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Modulation of Glucose Availability and Effects of Hypo- and Hyperglycemia on Status Epilepticus: What We Do Not Know Yet?

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Abstract

Status epilepticus (SE) can lead to serious neuronal damage and act as an initial trigger for epileptogenic processes that may lead to temporal lobe epilepsy (TLE). Besides promoting neurodegeneration, neuroinflammation, and abnormal neurogenesis, SE can generate an extensive hypometabolism in several brain areas and, consequently, reduce intracellular energy supply, such as adenosine triphosphate (ATP) molecules. Although some antiepileptic drugs show efficiency to terminate or reduce epileptic seizures, approximately 30% of TLE patients are refractory to regular antiepileptic drugs (AEDs). Modulation of glucose availability may provide a novel and robust alternative for treating seizures and neuronal damage that occurs during epileptogenesis; however, more detailed information remains unknown, especially under hypo- and hyperglycemic conditions. Here, we review several pathways of glucose metabolism activated during and after SE, as well as the effects of hypo- and hyperglycemia in the generation of self-sustained limbic seizures. Furthermore, this study suggests the control of glucose availability as a potential therapeutic tool for SE.

Keywords Glucose · Hypometabolism · Hypoglycemia · Hyperglycemia · Status epilepticus · Epilepsy

Introduction

Status epilepticus (SE) is a clinical emergency characterized by either a continuous self-sustained seizure or a sequence of short seizures with no return to baseline, unleashing a high mortality rate [1–8]. SE can be convulsive or nonconvulsive [9–16], and it is capable of promoting neuronal death, gliosis, and wide molecular changes in several brain areas [4, 11, 12, 17, 18]. Furthermore, SE leads to temporal lobe epilepsy (TLE), which is characterized by spontaneous recurrent seizures, abnormal synaptic reorganization, mossy fiber sprouting, hippocampal neurodegeneration, and neurogenesis [19–23]. SE induction in rodents by electrical or chemical stimulation have been used to model epileptogenesis process and TLE clinical features [4, 8, 10–13, 24–32]. Local or systemic administration of the pilocarpine (PILO) or kainic acid leads to a pattern of repeated limbic seizures and/or SE, which can endure for many hours [4, 8, 19, 30, 32].

Recent [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) studies with patients and animal models showed that SE induces secondary hypometabolism in the epileptogenic areas, including hippocampus, cortex, and striatum [33–40]. Secondary hypometabolism has also been associated to specific patterns of SE in studies with humans and animal models [33, 41–43]. During an epileptic seizure or SE, the overexcited neurons must increase glucose uptake [44–46] above organism's supply capacity, resulting in adenosine triphosphate (ATP) deficit in the nervous tissue [47], where energy consumption is much higher than in several other body

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tissues [48]. Glucose is taken up into brain cells by two major groups of transporters: (1) glucose transporters (GLUTs) for facilitated diffusion and (2) sodium/glucose cotransporters (SGLTs) for its secondary active transport [49–54]. Glucose transporter 1 (GLUT1) is expressed in both blood–brain barrier and glial cells [55], while glucose transporter 3 (GLUT3) presents high glucose affinity and transport capacity in neurons [54, 56–59]. Sodium/glucose cotransporters 1 and 2 (SGLT1 and SGLT2) have been observed in hippocampus [50, 51]. Despite the evidence of glucose availability modulating brain damage, it has been difficult to define the role of glucose transporters and associated glucose metabolism in isolated epileptic seizures or during and after SE.

Here, we review recent advances regarding regulation of glucose supply during self-sustained epileptic seizures. Our purpose was to survey the main data associated with the modulation of glucose in seizures, in order to discuss the possible pathways that could explain the alterations on seizures susceptibility in hypo- and hyperglycemic conditions. Furthermore, we summarize these findings and draw an overview to contribute for new insights in treatment strategies that could effectively reduce neuronal damage associated with TLE, in the absence of counteractive side effects.

Intracellular Metabolism of Glucose and SE

The physiological pattern of the brain requires high amounts of energy supply, in constant demand, comprising an average of 20% of the body's energetic consumption [60]. Glucose is converted into glucose-6-phosphate (glucose-6P) immediately after being transported to the intracellular environment. Glucose-6P is processed through glycolysis, resulting in two molecules of pyruvate which are metabolized during the tricarboxylic acid cycle and the oxidative phosphorylation in the mitochondria [61].

Functional brain imaging techniques, such as FDG-PET and functional magnetic resonance imaging (fMRI), allowed for the conduction of integrative studies between regional brain energy metabolism (energy delivery and use) and neural cell activity [62–65]. FDG-PET detects alterations in regional cerebral blood flow, as well as in glucose and oxygen consumption [9, 66–68] while fMRI provides data on regional blood oxygenation levels [69]. It was demonstrated that cerebral glucose metabolism is altered in epilepsy as well as in other neurological disorders [70–75].

Glucose Metabolism in Clinical Studies

SE promotes a sharp increase of regional cerebral blood flow and oxygen consumption correlated with enhancement in glucose utilization [76]. In an 11-year-old girl, an intense hypometabolism was observed in most of the left hemisphere, 6 weeks, and 8 months after one SE episode. The right hemisphere, however, showed a heterogeneous increase in the metabolic rate of glucose only at 8 months after the SE occurred [77]. Similarly, a severe hypometabolism was observed in the left hemisphere of a 48-year-old right-handed man with Alien hand syndrome after a complex partial SE. Notably, the periodic lateralized epileptiform discharges (PLEDs) generated during the SE were only detected in the left hemisphere, especially in areas such as basal ganglia and thalamus [78]. Moreover, a patient presenting right hemispheric PLEDs due to SE showed right hypometabolism in the temporal, parietal, and occipital lobes [79]. The same pattern has been seen in an elderly patient with permanent sensorimotor dysphasia after SE [42]. These authors suggest that both lateralized seizures and hypometabolism are directly correlated with the pattern of neuronal death observed in hippocampal formation and adjacent areas [11, 12, 80].

In other clinical studies, FDG-PET showed scattered areas of regional hypometabolism in pediatric and adult patients with refractory and nonconvulsive SE [9, 81, 82]. A recent study showed hypometabolism in cortical areas, such as frontal, parietal, and posterior cingulate cortices, and hypermetabolism in thalamic, caudate and dentate nuclei, and cerebellar vermis, of a 17-year-old girl with absence of SE [83]. According to the authors, these findings indicate a relevance of the thalamus in absence of SE, as well as modulation of cortical and cerebellar regions associated with the control of epileptiform discharges. Table 1 shows a summary of clinical studies related to cerebral glucose metabolism.

Glucose Metabolism in Animal Models

Since the 1990s, distinct animal models of SE have shown alterations in the metabolism of cerebral glucose during or after self-sustained seizures [10, 28]. In 1991, VanLandingham and Lothman, using continuous hippocampal stimulation (CHS), developed a nonconvulsive model of self-sustained limbic SE (SSLSE). This model was used to evaluate the regional cerebral glucose utilization (RCGU) after 90 min of CHS [10, 28]. RCGU was observed in acute (1 h after induction) and chronic (1 week or 1 month) periods. During the acute period, RCGU was elevated in some brain regions, such as hippocampus, retrohippocampal area, and limbic and nonlimbic structures, while hypometabolism was observed in neocortical structures. In the chronic period, 1 week after SE, an increase of RCGU was recorded in some limbic regions, but RCGU levels returned to baseline at 30 days after SE [10]. On another study, rats were submitted to the same protocol with or without hippocampal commissurotomies, in order to evaluate whether hippocampal commissures were necessary for the initiation and maintenance of SSLSE. These studies showed RCGU was bilaterally and symmetrically enhanced in hippocampus and other areas

Table 1 Main clinical studies related to cerebral glucose metabolism

Scientific articles	Main results
Van Bogaert et al. [77]	Hypometabolism in left hemispheric after 6 weeks and 8 months of SE (an 11-year-old girl)
Duane et al. [81]	Hypometabolism in areas of both hemisphere (a 7-year-old boy with left hemiparesis secondary)
Fernández-Torre et al. [42]	Left hemisphere and contralateral cerebellar cortex (a right-handed 74-year-old man) with hypometabolism
Kim et al. [78]	Hypometabolism in left cerebral hemisphere, affecting the basal ganglia and thalamus (a 48-year-old right-handed man)
Sakakibara et al. [79]	Hypometabolism in right cerebral hemisphere, affecting temporal, parietal, and occipital lobes (a man with PLED)
Barros et al. [82]	Hypometabolism in left occipital lobe (a 7-year-old boy with super-refractory partial SE)
Pari et al. [9]	Widespread hypometabolism in posterior regions bilaterally (19-year-old woman with nonconvulsive SE)
Shimogori et al. (2014)	Cortical hypometabolism (absence SE)
Shimogori et al. [83]	Hypermetabolism in thalamic and cerebelar structures (a 17-year-old girl with absence SE)

(retrohippocampal, limbic, and nonlimbic structures) in the group with preserved commissures, while both groups presented bilateral hypometabolism in neocortical regions [28].

Glucose hypometabolism was also shown in rodent SE models induced by kainic acid or PILO. In lithium-PILO model of SE in rats, a severe glucose hypometabolism occurred in hippocampus, cortex, and striatum during epileptogenesis, and this alteration was associated to other pathological changes, such as hippocampal, atrophy, neuronal death, and gliosis [33, 84]. This hypometabolism was partially recovered in the chronic phase, maybe due to increased cell number associated with astrogliosis [68]. Similarly, in the early phase after systemic PILO-induced SE, glucose utilization was reduced severely in limbic structures, such as hippocampus; however, glucose levels were restored during the chronic period [39]. Controversially, other authors have reported that reduced glucose metabolism gradually expands to limbic regions in the chronic phase [36]. Furthermore, in the kainic acid-induced SE model in rats, FDG-PET demonstrated hippocampal hypometabolism after 24 h of SE, which tended to decrease in the early phase of epileptogenesis and then stood out again with the emergence of CREs, what was accompanied by an increase in the expression of GLUT1 and synaptophysin in the same area [43]. These authors concluded that the glucose hypometabolism precedes neuronal loss and CRE. In addition, in a mouse model of PILO-induced SE, mitochondria were metabolically dysfunctional in hippocampal formation and cortex, 3.5 to 4 weeks after SE [85]. Moreover, a recent study showed a significant increase in glucose uptake in rat hippocampus after 4 and 24 h of SE induced by lithium-PILO, later returning to baseline levels [86]. Controversially, these same authors observed a hippocampal hypometabolism in chronic epileptic rats [86]. Table 2 shows a summary of preclinical studies of SE related to cerebral glucose metabolism.

Taken together, these clinical and experimental findings support the idea that SE compromises intracellular glucose metabolism, which may contribute to the activation of inflammatory mechanisms, neuronal loss and gliosis, and may also predispose the brain to develop epilepsy [87]. Therefore, restoring glucose metabolism during and after continuous self-sustained seizures may be an effective way of dealing with epileptogenesis and its complications. Additionally, because of the different pathophysiological findings, experimental models, brain areas, and phases of epileptogenesis, the precise mechanism among the possible factors that contribute to hypometabolism or hypermetabolism in these conditions has not been reported in current literature. Therefore, new clinical and preclinical trials should be carried out to address this issue.

Hypo- and Hyperglycemic Mechanisms Associated with SE Generation

Metabolic disorders are often associated with epileptic seizures; however, their relationship is poorly understood. The importance of glucose balance has emerged from studies demonstrating that epileptic seizures can be accentuated under conditions of hyper- or hypoglycemia [47].

Hypoglycemia and SE

Hypoglycemia is a clinical condition characterized by low plasma glucose concentration affecting both diabetic and non-diabetic patients. Hypoglycemia and hypoglycemic seizures may occur due to an increase in the amount of insulin in the plasma, being common in patients who are under treatment with insulin [88].

Neuronal excitation is tightly tied to brain energy metabolism. Severe hypoglycemia represents a serious threat for normal brain metabolism causing unbalance between inhibitory and excitatory neuronal networks, what leads to increased seizure susceptibility and risk for brain damage. The functional and structural injuries induced by severe hypoglycemia may persist when normal glucose levels are restored, leading to

Table 2 Main preclinical studies of SE related to cerebral glucose metabolism

Scientific articles	Main results
Hippocampal stimulation	
VanLandingham and Lothman [10]	Acute: ↑ glucose utilization (hippocampus and other structures) and hypometabolism in neocortical structures Chronic: ↑ glucose utilization (1 week/limbic regions) Return to baseline levels (30 days)
Kainic acid model	
Jupp et al. [43]	↓ Glucose metabolism in hippocampus (24 h after SE) Hypometabolism tend to decrease (by 1 week) and more intense during SRSs ↑ GLUT1 and synaptophysin
Pilocarpine model	
Guo et al. [39]	↓ Glucose utilization (hippocampus and limbic structures)—early phase after SE Glucose utilization restored—chronic phase after systemic pilocarpine-induced SE in rats
Lee et al. [36]	↓ Glucose metabolism gradually expands to limbic regions—chronic phase after SE Lithium-pilocarpine induced SE in rats
Smeland et al. [85]	Mitochondrial metabolic dysfunction (hippocampal formation and cortex)—pilocarpine-induced SE in mice
Zhang et al. [68]	↓ Glucose metabolism—epileptogenesis partial recovery glucose uptake (hippocampus)—chronic phase after SE—systemic pilocarpine-induced SE in rats
García-García et al. [33, 84]	↓ Glucose metabolism (hippocampus, cortex and striatum)—lithium-pilocarpine model in rats Associated to hippocampal neurodegeneration and gliosis

permanent cognitive dysfunction, EEG abnormalities, and predisposition for unprovoked seizures [89].

According to several studies, there is a not fully understood relationship between hypoglycemia and epileptic seizures [90–94]. It is well established that low glucose concentrations can change cortical excitability [95] and stimulate glutamate release, inducing cerebral hyperexcitability and, consequently, NMDA receptor-mediated excitotoxicity [96], with hippocampus showing particular susceptibility to these effects [97].

Studies aiming to describe epileptic manifestations associated with hypoglycemia have been carried out since the 1980s. Sapolsky and Stein [98], following a kainic acid-induced SE in rats, showed that hippocampus of hypoglycemic animals presented more damage when compared with normoglycemic or hyperglycemic ones, suggesting that limited energy compromises the survival of neurons in seizures. Severe acute cases of hypoglycemia in humans as a complication of therapy for insulin-dependent diabetes mellitus [90] or due to the excessive consumption of alcohol [99] are often associated with neurological side-effects [100, 101], resulting frequently in generalized seizures [102, 103]. A study evaluated causes of symptomatic convulsive SE in children, and found that most of them had metabolic disorders, such as electrolyte imbalance, hypoglycemia, hypocalcemia, or hypomagnesemia [91]. Other authors found that 11% of adult patients with SE presented a metabolic disfunction as cause of convulsive SE [104]. Unfortunately, these studies did not separate the isolating effect of blood glucose from other metabolic disturbances [105]. In rats, insulin-induced hypoglycemia also leads to generalized seizures [92, 106].

There is relative limitation in studies that have evaluated the relationship between hypoglycemia and epilepsy in animal models. One such study investigated this relationship by evaluating the modulation, by glycemic levels, of kainate-induced seizure susceptibility, as well as its neuropathological consequences [47]. These authors found no difference in the severity of seizures between hypoglycemic mice and other groups, as evidenced by similar latency at the onset of the first severe seizure and its duration. However, their results demonstrated that mice with insulin-induced hypoglycemia had an increase in hippocampal neurodegeneration, with significant loss of cells in three hippocampal subfields (dentate hilus, CA3 and CA1) [47].

Diabetes is not directly related to seizures, however the hypoglycemic conditions eventually generated in this process may be associated. Seizures can occur in diabetic and non-diabetic rats [94], and seizures may be associated with acute hypoglycemia, as well as the death of animals is related to the frequency of seizures and not to blood glucose levels. This suggests that hypoglycemia would be a predisposing factor to seizures, therefore a morbidity and not a mortality factor. Furthermore, the same authors showed that severe hypoglycemia as a precondition for seizures was associated with animal deaths, and suggest that this is probably due to the brainstem involvement in the seizures, which may affect the cardiorespiratory system and lead to mortality [93, 94].

Unlike animal model studies, in the last years several, mostly cohort, studies in human patients have been conducted to elucidate the relationship between hypoglycemia and epilepsy. In 2015, Halawa and colleagues investigated an

association between different levels of hypoglycemia and the occurrence of epileptic seizures in patients without previous diagnosis of epilepsy; as a result, coma was reported as the neurological symptom mostly caused by hypoglycemia, with convulsions being a rare event. In addition, a cohort study with more than 2,000 patients with type 1 diabetes identified an increased risk for epilepsy in these patients with a history of hypoglycemia (16,5%) compared with patients without hypoglycemia (2,67%) [107]. Moreover, an elegant study showed that seizures associated with hypoglycemia occurred in 90 of 170 patients aged 0 to 4 years; in 68% of the patients, the first hypoglycemic seizure was brief and fast, whereas the remaining 32% had more severe conditions and evolved to SE or coma [108]. The evaluation of such events according to the age of the patients demonstrated that brief seizures were more frequent than SE in both age groups studied: 63% versus 37% in neonates and 71% versus 29% in infants/children; in fact, blood glucose levels seem to be critical for the type of seizures presented by these patients, as they were significantly lower in SE than in brief seizures events [108].

Comparing neonatal period with childhood, the sequelae of SE are more intense in early ages [108]. Hypoglycemia in the neonatal period is relatively more common than in the older age groups and is considered a possible cause of seizures in the first year of life [109]. The relationship between the first hypoglycemic event and seizures was observed and this outcome was more frequent in children under 3 years old [108]. In the first years of life, seizures may initially appear as spasms [110].

It is important to note that SE is not necessarily associated with systemic factors, including hypoglycemia, in human patients, therefore hypoglycemia does not work as an etiological agent of SE [111]. Although this study was performed through medical records and electroencephalograms of only three patients without systemic complications who had died between 11 and 27 days after triggering SE, other authors found a weak correlation between hypoglycemia and epileptic seizures [88, 112]. For example, in a case of 229 diabetic patients, only 2 presented hypoglycemia and epileptic seizures concomitantly, representing a total of 0.8% of the diabetic patients evaluated [88]. Table 3 shows a summary of clinical and preclinical studies that correlate hypoglycemia and SE.

Hyperglycemia and SE

Among metabolic disturbances, hyperglycemia has frequently associated with deleterious effects on the central nervous system (CNS) induced by epileptic seizures [113]. Both type I and type II diabetes increase the susceptibility to epileptic seizures in these patients, emphasizing the importance of glycemic control for seizure treatment [114, 115]. Neuronal excitability and epileptic seizures are related to the rapid use of glucose and glycolysis [116, 117]. Hyperglycemia may also be associated with other factors to become the cause of SE. It is known that age can influence the outcome and severity of convulsive SE [118, 119].

As in the clinical studies, it has been shown that diabetic animals frequently develop seizures, depending on the severity of an ischemic insult and blood glucose concentration [113, 120]. Additionally, rats with diabetic hyperglycemia had a higher severity of seizures which induced a greater damage of the hippocampus after SE, followed by a higher mortality rate, or worsening of the cognitive capacity for learning in surviving animals [117]. This corroborates with another study that showed an increase of kainate-induced cell loss after SE in mice with non-ketotic hyperglycemia and diabetes-induced hyperglycemia [47].

Currently, there are some studies that point out that hyperglycemia can facilitate the entry of glucose into the brain and be involved in cell death during SE [121], also triggering morphological changes at the presynaptic terminals of mossy fibers that play important roles in increasing neuronal damage. Acute and chronic hyperglycemia produces increased susceptibility to excitotoxic cell death, the same effect observed as a consequence of seizures [47, 122]. High levels of glucose in the brain may increase the amount of ATP, facilitating ATP-

Table 3 Main clinical and preclinical studies that correlate hypoglycemia and SE

Scientific articles	Main results
Clinical reports	
Schober et al. (2012)	Severe hypoglycemic events associated with epilepsy
Gataullina et al. [108]	↑ Correlation between hypoglycemic children and SE
Falip et al. [88]	↓ Correlation between hypoglycemia and epileptic seizures
Halawa et al. (2015)	↑ Risk for developing seizures associated with hypoglycemic events
Chou et al. [107]	↑ Risk of epilepsy in patients with DM1 and history of hypoglycemia
Arhan et al. (2017)	64% with hypoglycemia had intractable epilepsy
Animal model	
Schauwecker [47]	Severe hypoglycemic events in epilepsy patients
Maheandiran et al. [94]	Seizures were associated with acute hypoglycemia

dependent brain reactions. These results show that hyperglycemia by itself is able to kill neurons, especially in the hilus region of hippocampus [121]. On the other hand, infusing a certain concentration of glucose after kainic acid-induced SE can be profoundly neuroprotective against seizure-induced neuronal damage [47, 121]. In this context, this brain glucose modulation can protect neurons of specific hippocampi regions. Table 4 shows a summary of clinical and preclinical studies that correlate hyperglycemia and SE.

Glucose Transporters in the Brain and Their Involvement in SE Modulation

Although the brain accounts for only 2% of body mass, it receives 15% of cardiac output and 25% of glucose supply, being responsible for 20% of the organism's oxygen consumption [123]. Glucose is transported through the blood-brain barrier (BBB) to the cerebrospinal fluid via glucose transporters or by the capillaries of the circumventricular organs which do not have tight junctions nor exert barrier properties [60, 124–126]. Glucose passes through the cell membrane by a specific transport system, which includes two types of glucose transporters: (1) the facilitated diffusion GLUTs that transport glucose in favor of its concentration gradient and 2) the SGLTs that transport glucose in favor of the sodium concentration gradient [127].

Glucose Transporters

GLUT1 is expressed in the basal and luminal membranes of the BBB endothelial cells, as well as in astrocytes and cell bodies of neurons, but it has not been described in microglia [55]. GLUT3 is the most abundant in the brain and is expressed in neurons, mainly in axons and dendrites, having a transport capacity five times greater than that of GLUT1 [128]. Furthermore, GLUT3 adapts to the demands of neuronal metabolism [53]. Currently, it is known that other types of GLUTs are expressed in the brain. GLUT2 protein is present in hypothalamic neurons and serves as a glucose sensor in the regulation of food intake [129]; moreover, GLUT2 regulates synaptic activity and contributes to neurotransmitters release in hippocampal neurons. Besides, GLUT5 has been described only in microglia as a hexose transporter and its regulation is still poorly understood. Finally, GLUT4 and GLUT8 are insulin-regulated glucose transporters and these transporters, although expressed in cell bodies of cortex and cerebellum neurons, are mainly found in the hippocampus and amygdala [130].

Hypo- and hyperglycemia have been shown to be able to modulate the expression of GLUTs in the brain [131]. An interesting study showed that chronic hypoglycemia induced by insulin infusion for 1 week increased the expression of GLUT3, but not GLUT1, showing a correlation between the rate of cerebral glucose metabolism and GLUTs [132]. Similarly, upregulation of GLUT3 protein was observed in the brain of rats subjected to insulin infusion (25 U/kg) for 8 days, indicating that this transporter adapts to metabolic disorders such as chronic hypoglycemia [133]. Recently, other authors have shown the expression of GLUT3 in several models of hypoglycemia [134]. In this study, mice with severe insulin-induced hypoglycemia experienced seizures and a trended higher GLUT3 in the hippocampus and cortex, which returned to baseline levels after glucose reperfusion. In addition, these authors related the change in GLUT3 expression to the upregulation of the nitric oxide marker (nitrotyrosin), indicating that this scenario triggered by severe hypoglycemia with seizures may be associated with glutamate/NMDAreceptor/nitric oxide/GLUT3 axis pathway [135, 136]. Interestingly, Pitchaimani et al. [134] also showed a change in p-BADser155 expression, suggesting a metabolic preference for ketone bodies during hypoglycemia. In

Table 4 Main clinical and preclinical studies that correlate hyperglycemia and SE

Scientific articles	Main results
Clinical reports	
Huang and Reichardt [117]	Excitability and epileptic seizures are related to the rapid use of glucose and glycolysis
Toledo et al. [119]	Age influenced the outcome and severity of convulsive SE
Lavin [114]	Glycemic control for seizure treatment
Santiago et al. [121]	Be involved in cell death during SE
Thundiyil et al. (2011)	The control can interrupt the seizures without the use of antiepileptics
Xia et al. [113]	Associated with epileptic seizures and deleterious effect on the central nervous system
Animal model	
Huang and Reichardt [117]	Greater severity in the epileptic attack
Santiago et al. [121]	Is able to kill neurons especially in the hilus region
Schauwecker [47]	Higher susceptibility to seizure-induced cell death after SE

summary, severe insulin-induced hypoglycemia alters the expression of GLUT3 possibly as a way of adapting the brain to glucose uptake in order to preserve normal neuronal functioning [134, 137].

Additionally, it was showed that chronic streptozotocin-induced hyperglycemia was able to increase the use of local cerebral glucose, as well as promoting a moderate (7.5%) reduction in the average density of GLUT1, but not GLUT3 [138]. The reduction of GLUT1 expression in BBB suggests a neuronal protective effect of hyperglycemia in brain. Likewise, these authors have observed a downregulation of GLUT1 in brain regions, including cortex, amygdala, thalamus, and cerebellum. Similar data showed that GLUT1 expression is downregulated in the BBB after a week of diabetes in rats [139].

GLUTs are crucial energy sources for the brain and their disorder can lead to a series of neurological manifestations. Considered an epileptic encephalopathy, GLUT1 deficiency syndrome (GLUT1DS) is caused by *de novo* heterozygous mutation in SLC2A1 gene, and it affects the CNS due to impaired cerebral glucose uptake through the BBB, which also culminates in reduced glucose levels in the cerebral spinal fluid (hypoglycorrhachia) [140–143]. A number of clinical phenotypes are observed in GLUT1DS patients, such as delayed development, cognitive and learning deficits with mental retardation, movement damage, including ataxia, dystonia, or dyskinesia, as well as absence seizures and generalized tonic–clonic seizures [144–147]. GLUT1 deficiency or persistent childhood hypoglycemia can trigger neuroglycopenia, caused by a partial and persistent damage to the CNS glucose supply and that culminates in hyperexcitability, epilepsy, movement disorders and other neuropsychopharmacology manifestation [148]. These results in GLUT1 deficiency patients, may be associated with the activation of anaerobic glycolysis, flux from fatty acids to triglyceride, production of fatty acids and cholesterol esters, acting as a trigger for epileptogenesis [149]. The ketogenic diet has been used as the therapy of choice in GLUT1DS patients for reducing seizures and motility disabilities leading to remission of paroxysmal symptoms [142, 150, 151]. However, this treatment has already failed in GLUT1DS patients with refractory epilepsy [152]. In addition, it has been reported that acute hyperglycemia was able to promote a transient improvement in seizures and EEG recording, as well as in attention and motor activity of GLUT1DS patients [153]. Figure 1 summarizes the glucose transporters regulation in normoglycemic, hypoglycemic, hyperglycemic and GLUT1DS conditions.

Sodium/Glucose Cotransporters

SGLTs are transmembrane proteins that contribute to cellular homeostasis by performing secondary active glucose transport in favor of the electrochemical gradient of sodium ions. These proteins were initially identified in the brush border membrane of enterocytes and in the proximal kidney tubule cells [154]. SGLT1 is encoded by the SLC5A1 gene and is composed of 14 transmembrane segments, whose N-terminal face is directed towards the interstitial and the C-terminal face is anchored inside the plasma membrane [155]. A powerful role of water transport was associated with SGLT1, once the stoichiometric relationship of transport capacity was observed to be $2Na^+$:1glucose:264 H_2O molecules [156]. Sodium ions initially bind to the extracellular side of SGLT1, promoting a conformational change that allows glucose to attach to the binding site. A new conformational change of the protein allows the release of sodium ions and glucose in the intracellular environment, after what the transport cycle is completed, allowing for the return of the protein to its initial conformation [154]. SGLT1 is mainly expressed in the intestine, but is also present in the kidneys, salivary glands, trachea, skeletal muscle, heart, liver, testis, prostate and brain [49, 154, 157, 158]. Recently, expression of SGLT1 has been shown in various regions of the CNS, such as hippocampus (CA1 and CA3), parietal and frontal cortices, putamen, paraventricular nucleus of the hypothalamus, amygdala, and in the Purkinje cells of the cerebellum [51].

SGLT2 isoform is encoded by the SLC5A2 gene and carries the transport of only one sodium ion for each glucose molecule [159]. SGLT2 has been observed in the hippocampus and cerebellum. Functional assays with mouse brain slices suggest that SGLT2 is responsible for capturing 20% of total methyl-4-[F-18] fluoro-4-deoxy-D-glucopyranoside (Me-4FDG), a highly specific substrate of SGLT not transported by GLUTs [50].

Functional Role of Brain SGLTRegulation in Limbic Seizures and Neurodegeneration After PILO-Induced SE

In conditions of normoglycemia and adequate oxygen perfusion, glucose transport is probably mediated by GLUT3 and facilitated glucose diffusion may be sufficient for the energy supply of neurons [154]. However, reality may be different when energy supply is reduced and/or energy consumption is enhanced in pathological situations such as ischemia, hypoxemia, hypoglycemia, or epileptic seizures. The concentration of glucose in the firing microenvironment of the neurons can decrease greatly, being lower than the Km value of GLUT3 [49]. These authors induced an epileptic focus with penicillin in the frontal cortex and observed increased uptake of glucose via SGLTs, reflecting the upregulation of this protein in neurons. These findings show that on a low-glucose concentration, as what occurs during seizures, SGLTs may be essential for the survival of neurons.

Few studies have associated the SGLTs in SE modulation [11, 49–51]. Our group has recently demonstrated for the first

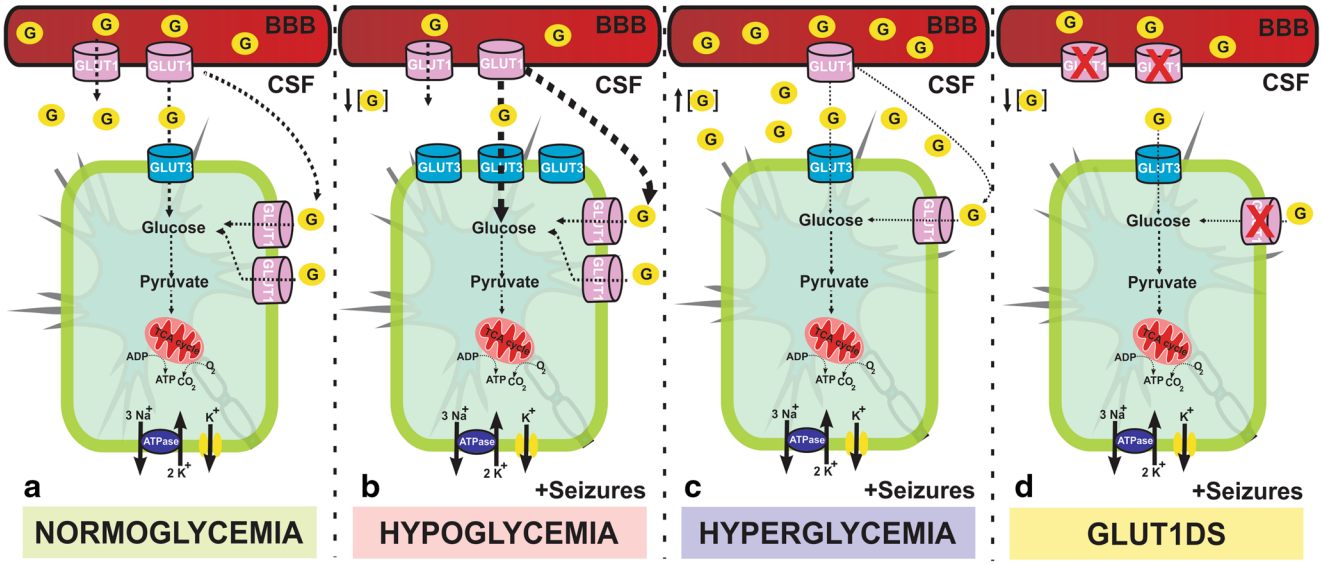


Fig. 1 Schematic drawing of the modulation of GLUTs expression in the brain under normal and pathological conditions. Under normoglycemic conditions, GLUT1 and GLUT3 are at baseline levels (**a**). However, when glucose concentration decreases in CSF during chronic insulin-induced hypoglycemia, GLUT3 expression increases as an adaptive mechanism (**b**). On the other hand, streptozotocin-induced hyperglycemia moderately decreases the expression of GLUT1 (**c**). During GLUT1DS, glucose concentration in the CSF decreases due to *de novo* heterozygous mutation in the SLC2A1 gene, compromising glucose uptake via the BBB (**d**). BBB (blood-brain barrier); CSF (cerebrospinal fluid); GLUT (glucose transporter); GLUT1DS (GLUT1 deficiency syndrome)

time an intrinsic association of SGLTs with neuronal survival during limbic self-sustained seizures induced by intrahippocampal PILO microinjection [11]. In this study, SGLTs were blocked by intrahippocampal administration of phlorizin (PZN), a nonspecific inhibitor of SGLTs, 30 min prior to PILO administration. Inhibition of SGLTs increased the number of wet dog shakes that occur during SE and can serve as an indicator of SE severity. In addition, aggravated self-sustained limbic seizures occurred during the 90 min of SE, showing a higher frequency of the most severe behaviors described by the Racine's scale (class 5) [160] in the PZN group. These behavioral findings indicate that the blockage of SGLTs intensify limbic seizures during SE.

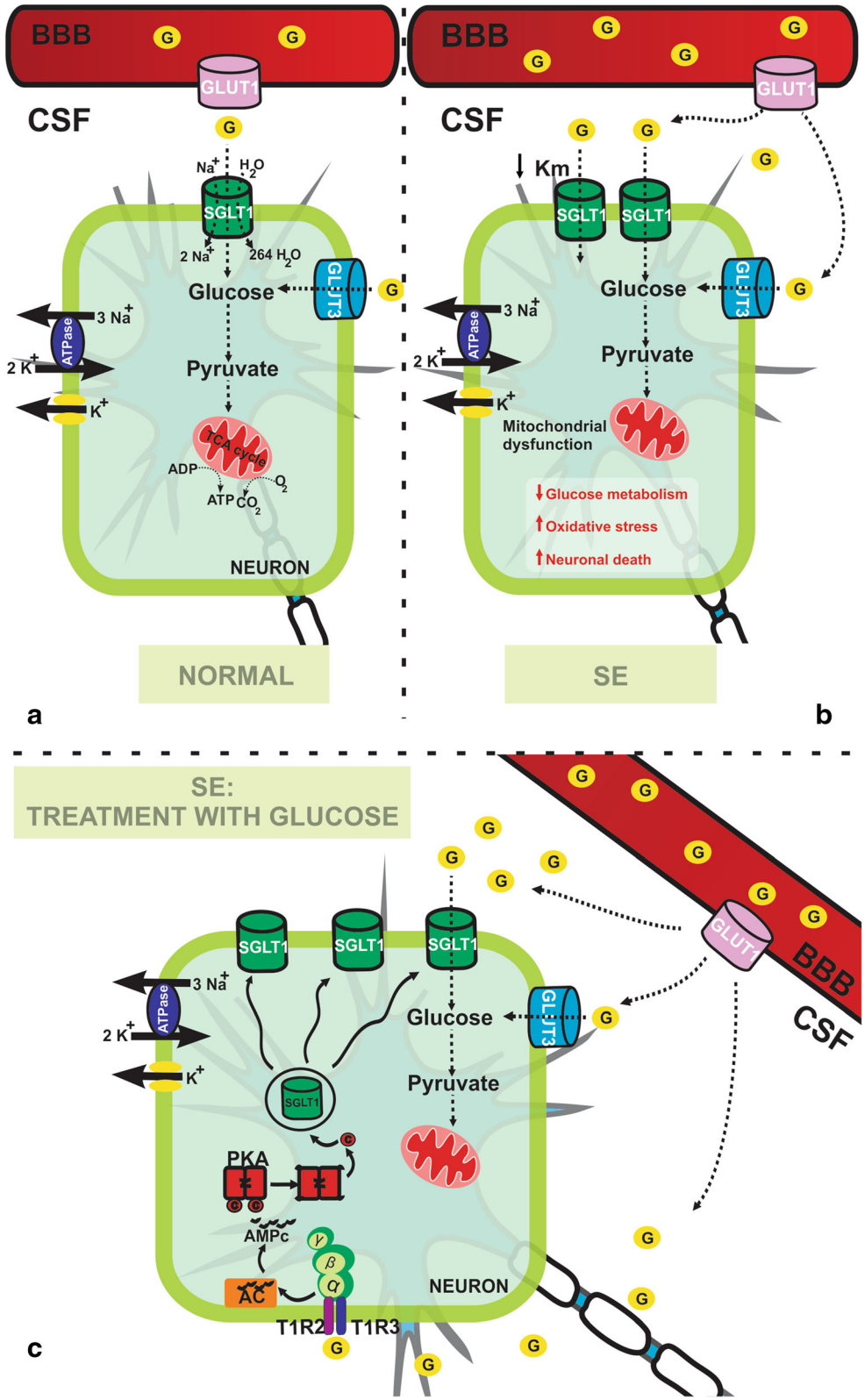
Additionally, 24 h after SE, the PZN increased the number of Fluoro-Jade-positive neurons, a marker of neural cells in degeneration [12, 161], in the regions of the dentate gyrus (DG), the hilus of the DG, CA3, and CA1 of hippocampus [11]. Taken together, these behavioral and histopathological results support the idea that SGLTs are fundamental tools in low-glucose concentration and high metabolic demand conditions, such as during prolonged limbic seizures, thus protecting neurons against degeneration.

New Insights for Action Mechanism of Glucose in the SE

Under normal physiological situation, glucose crosses the BBB through GLUT1 and can enter directly into neurons through GLUT3. Glucose is metabolized in cytoplasm by conversion into molecules of pyruvate, which pass through the tricarboxylic acid cycle and oxidative phosphorylation in mitochondria [60].

On the other hand, during prolonged epileptic seizures, such as seen in SE, glucose metabolism is compromised, which is directly associated with mitochondrial dysfunction, as well as increased reactive oxygen species levels. This metabolic deficit impairs cell survival, aggravating cell death rates. In an attempt to protect neurons against neuronal death, according to some authors [11, 50, 51], the affected brain areas increase uptake of glucose via SGLT1 [49], possibly by enhancing the expression of this transporter. Although greater GLUT3 expression also occurs during SE [43] to support the increased energy demand and glucose metabolism [33, 68, 82–84], SGLT1 expression is necessary in order to transport glucose in lower concentrations, that

Fig. 2 Schematic drawing on glucose modulation during SE and intracerebroventricular glucose treatment. In a physiological condition, glucose enters neurons through GLUT3, and it is metabolized to pyruvate, following the citric acid (TCA) cycle to generate ATP (**a**). However, neuronal hyperexcitability associated with hypermetabolism occurs during SE settlement, activating a compensatory pathway mediated by SGLTs' translocation in order to transport glucose in lower concentrations and attempt to protect neurons against degeneration (**b**). As this epileptogenic insult is continuous and self-sustaining, a mitochondrial dysfunction is triggered followed by oxidative stress, culminating in excitotoxic neuronal death. Possibly, increased SGLTs' translocation through modulation of brain glucose levels may protect neurons in the acute phase of epileptogenesis (**c**).



are below the Km of GLUT3 [49]. Therefore, increased expression of SGLT1 may function as an additional support to GLUT3, contributing to the survival of neurons in hypoglycemic conditions.

So far, control of glucose availability by modulating their transporters may be a form of protection against damage from SE. It is known that glucose sensors, such as T1R2/T1R3 heterodimer, are expressed in the hippocampus [162], and these sensors transduce signals for the translocation of SGLTs into enterocytes [163]. Our hypothesis is that increased hippocampal glucose concentration activates a higher SGLT translocation in neurons via T1R2/T1R3, protecting the neurons from degeneration. Figure 2 summarizes the glucose transporters and metabolic regulation in control, SE and SE associated with intracerebroventricular treatment of glucose.

Conclusion and Future Perspectives

During the early epileptogenesis, shortly after SE, glucose metabolism is elevated, suffering a significant decrease in the chronic phase [86]. Furthermore, glycemic disorders may increase the susceptibility to the genesis of epileptic seizures. As seen previously, hypo- and hyperglycemia can function as crucial factors for the SE generation, although the intrinsic pathophysiological mechanisms responsible for this association remain unclear. In addition, hypo- and hyperglycemia are able to accentuate SE-induced hippocampal damage in animal models [47]. Interestingly, these authors showed that adequate glucose supply protects hippocampal cells against seizure-induced excitotoxic cell death. Considering these, regulation of glucose availability appears to be a promising pathway capable of attenuating the severity of seizures as well as the seizure-induced brain damage in the earlier phase of epileptogenesis generated by SE. Likewise, the intracellular mechanisms of hypo- and hyperglycemia and glucose modulation associated with SE as possible therapeutic targets need to be further investigated.

Author Contributions ISM, RSS, and OWC conceived the original idea and designed the outlines of the study. ISS, ALDP, YMOS, LMF, and DCSPN wrote the draft of the manuscript. ISS, ALDP, and OWC prepared the figures for the manuscript. ISS, LCS, MD, DLGG, CQT, RSS, and OWC performed the literature review and aided in revising the manuscript. All authors have read and agreed to the final version of the manuscript.

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Compliance with Ethical Standards

Conflict of Interests The authors declare that they have no conflict of interest.

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