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Review

Hyperglycemia-Induced Brain Injury in Preterm Infants

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Abstract

Hyperglycemia soon after birth is common in extremely preterm infants. Hyperglycemia is associated with severe intraventricular hemorrhage and impaired neurodevelopmental outcome in these infants. Recent data in human infants and animal models demonstrate that hyperglycemia leads to decreased white matter content, abnormal synaptogenesis, microgliosis, and functional deficits in the absence of intraventricular hemorrhage. Data suggest that oxidative stress, inflammation, and abnormal substrate metabolism are responsible for these effects.

Keywords

Cerebral cortex; hippocampus; hyperglycemia; prematurity; oxidative stress; inflammation; neurodevelopment; microglia; synaptogenesis

1. Introduction

Hyperglycemia, typically defined as blood glucose concentration > 150 mg/dL [> 8.3 mmol/L], is common in preterm infants during the first two weeks of life, especially in those born before 28 weeks of gestation (extremely low gestational age newborns, ELGAN). Between 30-80% of the ELGAN population is affected. Hyperglycemia in this population results from multiple factors, including a relative hypoinsulinism, inability to suppress hepatic glucose release, lower availability of insulin-responsive peripheral tissues, and higher dextrose infusion rates required for nutrition [1-3]. Hyperglycemia is associated with increased mortality and morbidities, including severe (grades 3 and 4) intraventricular hemorrhage (IVH), sepsis, and retinopathy of prematurity (ROP) in the neonatal period, and growth deceleration, risk of hypertension, and neurological and behavioral deficits in childhood [4-8]. At present, management of hyperglycemia in ELGAN consists of lowering glucose infusion rates and/or insulin administration. However, there is a wide practice variation in tolerance for high glucose levels and how neonatal practitioners manage hyperglycemia [9]. More evidence in the neonatal population will help guide clinical decision-making at the bedside.

2. Background

2.1 Clinical Studies

Clinical studies from both adult and pediatric populations with diabetes mellitus offer evidence that high blood glucose levels have adverse effects on the brain. Type 2 diabetes (T2D) is a risk factor for the development of dementia later in life [10, 11]. Children with hyperglycemia due to early onset type 1 diabetes (T1D), have structural and functional hippocampal deficits [12]. Data in preterm neonates are sparse and conflicting. Alexandrou et al. reported that hyperglycemia on the first day of life in ELGAN is an independent risk factor for death as well as white matter reduction on MRI at term corrected age [13]. In a study of very low birth weight (VLBW) infants, hyperglycemia in the first 2 weeks of life was associated with poor growth in weight, length, and head circumference until 2 years corrected gestation age (CGA), although there were no measurable differences in neurodevelopment as determined by the Bailey Scales of Infant Development [5]. Similarly, a retrospective, observational cohort study of 443 infants born weighing <1500 g or <30 weeks of gestation demonstrated that hyperglycemic infants were less likely to survive without neurodevelopmental deficits at 2 years [14]. However, the association was lost after correction for gestation, birth weight z-score, and socioeconomic status. Tottman et al. published that tight glycemic control in preterm infants with hyperglycemia did not improve their survival without neurodevelopmental impairment at 7 years [8]. Conversely, a retrospective study comparing preterm infants with hyperglycemia treated with insulin and age-matched controls without hyperglycemia demonstrated a higher incidence of neurodevelopmental and behavioral problems in the hyperglycemia group at 2 years of life [6]. Our unpublished data show that infants who were born at <32 week gestation and had 5 or more days of hyperglycemia in the neonatal period had lower cognitive, psychomotor, and language scores at 12 months CGA, compared with those infants without hyperglycemia (Gonzalez J, personal communication). It is noteworthy that all of these studies demonstrate an association and there is a lack of randomized controlled trials to establish a causative role for hyperglycemia in the adverse effects.

2.2 Animal Studies

The clinical work provides framework for animal models of neonatal hyperglycemia to evaluate the mechanisms and pathways affected in the developing brain. In the following sections, we briefly describe the concepts of regional vulnerability and substrate utilization during normal development, followed by details of the animal models used in our investigations and the results.

2.2.1 Regional Vulnerability during Brain Development

Brain development spans the prenatal and postnatal periods in humans and rodents [15]. The period of peak development varies among the brain regions with some brain regions (e.g. striatum) developing earlier than the others (e.g., hippocampus and cerebral cortex). The peak development in a brain region is characterized by a parallel increase in its metabolic demand to support energy-demanding processes, such as synaptogenesis, myelination, and neurotransmission [16]. Synaptogenesis occurs in waves; with each wave an overproduction of synapses occurs, followed by stabilization of meaningful connections and elimination of redundancy [17]. The highest rate of synaptogenesis begins at 20-24 weeks gestation and continues through birth at an estimated rate of 40,000 new synapses being established per second [18]. The vulnerability of a brain region to injury depends upon its developmental stage and metabolic demands at the time of the insult. Furthermore, neurons and glia exhibit different vulnerability to injury, likely related to their metabolic demand and stage of development [19].

2.2.2 Substrate Utilization in the Developing Rodent Brain

Glucose is the primary energy substrate to the brain, including in the neonatal period [16]. The brain requires a continuous supply of glucose from plasma because it has minimal glucose stores in the form of brain glycogen. Cerebral glucose transport involves specific glucose transporters (GLUT); GLUT1 is primarily expressed in the microvasculature of the blood brain barrier (BBB), astrocytes and oligodendroglia and GLUT3 in the neurons [14]. GLUT1 expression in rodent models is thought to be comparable to its expression and function in the human brain [20]. In rats, GLUT1 expression is low until postnatal day (P) 14, doubles between P14 and P21 and then doubles again to reach the adult levels by P30 [21]. GLUT3 expression is also low until P7, but then steadily increases to reach the adult levels by P21-P30. Whereas there are no inter-regional variations in GLUT1 expression during normal development, GLUT3 expression varies among the brain regions, paralleling neuronal maturation and synaptogenesis in the region [21].

In addition to glucose, the developing brain is capable of using ketone bodies (β-hydroxybutyrate and acetoacetate), lactate, amino acids, fatty acids, and glycerol for its energy needs [16, 22]. A common transporter system – monocarboxylate transporters (MCT) – is responsible for transport of β-hydroxybutyrate, acetoacetate and lactate. MCT1 transports across the BBB and astrocytes, while MCT2 is the primary neuronal transporter [23]. MCT4 is primarily expressed in astrocytes and is responsible for lactate efflux into the extracellular space [24, 25]. Lactate availability is considered essential for synaptic development and plasticity [24, 26].

2.2.3 Rodent Models of Neonatal Hyperglycemia

Our lab has used two different rat models of neonatal hyperglycemia. In the first model, neonatal rats are subjected to recurrent hypoinsulinemic hyperglycemia from P3 to P12 using twice daily injections of octreotide (100 µg/kg, s.c.) followed by 30% dextrose (3 g/kg s.c.). Octreotide, a somatostatin analog, temporarily suppresses glucose-induced insulin secretion from the pancreas. Littermates in the control group are subjected to octreotide injection, followed by 0.9% saline injection [27]. Blood glucose levels measured 1 and 2 hours after dextrose administration confirm presence of hyperglycemia [blood glucose (mg/dL), 210 ± 15 vs. 147 ± 4 in controls at 1 hour, and 217 ± 17 vs. 128 ± 2 mg/dL in controls at 2 hours] [27].

The second model is one of sustained hypoinsulinemic hyperglycemia using the neonatal streptozotocin (STZ) model [28]. STZ causes hypoinsulinemic hyperglycemia through its selective cytotoxicity against pancreatic β cells. STZ (100 mg/kg, i.p.) is injected on P2 which results in hyperglycemia by P3 (blood glucose, 265 ± 15 mg/dL) that is sustained until P6 (blood glucose, 267 ± 28 mg/dL vs. 144 ± 3 mg/dL in controls). At adulthood (P90), hyperglycemia is observed in the STZ group in the fed state (blood glucose, 286 ± 69 vs. 153 ± 3 mg/dL in controls), but not in the fasting state (blood glucose, 123 ± 8 vs. 142 ± 9 mg/dL in controls) [29]. These time points are important from a brain development standpoint, because P2-P3 and P6 rat brains are developmentally similar to human brains at 25 and 32 weeks of gestation, respectively [30, 31].

3. Mechanisms of Hyperglycemia-Induced Injury in the Developing Brain

Studies from our lab and others suggest that three major mechanisms are involved in brain injury due to neonatal hyperglycemia: oxidative stress, inflammation, and abnormal substrate utilization (Figure 1).

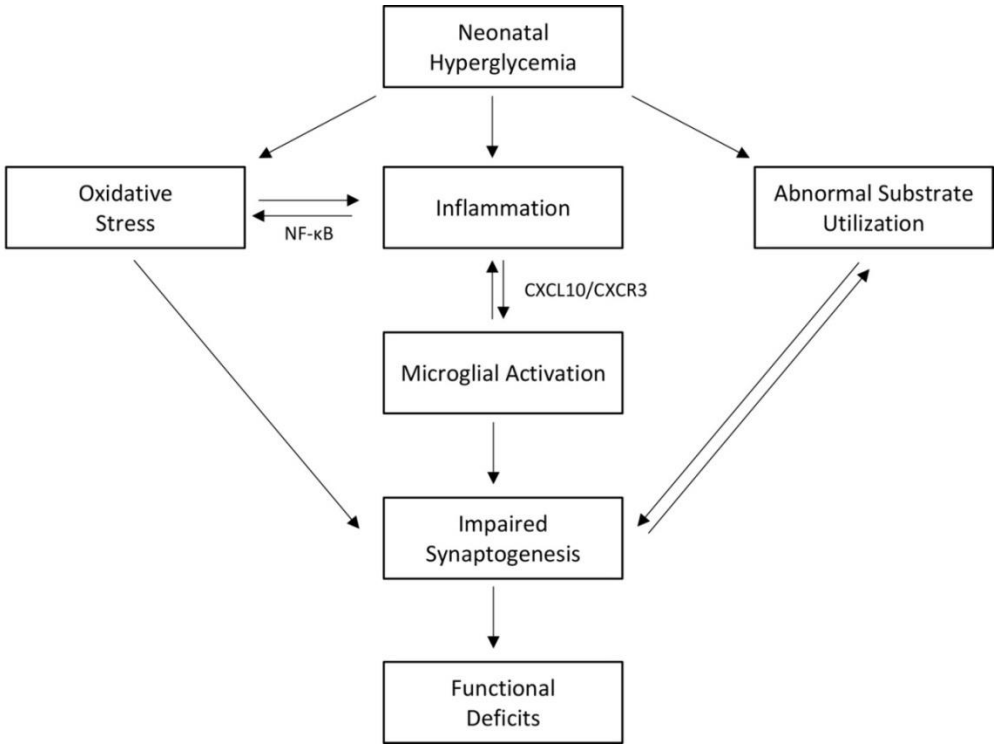

Figure 1 Mechanisms involved in neonatal hyperglycemia-induced brain injury.

3.1 Oxidative Stress

Adult and neonatal preclinical models of hyperglycemia demonstrate the presence of oxidative stress. Rosa et al. used the STZ model of neonatal hyperglycemia to provide evidence of oxidative stress in the whole brain tissue of hyperglycemic rat pups [32]. Compared with controls, glucose-6-phosphate dehydrogenase (G6PD) activity, superoxide anion production, antioxidant defenses, lipid peroxidation, and protein damage were increased in the STZ group [32]. Tayman et al. used the recurrent model of neonatal hyperglycemia (twice daily dextrose injections without octreotide pretreatment) to demonstrate evidence of apoptosis, increased lipid peroxidation and oxidative stress (caspase-8 positive neurons, increased tissue total oxidant status, xanthine oxidase, and malondialdehyde) in the hippocampus [33].

A unifying mechanism behind oxidative stress and cell injury that occurs during hyperglycemia is overproduction of superoxide by the mitochondrial electron-transport chain following increased metabolism of glucose through glycolysis and the tricarboxylic acid (TCA) cycle [34]. Oxygen and nitrogen-based free radicals form peroxynitrate that causes DNA breakage and activates poly(ADP-ribose) polymerase-1 (PARP-1) [35]. PARP-1 initiates DNA repair at breakage sites by poly(ADP-ribosyl)ating itself and other DNA repair proteins (DNA ligases, polymerases, and histones) in an NAD^+ dependent manner [36]. However, under pathophysiologic conditions, such as during hyperglycemia, that result in excessive DNA damage, massive PARP-1 activation causes NAD^+ depletion and release of apoptosis inducing factor (AIF) from the mitochondria resulting in cell death [37]. The brain is also targeted as evident from PARP-1 activation and DNA damage in rodent models of diabetes mellitus [38, 39]. In the neonatal brain, our studies in rat models of recurrent and sustained hypoinsulinemic hyperglycemia (see above) also show upregulation of PARP-1 in the cerebral cortex and hippocampus [27, 29]. In contrast to adult rodent models, however, we did not find upregulation of caspases or AIF, or evidence of apoptosis in either the cerebral cortex or the hippocampus, but rather increased anti-apoptotic enzyme Bcl-2 (B cell leukemia/lymphoma 2) mRNA expression [27, 29].

3.2 Inflammation

PARP-1 expression is associated with increased nuclear factor kappa B (NF-κB) expression in multiple models of hyperglycemia including our neonatal models [27, 29]. PARP-1 and NF-κB coregulation is a likely bridge between hyperglycemia and inflammation and has been implicated in end-organ dysfunction in diabetes mellitus [40, 41]. PARP-1 regulates NF-κB transcription; blocking PARP-1 reduces inflammatory markers; inducible nitric oxide synthase (iNOS), interleukin 1-beta (IL-1β), tumor necrosis factor alpha (TNFα) [42]. During physiologic conditions, NF-κB regulates the immune system, but pathophysiologic conditions lead to its upregulation and increased transcription of inflammatory products. In the cytosol, NF-κB is bound by its inhibitor IκB. Upstream signaling causes phosphorylation and degradation of IκB, allowing NF-κB to translocate to the nucleus for transcription of target genes [43]. Inhibiting NF-κB improves hyperglycemia-induced neuroinflammation [44]. The upregulation of PARP-1 and NF-κB as outlined above, leads to the upregulation of inflammatory cytokines and the activation of pro-inflammatory cells in the developing brain. In particular, C-X-C motif chemokine ligand 10 (CXCL10) and its receptor C-X-C motif chemokine receptor 3 (CXCR3) are important chemokines involved in signaling and synaptic activity [45].

Adult humans with CNS infections or neurodegenerative disorders demonstrate an association between increased CXCL10 levels in the CSF and cognitive deficits [46, 47]. Related to hyperglycemia in particular, the CXCL10/CXCR3 signaling pathway is associated with the pathogenesis of pancreatic β cell injury in T1D [48-50] with serum CXCL10 levels in humans with T1D being elevated [51, 52]. Together, these data suggest that CXCL10/CXCR3 signaling is at play in neonatal hyperglycemia-mediated brain injury.

Satrom et al. published to our knowledge the first evidence that neonatal hyperglycemia alters the CXCL10/CXCR3 pathway in the developing hippocampus of rat pups [29]. Using the neonatal STZ rat model, they demonstrated upregulation of mRNA transcripts CXCL10, CXCR3, PARP-1, NF-κB, and B-cell lymphoma 2 (BCL2) in the P6 hippocampus, in addition to downregulation of glutamate receptor, NR2b [29]. These findings, along with evidence of microgliosis, astrocytosis, and colocalization of CXCL10 and CXCR3 to both neurons and glia, suggest that oxidative stress leads to hippocampal inflammation mediated by CXCL10/CXCR3 signaling.

The exact mechanism of communication between cell types in the setting of hyperglycemia has yet to be determined. We propose that both neurons and microglia serve as targets of CXCL10, which is supported by work from our group and others showing that CXCR3 is expressed in both neurons and microglia [46, 53, 54]. Unlike CXCR3, all three cell types (neurons, astrocytes and microglia) appear to be the cellular sources of CXCL10. Further studies are needed to confirm this relationship and for exploring the transport of CXCL10 from systemic circulation across the BBB.

Neonatal - CNS inflammation mediated by hyperglycemia and abnormal CXCL10/CXR3 signaling may lead to altered NMDA receptor expression (suppressed NR2b mRNA expression as described above [29]) and therefore, long-term alterations in synaptic architecture. Our animal model of neonatal hyperglycemia demonstrated abnormal hippocampal function and decreased synaptic density in the hippocampus at adulthood on P90 as evidenced by impaired performance in Barnes Maze, decreased microtubule-associated protein 2 (MAP2) integrated density on immunohistochemistry, and lower postsynaptic density protein 95 (PSD95) expression [29].

This overall mechanism, from oxidative stress to inflammation to altered synaptogenesis, provides a plausible pathway connecting neonatal hyperglycemia to functional neurodevelopmental impairments. Abnormal substrate transport and utilization as described below (see 3.3), also may play a role in abnormal synaptogenesis and function.

PARP-1 and NFκB upregulation also result in increased activation of microglia in the cerebral cortex and hippocampus of neonatal rats [27, 29]. Previous studies in adult preclinical models demonstrate that hyperglycemia results in an increased number and altered morphology of microglia, changing from a ramified phenotype with long thin processes to an activated amoeboid phenotype with a larger cell body and thicker, shorter processes [55]. A hallmark of microglial activation is inflammation, both as the stimulus to activation and as a resultant product. Inflammatory cytokines, including TNFα and IL-6, and chemokines CCL-2 and CXCL10 are increased in the adult and developing brain following episodes of hyperglycemia [29, 44, 56].

3.2.1 Role of Microglia in Neurodevelopment and Synaptogenesis

Changing microglial function related to hyperglycemia is important for neonatal brain development and potential injury. Microglia are the resident mononuclear macrophages of the brain. Unlike circulating macrophages that develop from bone marrow, microglia are derived from

yolk sac myeloid precursors that enter the brain during early embryogenesis and steadily increase in numbers through gestation and after birth [57]. Through normal development, microglia are involved in critical regulatory and developmental processes. Perhaps most important is the pruning of synapses; deficiency of pruning results in immature synapses, excess dendritic spines, and immature circuitry [58]. Other developmental roles include promotion of axonal elongation and pathfinding and myelination, production of neurotrophic factors, and strengthening of synapses [59]. Under adverse conditions such as infection, hypoxic-ischemic encephalopathy, and hyperglycemia, as stated above, microglia alter function to produce cytokines, present antigens, and induce adaptive immunity [60, 61]. The change in function from normal development to immune response is a change from quiescent monitoring to activation of M1 proinflammatory polarization. The defining markers of M1 polarization are production of inflammatory cytokines (e.g. IL-1β, TNFα, IL-6), nitric oxide, and co-stimulatory proteins such as CD40 and MHC-II [60]. This change in phenotype suggests that microglia may inadequately perform other tasks such as synaptic pruning or growth factor production during critical neurodevelopmental windows. Developmental synaptic pruning is a highly regulated process involving specific synaptic signaling molecules and corresponding microglial receptors that prevent or target for phagocytosis [62]. Imbalance of signals in either cell may result in over- or under-pruning of synapses [63-65]. Hyperglycemia appears to be a cause of imbalance.

3.3 Abnormal Substrate Transport and Utilization

In adult rodents, hyperglycemia is associated with increased plasma lactate and pyruvate concentrations, and a 7-17% upregulation of MCT1 expression in endothelial cells and astrocytes in the cerebral cortex and hippocampus [66]. An increased transport from plasma across the BBB is most likely responsible for increased brain lactate, although local production by the astrocytes also could be contributory [67]. In the hippocampus, glycogen concentration is increased and the expression of MCT2 (neuronal MCT transporter) is decreased [68]. The expression of MCT4, the transporter responsible for lactate efflux from astrocytes is not altered.

Whether a similar effect occurs in the developing brain exposed to hyperglycemia was tested in a recent study from our laboratory [69]. Two non-overlapping experiments were performed. In experiment 1, neonatal rats were subjected to recurrent moderate (blood glucose, 214.6 ± 11.6 mg/dL) and severe hyperglycemia (blood glucose, 338.9 ± 21.7 mg/dL) from P3 to P12. Blood glucose concentration in the control group was 137.7 ± 2.6 mg/dL. The neurochemical profile of the hippocampus was determined on P30 using *in vivo* ultra-high-field (9.4T) ^{1}H NMR spectroscopy (MRS), followed by tissue harvest for determination of dendritic arborization using MAP-2 histochemistry. In experiment 2, the effect of hyperglycemia on the mRNA transcript expression of glycogen synthase 1 (*Gys1*) and lactate dehydrogenase (*Ldh*), the enzymes responsible for glycogen synthesis and lactate production, respectively, and *Glut1*, *Glut3*, *Mct1*, *Mct2* and *Mct4* in the hippocampus was determined on P6 in the neonatal STZ rat model [29].

In experiment 1, MRS demonstrated lower lactate concentration and glutamate/glutamine ratio in the severe hyperglycemia group, compared with the control group. Phosphocreatine/creatine (PCr/Cr) ratio was increased in both hyperglycemia groups. MAP-2 histochemistry demonstrated longer apical segment length of the dendrites in the two hyperglycemia groups, indicating an immature pattern and abnormal synaptic efficacy [70, 71]. In

experiment 2, the expression of *Glut1*, *Gys1* and *Mct4* mRNA transcripts was lower, and that of *Mct1* higher in the hyperglycemia group, relative to the control group.

Lower lactate concentration in the setting of decreased *Glut1* and *Gsy1* expression suggests decreased astrocytic glucose uptake, storage and conversion to lactate. *Mct1* upregulation may be a compensatory response for increasing lactate and ketone body transport across the BBB and astrocytes. Although the expression of *Mct2*, responsible for neuronal lactate uptake was not altered, the expression of *Mct4*, responsible for lactate efflux from astrocytes was suppressed. Collectively, these data suggest that neonatal hyperglycemia is associated with decreased lactate availability to the hippocampal neurons. Given the essential role of lactate in neurite growth and synaptic plasticity [24, 26], decreased lactate availability could be responsible for the abnormal dendritogenesis in the formerly hyperglycemic animals. Combined with the lower glutamate/glutamine ratio and increased PCr/Cr ratio, these data suggest an overall dampening of neuronal activity in the context of impaired oxidative energy metabolism in the formerly hyperglycemic hippocampus, as has been demonstrated in rodent models of impaired energy production [e.g., due to chronic hypoxia [72]] and suppressed neuronal activity [e.g., following ethanol administration [73]] and could explain the hippocampus-mediated functional deficits we have reported previously [29].

4. Working Model

In review of available data from our lab and other labs, we propose a working model in which neonatal hyperglycemia leads to oxidative stress mediated by NF-kB. NF-kB then leads to the upregulation of CXCL10/CXCR3 pathway in the brain regions, with CXCR3 being expressed in both neurons and microglia and CXCL10 originating locally, and possibly systemically as well [29]. The CXCL10/CXCR3 inflammatory cascade leads to suppression of NMDA glutamate receptor, which in turn, impairs synaptogenesis and function [74, 75]. A shift in substrate utilization and lower lactate availability may further worsen synaptogenesis and plasticity. We propose that unlike the adult brain, when hyperglycemia causes upregulation of apoptotic mediators and neuronal injury [27], the neonatal brain has protective mechanisms to prevent neuronal injury. This may occur through microglia-derived neurotrophic growth factors and upregulation of the antiapoptotic BCL2 expression [27, 76]. However, given the abnormal synaptic structure at adulthood, long-term functional deficits are likely following neonatal hyperglycemia, despite the lack of neuronal injury.

5. Future Directions

In conclusion, this review focuses on how animal models inform the likely mechanisms involved in hyperglycemia-induced neonatal brain injury. These preclinical models allow for in-depth assessments of the specific brain regions, cell-types, and molecular pathways involved in a controlled fashion, that are not possible in human studies. The rodent models in particular allow for the assessment of effects on the developing preterm brain, as the early postnatal period in a rodent neurodevelopmentally approximates the third trimester of human gestation when preterm infants at high risk for hyperglycemia are born [30]. The major limitation to these animal models is that they often lack the clinical complexity involved in the care of a critically ill human preterm infant, including comorbidities and consequences of various interventions, as well as the complex neurobehavioral repertoire of human infants.

Future directions include the evaluation of the influence of comorbidities that commonly occur with hyperglycemia in extremely preterm infants on brain injury. These include hypoxia/ischemia, anemia, and inflammation or infection. Some of these conditions may be causative factors for hyperglycemia itself, through catecholamine and cortisol-mediated pathways, and contribute to brain injury. Hyperglycemia is known to worsen brain injury due to hypoxic-ischemia or hypoglycemia in term human newborn infants and animal models [14, 77, 78]. We also need a better understanding of the effects of treatment of hyperglycemia on the neurological outcomes. The current management of neonatal hyperglycemia includes glucose restriction and insulin administration, both of which have side-effects, including poor nutrition and risk for hypoglycemia, respectively. Glycemic fluctuations are associated with greater risk of neuronal injury, mitochondrial membrane potential and oxidative stress [79]. There is a cascade of effects with insulin therapy as well, including the need for central lines for frequent lab monitoring, phlebotomy-induced anemia due to frequent lab draws, and risk for hypoglycemia and/or fluctuating blood glucose levels due to difficulties titrating continuous insulin infusions. Finally, we have focused our review to the effects of hypoinsulinemic hypoglycemia on specific brain regions and pathways, but other brain regions and pathways may be affected in hypoinsulinemic and other causes of hyperglycemia during development.

Author Contributions

Dr. Satrom, Dr. Gisslen, and Dr. Rao all contributed equally to the conception of this paper including the interpretation of the data presented. Dr. Satrom drafted the initial manuscript, and Dr. Gisslen and Dr. Rao revised it critically for important intellectual content. Each author approved the final version to be published and agree to be accountable for all aspects of the work.

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Competing Interests

The authors have declared that no competing interests exist.

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