuroglycopenic symptoms (hypoglycemia unawareness). The unawareness of hypoglycemia and the failure of the autonomic response lead to the so-called hypoglycemia-associated autonomic failure, which increases the risk of severe hypoglycemia by 25 times or more, with high chances of coma, irreversible brain damage and death. Clinical data suggest that about 25% of diabetic patients suffer hypoglycemia without realizing it [37, 39, 42]. Hypoglycemia occurs in 25–30% of diabetic patients, with type 1 diabetics being more affected, followed by type 2 diabetics, although in them it usually happens in advanced stages of the disease. The incidence of hypoglycemia episodes depends on the age and duration of the disease. The mortality rate is between 4 and 10% and is attributable to severe hypoglycemia in type 1 diabetic patients with the long-standing disease (7–30 years), this is because the continuous administration of insulin or insulin-releasing drugs leads to glucose uptake in fat, muscle and liver, inhibiting gluconeogenesis and glycogenolysis, as well as lipolysis and glucagon secretion from pancreatic cells. As a consequence, the first response to hypoglycemia (inhibition of insulin secretion) is lost, glucagon secretion is suppressed, and epinephrine is secreted at lower glucose levels [37, 38, 42].

4.1 Moderate or severe hypoglycemia

According to histological studies, hypoglycemic coma induces neuronal damage in the cortex, particularly in the insular cortex, hippocampus, caudate nucleus and putamen; lesions have also been identified in the thalamus, globus pallidus and a significant volume decrease in the white matter and gray matter in all cerebral lobes with occipital and parietal predominance. There is a close correlation between the duration of the isoelectric period and the spread of neuronal damage. The most

Organ involved	Response	Effects	
Pancreatic a cells	Decreased insulin synthesis	Blood glucose mobilization is reduced.	
Hypophysis	Increased GH y ACTH	Lipolysis and ketogenesis	Glyconeogenesis
Pancreatic β cells	Increased glucagon	Glycogenolysis	
Adrenal glands	Increased epinephrine and cortisol		

Table 1.
Brain protection mechanisms in neuroglycopenia.

vulnerable brain regions include superficial layers 2 and 3 of the cerebral cortex, CA1, the subiculum and crest of the dentate gyrus, as well as neuronal damage in the dorsolateral region of the striatum [43].

5. Clinical manifestations in neuroglycopenia

Signs and symptoms for hypoglycemia depend on glucose levels (mild, moderate or severe), frequency and duration of episodes. Symptomatology can be divided into two big groups: The first group included sympathoadrenal or neurogenic symptoms due to the activation of the autonomic nervous system and the release of epinephrine and norepinephrine, triggered in moderate hypoglycemia. The symptoms can be hunger, sweating, tingling, tremors, palpitations and anxiety (the initial symptoms that allow the patient to notice the hypoglycemic state). If glucose levels continue dropping to moderate or severe, the patient would develop the second group of symptoms (neuroglycopenic symptoms) which include blurry vision, confusion, dizziness, irritability, bradylalia, lipothymia, drowsiness, bradypsychia, seizures and coma. However, they do not always present the same way, actually, it is one of the first diseases that mimic brain stroke symptoms, among other acute neurologic diseases (hypoglycemic encephalopathy) [34, 35, 44]. Hypoglycemia recurrence induces the body to adapt, and the clinical signs can be minimal or absent until the glucose levels decrease deeply, taking the patient to an impaired consciousness state (**Table 2**) [29, 44].

Mild hypoglycemia has subtle symptoms which are inconspicuous with cognitive changes. Multiple studies have done experiments on both humans and animals, finding an association between hypoglycemia and cognitive impairment, affecting complex abilities more than simple ones, regulated by the hippocampus [45, 46]. After a severe hypoglycemia episode, the cognitive deterioration in different cerebral domains appears in healthy individuals with glucose blood levels between 2.6 and 3.3 mmol/l [47]. Severe hypoglycemia causes a decrease in the performance of cognitive tasks, such as verbal fluency, reaction time, arithmetic abilities and verbal and visual memory [48]. The cognitive function drop is seen after the activation of the counterregulatory response and the presence of neuroglycopenic symptoms in diabetic

Sympathoadrenal symptoms	**Neuroglycopenic symptoms**	**Other symptoms of severe neuroglycopenia**
Hunger	Blurred vision	Cognitive changes
Sweating	Confusion	Difficult memory
Paresthesias	Dizziness	Troubles with language
Tremor	Irritability	
Palpitations	Bradylalia	Bradykinesia
Anxiety	Lipothymia	
	Drowsiness	
	Bradypsychia	
	Seizures	
	Coma	

Table 2.
Clinical manifestations of neuroglycopenia.

patients, however, this response changes in non-diabetic patients in whom the cognitive function is immediately impaired, even before the counterregulatory neuroendocrine response starts and senses the neuroglycopenic symptoms (**Table 2**) [47, 48].

In 1990, Ryan et al., evaluated the cognitive effects after a hypoglycemic event in children, using the hypoglycemic clamp technique, with a control group with normal glucose levels. Hypoglycemic values were 3.1–3.6 mmol/l and the euglycemic values were from 5.5 mmol/l onwards, noticing a significant decrease in the trail-making test (mental flexibility), attention and decision making in the mild hypoglycemic group. Also, once the glycemic values were restored (>5.5 mmol/l), there was no recovery observed in the attention or reaction time tests, which suggests a long-term neurological effect [49].

Other studies have documented attention, intelligence and memory disturbances in children with a history of severe hypoglycemia [48, 49]. Childhood hypoglycemia represents an essential factor that affects specific cognitive capabilities such as memory, learning, intelligence and attention, being the most vulnerable cognitive domains to hypoglycemia in children [50, 51]. However, no studies have been made comparing the history of hypoglycemia with long-term control groups, therefore, the sequels that may develop are unknown with certainty.

Also, there have been reported mood disorders associated with repeated events of severe hypoglycemia, especially in depressive disorder until 24 hours after the event. Acute hypoglycemia changes the state of mind causing the patient to feel exhausted and reducing the hedonic tone. The consequence of long-term and repetitive periods of moderate hypoglycemia to neuronal damage and cognitive function is not well understood, however, prolonged hypoglycemia with the absence of isoelectricity can also induce neuron death restricted mainly to the cerebral cortex. Glucose blood concentrations of 30–35 mg/dl for 75 minutes can cause significant neuron damage in the medial prefrontal cortex, piriform cortex and orbital cortex [52].

5.1 Imaging in neuroglycopenia

Objective damage from repeated hypoglycemia events is difficult to document because routine imaging studies are not usually performed in this type of patient, as it is an event that is treated in the emergency room and it usually subsides in a few minutes. However, some studies have evaluated diabetic patients with recurrent hypoglycemia events trying to correlate cognitive alterations and imaging findings in MRI [53]. It has been reported cortical atrophy in type 1 diabetic patients with severe recurrent hypoglycemia events while in patients who do not have recurrent events these findings were not present, nevertheless, these findings were not related to the cognitive alterations. There are also case reports in which the MRI shows a reduction in the white matter of the hippocampus, thalamus and globus pallidus, correlating this with memory loss and anterograde amnesia, however, these findings are not common, which make them statistically insignificant.

6. Neuroglycopenia with and without hypoglycemia in medical scenarios

The physiology of glucose in the human brain has already been discussed thoroughly, its' way through the blood-brain barrier and molecular, cellular, tissue and systemic conditions, on the other hand, it is important to mention some clinical scenarios where these events take place even though there are not evident and can explain part of the symptoms and prognostic in each entity. This section will briefly

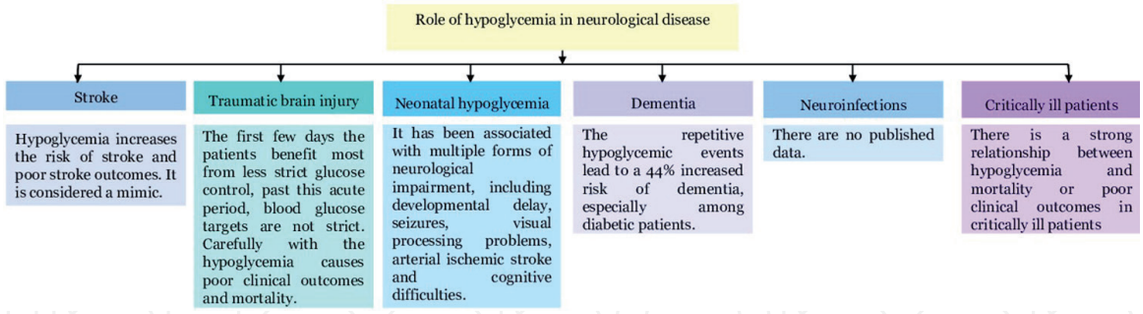

Figure 6.
Hypoglycemia negatively affects diseases of the central nervous system.

describe neuropathologic things that cause glucose levels alterations at the central nervous system and important treatment aspects (**Figure 6**).

6.1 Glucose brain concentration in the intensive care unit

The relationship between changes in glucose values and cardiovascular events, such as stroke and acute myocardial infarction, has been well established. Both hyperglycemia and hypoglycemia are factors that vary patient prognosis [54]. Glucose dysregulation is a common situation in neurocritical patients. Since 1849, the association between hyperglycemia and prognosis has been described in patients with cerebral infarction, a situation that has been repeated in more recent studies [55, 56], which also include patients with acute brain injury secondary to other situations such as meningitis and cranioencephalic trauma [57].

From several years, it has been thought that intensive glucose control by continuous infusion, even to near-normal levels, might be beneficial to the patient; however, the NICE-SUGAR study group conducted a randomized clinical trial comparing intensive glucose control (from 81 to 108 mg/dl) with a group in which glucose levels were more permissive (up to 180 mg/dl), with subcutaneous bolus insulin administration. Glucose below 140 mg/dl was associated with increased hypoglycemia events and increased cardiovascular mortality, whereas glucose levels above 180 mg/dl were associated with the worse neurological recovery and increased likelihood of sequelae [58, 59]. Multiple studies have reached the same conclusion, including the SHINE study, in which intensive control compared with the standard modality did not make a significant difference in functional outcome (Rankin scale at 90 days) [60].

Very loose glucose control was associated with worse neurological recovery, although it does not significantly influence mortality in the neurocritical patient, some sequelae may impact functionality [61].

6.2 Brain glucose concentrations in cerebral infarction

Several clinical trials have shown that cerebral stroke patients with acute elevation of glycemia at the onset of the event suffer worse functional outcomes, longer hospital stay and higher mortality with a higher rate of bleeding after the ischemic event [62]. The definition of hyperglycemia is debated, the reference cohort for different authors usually varies according to the results obtained in clinical trials, where the objective is the correlation between glucose levels and increased mortality, findings are diverse, finding favorable results with levels of 110–155 mg/dl [63, 64]. It has been shown that patients with ischemic stroke who are treated with tissue plasminogen

activator benefit from glucose levels below 140 mg/dl in the first hours of treatment, which correlates with the benefit of the fibrinolytic drug, since patients with adequate initial glycemic control had higher reperfusion rates, smaller infarcts, and better functional prognosis than patients with higher glucose levels, this is independent of chronic glycemic dyscontrol [65, 66]. Although evidence indicates that intensive glucose control does not impact mortality, hypoglycemia could have an impact on the development of neurological damage and long-term sequelae, perpetuating the damage already established by previous injuries in the neurocritical patient [67].

6.3 Brain glucose concentrations in patients with traumatic brain injury

During traumatic brain injury there is a net decrease in glucose in microdialysis, but an increase in glutamate and lactate/pyruvate in microdialysis, with an adverse effect on the long-term recovery of neurological function [68]. Care should be taken in the management of these patients, as it is known that during traumatic injury there is hyperglycemia, using insulin to control it and decrease brain damage due to hyperglycemia, however, adequate monitoring should be performed, as lowering glucose levels with insulin may induce and aggravate secondary brain injury [69].

A hypothesis suggests that post-traumatic reductions in extracellular glucose levels are not due to ischemia, but are associated with poor neurological outcomes. Neurosurgical data from the microdialysis catheter in uninjured brain tissue with a perfusion rate of 2 uL/min suggest that glucose values of 0.5–1 mmol/L and lactate of 0.6–1.1 mmol/L are considered normal. In patients with epilepsy versus non-epileptic tissue perfused at 2.5 uL/min, mean glucose values of 0.82 ± 0.27 mmol/L and mean lactate levels of 1.3 ± 0.49 mmol/L were observed [70]. In minimally injured brain trauma patients perfused at a rate of 2 uL/min and under conditions of normal intracranial pressure and normal tissue oxygenation, reports of mean glucose values have ranged from 0.5 to 1.1 mmol/L, demonstrating that glucose variations are not significant during direct trauma [71]. The extracellular glucose level is generally reduced after severe traumatic brain injury and is associated with poor neurological recovery, but is not associated with ischemia [72].

Due to these findings, blood glucose control in patients with traumatic brain injury has recently been the subject of much research [68, 72]. A retrospective study included a total of 228 patients with severe trauma who were treated with insulin. In the first week (acute stage), a blood glucose target of 90–144 mg/dL (5–8 mmol/L) was associated with a reduced mortality rate and a decrease in intracranial pressure (ICP) compared with a blood glucose target of 63–117 mg/dL (3.5–6.5 mmol/L). However, in the second week, the groups appeared to have the reverse results: compared to the target group of 5–8 mmol/L, the 3.5–6.5 mmol/L group demonstrated a lower incidence of ICP and a reduction in infectious complications. Therefore, slightly higher blood glucose (5–8 mmol/L) appears to provide benefits during the first week, whereas lower blood glucose (3.5–6.5 mmol/L) may be more favorable during the later stages of recovery [69, 72]. Another study showed that blood glucose < 6–11 mmol/L could reduce mortality in patients with mild trauma, whereas, in severe cases, the ideal blood glucose target was 7.77–10.0 mmol/L.

Both hyperglycemia and hypoglycemia are harmful [70, 73]. Therefore, methods to improve intensive insulin therapy without inducing secondary complications should be investigated, and attention should also be focused on the prevention of hypoglycemia in patients with head injury [73]. It can be concluded that, in the first

few days following traumatic brain injury, patients benefit most from less strict glucose control, and that, past this acute period, blood glucose targets should be modified.

6.4 Hypoglycorrhachia without hypoglycemia

An objective way to demonstrate neuroglycopenia without symptoms is by measuring glucose in the cerebrospinal fluid (CSF). There are multiple etiologies that lower glucose centrally and are recognized not by the symptomatology of neuroglycopenia but by the characteristic symptoms of each disease and the presence of hypoglycorrhachia (there are multiple definitions, however, the most accepted is CSF glucose/serum glucose ratio ≤ 0.5, and < 40 mg/dl is considered severe) [74, 75]. The etiologies are diverse in both children and adults (**Table 3**) [74–76]. Treatment is disease-specific and hypoglycorrhachia is not specifically treated.

6.5 COVID-19

Neuro-COVID has been described for its clinical manifestations and findings in acute neurological disease, and the data that have caused the most impact when talking about encephalitis secondary to COVID-19 is hypoglycorrhachia and changes in the electroencephalogram [77]. Based on the above, our team conducted an investigation during the current SARS-CoV2 pandemic in 30 patients with a diagnosis and positive polymerase chain reaction for SARS-CoV2, without any obvious neurological manifestations, and performed a clinical history, complete physical and neurological examination, lumbar puncture and electroencephalogram, obtaining the following results: We found a high prevalence of minor neurological manifestations, such as headache, anosmia, dysgeusia and hypoaesthesia predominating in the early stages [78]. Other frequent abnormal findings were in the CSF with hypoglycorrhachia >70% and less frequently in the electroencephalogram of the scalp with focal and generalized dysfunction in <20%.

Infectious diseases	**Non-infectious diseases**
Meningitis caused by typical bacteria, atypical bacteria, viruses, parasites, mycobacteria or fungal etiology.	Carcinomatous meningitis.
	GLUT-1 deficiency syndrome.
Amebic meningoencephalitis.	Leukemia or lymphoma involving CNS.
Cytomegalovirus.	Subarachnoid hemorrhage.
Other causes of hypoglycorrhachia	
Malignant atrophic papulosis.	Neurosarcoidosis.
	Meningitis of rheumatoid etiology.
Cholesterol-induced leptomeningitis.	Behcet's disease.
Rheumatoid meningitis	Dermoid cyst.
Granulomatous angiitis of the central nervous system.	Systemic lupus erythematous with CNS involvement.

Table 3.
Diseases with hypoglycorrhachia without neuroglycopenia.

7. Conclusion

Glucose is the main fuel for the appropriate functioning of the central nervous system. It has been described the main mechanism of entry and use of glucose at the molecular and cellular levels. We emphasize that neurons and astrocytes interact to form common metabolic cooperation generating a neuroprotective effect to avoid hypoglycemic coma or a major brain injury that leads to cellular death. We cannot forget that when a patient has already had neuroglycopenia secondary to hypoglycemia, he/she already has a change in his/her metabolism and recurrence becomes more frequent with each episode, which is why some insulin-dependent diabetics die. The management of glucose in critically ill patients or at the brain level is different and the ideal treatment and glucose values at central and serum levels are not clear. Central nervous system diseases that cause hypoglycorrhachia are treated by etiology and not by low central glucose. Finally, at the time of writing this chapter we faced with the fact that the amount of published information is old and repetitive, it is important to continue research on the damage, prevention and prognosis of glucose levels at the central level in different scenarios.

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Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

AMPA	a-amino-3-hydroxy-methyloxazole-4propionic acid
AIF	apoptosis inducing factor
ATP	adenosine triphosphate
APAF1	apoptotic protease-activating factor 1
BBB	blood brain barrier
Ca2+	calcium
Cit C	cytochrome C
dl	deciliters
DNA	deoxyribonucleic acid
FJB	Fluoro-Jade B
H+	hydrogen
GLUT	glucose transporter
G6P	glucose-6-phosphate
K+	potassium
LAC	(lactate)
LDH	lactate dehydrogenase
MCT	medium-chain triglycerides
mg	milligrams

Mg/dl	milligrams per liter
Mg2	magnesium
mM	millimoles
mmol/l	millimoles per liter
Na+	sodium
NADH	nicotinamide adenine dinucleotide reduced
NAD+	nicotinamide adenine dinucleotide oxidized
NMDA	N-methyl-D-aspartate
nNOS	neuronal nitric oxide synthase
NO+	derived from oxygen species
ROS	reactive oxygen species
SGLT	sodium dependent glucose transport
PARP	poly-ADPribose
Pyr	pyruvate

Author details

Daniel Arturo Martínez-Piña[1*], Gustavo Alexis Alvarado-Fernández[2], Edith González-Guevara[1], Carlos Castillo-Pérez[1], Gerardo Romero-Luna[1] and Jorge Alejandro Torres-Ríos[1]

1 National Institute of Neurology and Neurosurgery, Mexico City, Mexico

2 Hospital Gustavo A Rovirosa Perez, Villahermosa, Mexico

*Address all correspondence to: daniel_264mx@hotmail.com

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