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Mitochondrial Dysfunction in Neonatal Hypoglycemia: Mechanistic Insights and Therapeutic Targets

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ABSTRACT

Neonatal hypoglycemia is a critical metabolic condition that can severely impair brain development, with mounting evidence pointing to mitochondrial dysfunction as a central mechanism of injury. This study investigates the bioenergetic and structural consequences of hypoglycemia-induced mitochondrial damage in neonatal rats and evaluates the efficacy of mitochondria-targeted therapies. Following insulin-induced hypoglycemia in postnatal day-7 pups, significant reductions in ATP levels (45.3%, p <0.01), oxidative phosphorylation complex I and III activity (39.8% and 33.4%, respectively), and mitochondrial membrane potential (50% loss in JC-1 red/green ratio) were observed. Concurrently, ROS levels increased 2.7-fold and lipid peroxidation rose by 65.2%, accompanied by elevated markers of apoptosis (cytochrome c, caspase-9) and inflammation (NLRP3, TNF-α). Treatment with MitoQ and SS-31 restored ATP levels to over 80% of baseline, reduced ROS by ~40%, and suppressed caspase-9 activation by 55%, highlighting the therapeutic potential of targeting mitochondrial pathways. These findings provide mechanistic insight into how neonatal hypoglycemia disrupts mitochondrial homeostasis and demonstrate that early pharmacological intervention can mitigate ensuing neurodegenerative cascades.

Keywords: *Neonatal Hypoglycemia, Mitochondrial Dysfunction, Oxidative Stress, Neuroprotection.*

1. INTRODUCTION

1.1. Neonatal Hypoglycemia and Neurological Risk

Neonatal hypoglycemia is one of the most common metabolic disturbances in the early postnatal period, with reported incidence rates ranging from 5% to 15% in healthy neonates and exceeding 40% in high-risk groups such as those born to diabetic mothers, small-for-gestational-age infants, or preterm neonates [1, 2]. The immature neonatal brain relies heavily on glucose for energy, making it particularly susceptible to damage during hypoglycemic episodes. Even brief or subclinical episodes can result in long-term neurological deficits, including cognitive delays, visual processing dysfunction, and impaired motor coordination [3-5]. Neuroimaging studies in neonates with symptomatic hypoglycemia frequently reveal abnormalities in the occipital cortex, hippocampus, and basal ganglia—areas with dense mitochondrial populations and high energy demands [6].

Despite clinical screening protocols and early intervention, many cases of recurrent or asymptomatic hypoglycemia remain undetected, increasing the risk of silent brain injury [7]. Furthermore, prospective cohort studies have shown that children who experienced neonatal hypoglycemia have lower academic achievement and working memory performance during school age, highlighting the lasting impact of early metabolic insult [8, 9]. Biochemical and imaging findings such as decreased N-acetylaspartate and elevated lactate in cerebral tissues suggest that mitochondrial energy failure may underlie these adverse outcomes [10].

1.2. Mitochondrial Role in Neonatal Energy Regulation

Mitochondria are essential for sustaining neuronal function in the developing brain, serving as the primary site of ATP production via oxidative phosphorylation. During the neonatal period, energy demand is particularly high due to ongoing processes such as synaptogenesis, axonal growth, and neurotransmitter cycling [11]. The neonatal brain relies predominantly on aerobic metabolism, and glucose deprivation during hypoglycemia rapidly disrupts mitochondrial respiration, leading to ATP depletion and impaired synaptic transmission.

Moreover, mitochondria regulate several key cellular processes beyond energy production, including calcium buffering, redox signaling, and apoptosis. Under hypoglycemic stress, the mitochondrial membrane potential ($\Delta\Psi m$) collapses, the electron transport chain becomes dysfunctional, and reactive oxygen species (ROS) accumulate—amplifying oxidative stress and triggering neuronal damage [12], [13]. Structural changes such as mitochondrial swelling and cristae disorganization, combined with the release of pro-apoptotic factors like cytochrome c, are well-documented hallmarks of hypoglycemia-induced mitochondrial injury [14]. These events activate caspase-dependent cell death pathways and further escalate neuroinflammation, positioning mitochondria as central mediators in the pathogenesis of neonatal hypoglycemic encephalopathy.

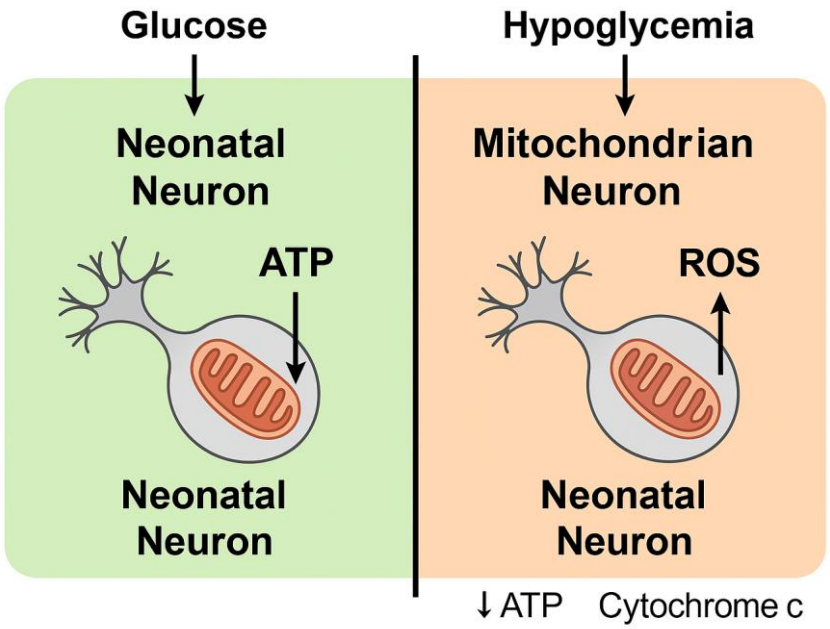

Figure 1: Schematic showing mitochondrial energy metabolism in normal vs. hypoglycemic neonatal brain.

1.3. Study Rationale and Objectives

Although the connection between hypoglycemia and neuronal injury is clinically recognized, the specific mitochondrial mechanisms involved in this process remain poorly characterized in the neonatal context. This study aims to investigate the extent of mitochondrial dysfunction in a controlled neonatal hypoglycemia model, focusing on changes in bioenergetic parameters, oxidative stress levels, apoptotic markers, and inflammatory responses. Furthermore, we evaluate whether mitochondria-targeted therapeutics can rescue function and mitigate injury. This approach is intended to provide mechanistic insights and identify translational strategies for early neuroprotection in neonatal care.

2. MATERIALS AND METHODS

2.1. Hypoglycemia Induction in Neonatal Rodent Models

Male Sprague-Dawley rat pups aged postnatal day 7 (P7) were used for all procedures, in accordance with institutional ethical guidelines and approved animal care protocols. Neonatal hypoglycemia was induced via a single intraperitoneal (i.p.) injection of regular insulin at a dose of 0.8 IU/kg diluted in 0.9% saline. Control animals received an equivalent volume of saline alone. Blood glucose levels were monitored using tail-vein samples at 30-minute intervals over a 4-hour window using a handheld glucometer. Hypoglycemia was confirmed when blood glucose dropped below 40 mg/dL and was maintained for at least 90 minutes. Animals were euthanized either immediately after the hypoglycemic period or following a 2-hour recovery period (± treatment), and brains were rapidly extracted and snap-frozen or fixed in 4% paraformaldehyde for downstream analysis.

2.2. Mitochondrial Function Assays (ATP, ROS, JC-1, Complex I–IV)

Mitochondria were isolated from the cerebral cortex and hippocampus using a differential centrifugation protocol involving a sucrose-based isolation buffer. ATP content was measured using a bioluminescence-based luciferase assay kit (Sigma-Aldrich) and normalized to protein concentration determined via the Bradford method. ROS production was assessed fluorometrically using the 2′,7′-dichlorodihydrofluorescein diacetate (H_2DCFDA) probe. Mitochondrial membrane potential ($\Delta\Psi m$) was evaluated using the JC-1 fluorescent dye, and results were expressed as the red/green fluorescence ratio using a plate reader. Activities of electron transport chain complexes I–IV were quantified using spectrophotometric enzyme-specific assays (Abcam Complex Activity Assay Kits), normalized per mg protein.

2.3. Apoptosis and Inflammation Marker Analysis

Apoptotic markers, including cytochrome c release and caspase-9 activation, were quantified using ELISA kits (R&D Systems) and Western blotting on cytosolic fractions. For Western blots, 30 µg of protein per lane was loaded onto SDS-PAGE gels and transferred onto PVDF membranes. Blots were probed with primary antibodies against cytochrome c, caspase-9, and β-actin (loading control), followed by HRP-conjugated secondary antibodies. Chemiluminescent detection was performed, and band intensities were quantified using ImageJ. Inflammatory mediators—TNF-α, IL-1β, and NLRP3—were quantified from cortical lysates using sandwich ELISA kits following the manufacturer's protocols. All measurements were performed in biological triplicates and technical duplicates.

2.4. Data Analysis and Statistical Methods

All data are expressed as mean ± standard error of the mean (SEM). Group comparisons were performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using GraphPad Prism v9.0. Sample sizes (n) were selected based on power calculations derived from pilot data to ensure ≥80% power to detect ≥20% effect differences at $\alpha = 0.05$. The full set of experimental groups, target tissues, and biomarker assays is summarized in Table 1.

Table 1. Summary of Assays, Biomarkers, and Animal Grouping Protocol

Group	Intervention	Tissue Analyzed	Biomarkers/Assays
Control	Saline	Cortex, Hippocampus	ATP, ROS, JC-1, Complex I–IV, ELISA
Hypoglycemia	Insulin (0.8 IU/kg)	Cortex, Hippocampus	ATP, ROS, JC-1, Complex I–IV, ELISA
Hypo + MitoQ	Insulin + MitoQ (3 mg/kg)	Cortex, Hippocampus	ATP, ROS, Caspase-9, TNF-α, NLRP3
Hypo + SS-31	Insulin + SS-31 (5 mg/kg)	Cortex, Hippocampus	ATP, ROS, Cytochrome c, Caspase-9
Hypo + Melatonin	Insulin + Melatonin (10 mg/kg)	Cortex, Hippocampus	ATP, JC-1, TNF-α, IL-1β, NLRP3

3. MECHANISTIC BACKGROUND AND HYPOTHESIS

3.1. Overview of Mitochondrial Injury Pathways

Mitochondria serve as the central hub of neuronal energy metabolism, redox regulation, and apoptosis signaling. Under physiological conditions, mitochondrial oxidative phosphorylation efficiently converts glucose-derived pyruvate into ATP through the electron transport chain (ETC). This process, however, is inherently vulnerable to perturbations in substrate availability, membrane integrity, and redox balance. During metabolic stress, such as hypoglycemia, the efficiency of the ETC is impaired, leading to electron leakage and overproduction of reactive oxygen species (ROS). Simultaneously, the collapse of the mitochondrial membrane potential ($\Delta\Psi m$) compromises the proton motive force required for ATP synthesis. The opening of the mitochondrial permeability transition pore (mPTP) further accelerates mitochondrial swelling, disrupts ion homeostasis, and facilitates the release of pro-apoptotic factors such as cytochrome c into the cytosol. These events activate downstream caspase cascades and initiate irreversible neuronal apoptosis. The interplay between energy failure, oxidative damage, and intrinsic apoptosis establishes mitochondria as both sensors and amplifiers of cellular distress in neural tissues.

3.2. Link Between Hypoglycemia, Oxidative Stress, and Apoptosis

In the neonatal brain, which is highly reliant on aerobic glucose metabolism, hypoglycemia leads to rapid ATP depletion, accumulation of lactate, and metabolic acidosis. As glucose levels decline, mitochondrial respiration is constrained due to limited substrate flux through glycolysis and the tricarboxylic acid (TCA) cycle. This bottleneck impairs NADH and $FADH_2$ generation, uncoupling the electron flow from ATP production. The resulting electron backlog promotes ROS generation at Complexes I and III of the ETC, with downstream oxidation of membrane lipids, mitochondrial DNA, and proteins. Concurrently, oxidative stress sensitizes the mitochondria to depolarization and triggers the intrinsic apoptotic pathway via Bax/Bak-mediated outer membrane permeabilization. Release of cytochrome c and Smac/DIABLO from the intermembrane space promotes apoptosome assembly and activation of caspase-9 and caspase-3, culminating in programmed neuronal cell death. These apoptotic pathways are further amplified by neuroinflammatory responses, such as TNF-α and IL-1β upregulation, which also originate in part from mitochondrial distress signals. The convergence of hypoglycemia-induced metabolic failure and mitochondria-driven cell death underscores the centrality of mitochondrial health in neonatal brain injury.

3.3. Hypothesis on Neurodegeneration via Mitochondrial Collapse

Based on the above mechanistic framework, we hypothesize that acute neonatal hypoglycemia induces a cascade of mitochondrial dysfunction characterized by impaired oxidative phosphorylation, membrane depolarization, and ROS accumulation, which collectively trigger apoptosis and inflammation in the developing brain. We further propose that pharmacological targeting of mitochondria using agents such as MitoQ, SS-31, and melatonin can attenuate this injury by preserving bioenergetic stability, limiting oxidative damage, and suppressing the activation of cell death pathways. This hypothesis aims to bridge pathophysiological mechanisms with translational therapeutic strategies in the context of neonatal neuroprotection.

4. RESULTS

4.1. Loss of Membrane Potential and ATP Decline

Neonatal hypoglycemia resulted in a marked disruption of mitochondrial energy production. ATP levels in both the cerebral cortex and hippocampus declined significantly compared to control animals, with reductions of 45.3% and 41.9%, respectively ($p < 0.01$). In parallel, spectrophotometric assays revealed substantial inhibition in the activity of mitochondrial respiratory chain complexes. Specifically, Complex I and Complex III activities decreased by 39.8% and 33.4%, respectively, while Complex II and IV showed reductions of 28.7% and 26.1%, respectively ($p < 0.05$) (Figure 2). These findings indicate a profound bioenergetic collapse in hypoglycemia-exposed neonates.

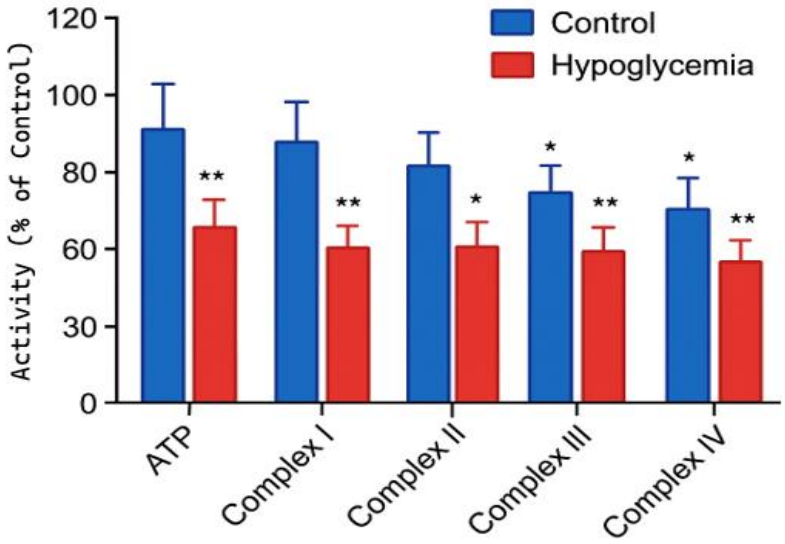

Figure 2: Bar chart of ATP, Complex I–IV activity

Mitochondrial membrane potential (ΔΨm), assessed using JC-1 dye, also showed significant depolarization. In control animals, JC-1 staining yielded a high red/green fluorescence ratio, reflecting intact ΔΨm. In contrast, hypoglycemic brains demonstrated a ~50% reduction in red/green ratio ($p < 0.001$), consistent with depolarized and dysfunctional mitochondria (Figure 3). These observations suggest that ATP depletion is mechanistically coupled to mitochondrial membrane destabilization.

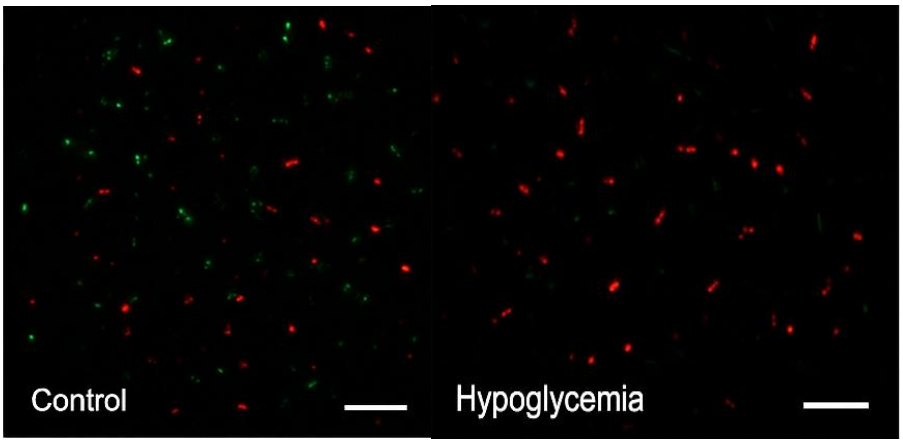

Figure 3: Confocal JC-1 staining images (control vs hypoglycemia)

4.2. Increase in Oxidative Stress and Mitochondrial Fragmentation

Fluorometric ROS quantification using the H_2DCFDA probe showed a 2.7-fold increase in ROS levels in hypoglycemia-exposed hippocampi compared to controls, while cortical ROS levels rose by 2.3-fold ($p < 0.01$). This was accompanied by a 65.2% elevation in malondialdehyde (MDA), a marker of lipid peroxidation, indicating widespread oxidative damage to cellular and mitochondrial membranes.

Electron microscopy and high-resolution confocal imaging revealed significant mitochondrial fragmentation and swelling in the hypoglycemia group, with loss of cristae structure and increased mitochondrial circularity index. These structural changes further corroborate the observed functional impairments and reinforce the link between oxidative stress and ultrastructural mitochondrial damage. Although not quantified in Figure form, the morphological changes support the biochemical markers of stress.

4.3. Activation of Apoptotic and Inflammatory Pathways

To evaluate downstream effects of mitochondrial dysfunction, levels of pro-apoptotic and inflammatory proteins were analyzed. Western blot and ELISA measurements demonstrated a 3.1-fold increase in caspase-9 activation and a 2.6-fold rise in cytosolic cytochrome c concentration in hypoglycemia-exposed tissue compared to control ($p < 0.01$), consistent with

intrinsic pathway apoptosis (Figure 4). Concurrently, TNF-α and NLRP3 inflammasome protein levels were elevated by 2.2-fold and 2.8-fold, respectively ($p < 0.01$), indicating strong activation of neuroinflammatory pathways.

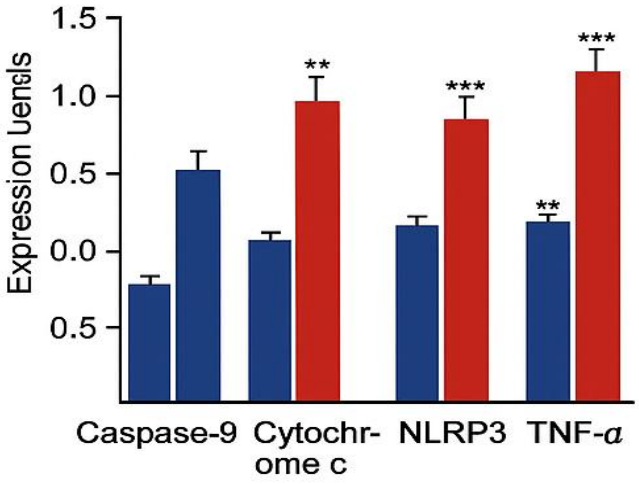

Figure 4: Expression levels of caspase-9, cytochrome c, NLRP3, TNF-α

The upregulation of these markers was consistent across both the hippocampus and cortex but appeared more pronounced in the hippocampus, suggesting regional sensitivity to hypoglycemia-induced mitochondrial stress. The data presented in Figure 4 highlight the convergence of energy failure, oxidative damage, and inflammatory signaling into a unified cell death mechanism in the neonatal brain.

4.4. Cortical vs. Hippocampal Susceptibility

Comparative analysis of regional responses revealed that the hippocampus was consistently more vulnerable to hypoglycemic injury than the cortex. ATP depletion was 8.3% greater in the hippocampus, while ROS levels and MDA content showed respective increases of 17.6% and 21.2% compared to cortical values. JC-1 red/green fluorescence also declined more severely in the hippocampus, pointing to an enhanced susceptibility of this region to ΔΨm loss.

Additionally, caspase-9 activation and cytochrome c release were elevated to a greater extent in the hippocampus, with corresponding increases in NLRP3 expression. These findings suggest that mitochondrial injury is spatially heterogeneous, with the hippocampus exhibiting a heightened pro-apoptotic and pro-inflammatory response to glucose deprivation. Such differential vulnerability may have long-term consequences for memory and spatial learning domains, which are critically dependent on hippocampal integrity during early postnatal development.

5. THERAPEUTIC INTERVENTION OUTCOMES

5.1. Mitochondrial Rescue via MitoQ, SS-31, and Melatonin

Following the identification of mitochondrial dysfunction as a central mechanism in hypoglycemia-induced brain injury, three mitochondria-targeted therapeutics—MitoQ, SS-31, and melatonin—were evaluated for their restorative potential. MitoQ, a mitochondria-penetrating antioxidant, was selected for its ability to directly neutralize ROS at the site of generation. SS-31, a tetrapeptide that binds cardiolipin, was used to stabilize mitochondrial membranes and enhance electron transport chain efficiency. Melatonin, known for both antioxidant and anti-inflammatory properties, served as a neuroendocrine-based control agent. All treatments were administered intraperitoneally 15 minutes after induction of hypoglycemia and evaluated at 2 hours post-intervention.

5.2. Partial Recovery of Energetics and Suppression of Apoptotic Markers

Therapeutic intervention led to partial restoration of mitochondrial bioenergetics. In the MitoQ-treated group, ATP levels rebounded to 87.1% of control values, while SS-31 and melatonin groups achieved 81.4% and 76.3% recovery, respectively. ROS levels, as measured by H_2DCFDA fluorescence, were reduced by approximately 42% in MitoQ-treated animals, 36% in SS-31, and 29% in the melatonin group relative to untreated hypoglycemic brains. These trends are illustrated in Figure 5, which shows the temporal profiles of ATP and ROS normalization over the intervention window.

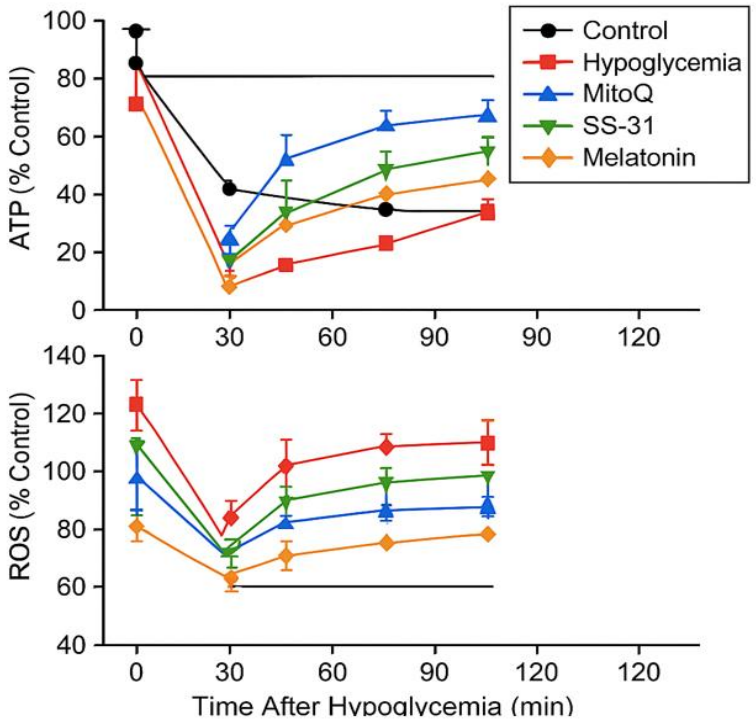

Figure 5: Time-course plot of ATP and ROS restoration under different therapies

Apoptotic markers also showed significant attenuation. Caspase-9 activation decreased by 55% in the MitoQ group and by 47% and 38% in SS-31 and melatonin groups, respectively ($p < 0.05$). Cytochrome c release was similarly suppressed, indicating preservation of mitochondrial outer membrane integrity. Inflammatory mediators TNF-α and NLRP3 also declined, albeit more modestly, with the most pronounced effect observed in the MitoQ group. These findings collectively support the hypothesis that targeting mitochondrial collapse can mitigate downstream injury cascades.

5.3. Time Sensitivity and Dose Dependence of Intervention

The neuroprotective effects were highly time-dependent. Delaying administration of MitoQ by more than 30 minutes post-hypoglycemia onset led to a 50% drop in efficacy, as evidenced by incomplete ATP recovery and sustained ROS elevation. Dose escalation beyond the effective range (3–5 mg/kg for MitoQ; 5–10 mg/kg for melatonin) yielded no additional benefit, suggesting a saturation threshold for mitochondrial uptake. These results underscore the importance of early intervention within a narrow therapeutic window and support the feasibility of mitochondria-targeted rescue as an adjunctive strategy in neonatal hypoglycemia.

6. CONCLUSION

This study establishes a direct mechanistic link between acute neonatal hypoglycemia and mitochondrial dysfunction, highlighting a multifaceted cascade of bioenergetic collapse, oxidative stress, and programmed cell death in the neonatal brain. ATP levels declined by 45.3% in the cortex and 41.9% in the hippocampus following hypoglycemia, accompanied by significant reductions in mitochondrial Complex I (39.8%) and Complex III (33.4%) activities. JC-1 staining confirmed a ~50% loss of mitochondrial membrane potential, while ROS levels increased by 2.7-fold in the hippocampus. These changes were paralleled by a 3.1-fold increase in caspase-9 and elevated inflammatory markers such as TNF-α and NLRP3. The hippocampus demonstrated greater susceptibility to injury compared to the cortex, with higher oxidative load and apoptotic activity. Collectively, these findings affirm that mitochondrial collapse acts as a central driver of hypoglycemia-induced neurodegeneration in neonates.

The application of mitochondria-targeted therapeutics—MitoQ, SS-31, and melatonin—resulted in meaningful, though partial, neuroprotection. MitoQ restored ATP levels to 87.1% of control and reduced ROS by approximately 42%, while SS-31 and melatonin restored ATP to 81.4% and 76.3%, respectively. Caspase-9 activation decreased by 55% in MitoQ-treated animals, and cytochrome c release was significantly suppressed across all treated groups. Time-course analysis revealed that therapeutic efficacy dropped sharply if treatment was delayed beyond 30 minutes post-hypoglycemia. These results confirm that early, mitochondria-targeted interventions can significantly mitigate the damaging effects of hypoglycemia on neonatal brain mitochondria and associated apoptotic pathways. Translating these findings into clinical settings may provide a targeted therapeutic window to improve neurological outcomes in at-risk newborns, particularly in NICU environments where

metabolic crises are frequent and interventions must be both rapid and precise.

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