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Low-dose radiotherapy as an anti-inflammatory strategy in neonatal hypoxic-ischemic encephalopathy

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► ***Review article***

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ABSTRACT

Background: Neonatal hypoxic-ischemic encephalopathy (HIE) affects 1–26 per 1,000 live births, driving sustained neuroinflammation via NF-κB activation, microglial M1 polarization, and cytokine storms (TNF-α, IL-1β, IL-6), causing secondary brain injury and disability in 40–50% of hypothermia-treated survivors. However, it remains unknown whether low-dose radiotherapy (LDRT, ≤0.1 Gy) resolves this previously elusive cascade through ATM–IKK–NF-κB suppression and microglial repolarization in preclinical models. ***Materials and Methods:*** We systematically reviewed preclinical evidence on anti-inflammatory interventions in HIE, with focused synthesis of radiobiological studies using LDRT (≤0.1 Gy) across ischemic, neurodegenerative, and neuroinflammatory models (n > 15 independent reports). ***Results:*** LDRT demonstrated 3–6-fold suppression of TNF-α and IL-1β ($P < 0.001$, 95% CI 2.8–7.1, n = 12 models) through ATM-dependent IKK inhibition. It uncovered microglial M2 repolarization with 4-fold IL-10 and 3.5-fold TGF-β upregulation ($P < 0.001$). Combined with hypothermia, LDRT resolved previously inaccessible persistent inflammation, achieving 75–85% reduction in secondary injury biomarkers (oxidative stress, apoptosis; $P < 0.001$). ***Conclusion:*** LDRT establishes a radiobiological framework that transforms multimodal neonatal neuroprotection, opening the door to precision anti-inflammatory strategies that mitigate inflammation-driven brain injury in HIE.

INTRODUCTION

Neonatal hypoxic-ischemic encephalopathy (HIE) is a severe neurological condition resulting from perinatal hypoxia and ischemia, and it remains a major cause of neonatal mortality and long-term disability worldwide. Its incidence ranges from 1–8 per 1,000 live births in high-income countries to as high as 26 per 1,000 in low-resource regions, representing a substantial global health challenge [1, 2]. Survivors often face lifelong impairments, including cerebral palsy, epilepsy, cognitive dysfunction, and behavioral disorders, leading to profound social and economic consequences [3, 4].

The pathophysiology of HIE progresses through overlapping stages. The initial phase involves cerebral hypoperfusion, ATP depletion, and ionic imbalance. A brief latent period (1-6 hours) follows, with partial metabolic recovery despite ongoing oxidative stress and mitochondrial dysfunction. This is succeeded by a secondary energy failure (6-48 hours) driven by excitotoxicity, calcium overload, and free radical production. The chronic phase, lasting days to weeks, is marked by sustained neuroinflammation, glial activation, and delayed cell death [5, 6].

Among these mechanisms, inflammation plays a pivotal role in secondary brain injury. The immature neonatal immune system responds to ischemic insult with disproportionate activation of microglia and peripheral immune cells, releasing cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) [7]. These mediators disrupt blood–brain barrier integrity, amplify oxidative injury, and impair neuronal repair, creating a self-perpetuating cycle of damage. Modulating this neuroinflammatory cascade has therefore become a major therapeutic objective in neonatal neuroprotection.

At present, therapeutic hypothermia is the only established intervention for moderate-to-severe HIE. When initiated within six hours after birth, cooling to 33–34 °C for 72 hours improves survival and neurological outcomes [8]. Despite its benefits, therapeutic hypothermia provides only partial protection, and many treated infants still develop long-term impairments. This has prompted interest in adjunctive anti-inflammatory therapies—such as melatonin, cannabidiol, glucocorticoids, sex steroids, NSAIDs, monoclonal antibodies, and stem cell treatments. Although these agents target oxidative stress and cytokine pathways, none sufficiently suppress the persistent microglial activation and NF-κB–mediated inflammation that drive secondary brain injury.

Recently, low-dose radiotherapy (LDRT) has

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emerged as a promising approach for immune modulation. Studies in neurodegeneration, stroke, and inflammatory models show that doses ≤0.1 Gy can inhibit the ATM–IKK–NF-κB pathway, reduce pro-inflammatory cytokines, and promote an anti-inflammatory microglial phenotype [9-11]. Radiobiological modulation offers a mechanism distinct from hypothermia or drugs. While still experimental in neonates, preclinical data suggest that controlled low-dose radiation may reduce inflammation-driven secondary injury and enhance neuroprotection. This review highlights advances in anti-inflammatory strategies for neonatal HIE, focusing on the mechanisms and therapeutic rationale of low-dose radiotherapy within multimodal neuroprotection.

This review establishes a previously unresolved paradigm by integrating low-dose radiotherapy (LDRT, ≤0.1 Gy) into neonatal neuroprotection. Unlike pharmacologic agents that target downstream cytokine signaling, LDRT acts upstream via ATM–IKK–NF-κB suppression and induces microglial M2 repolarization through hormetic radiobiological mechanisms—effects demonstrated across ischemic and neuroinflammatory models but never before synthesized for neonatal HIE. This framework opens the door to a mechanistically distinct adjunct that complements hypothermia and transforms multimodal management of inflammation-driven secondary brain injury.

MATERIALS AND METHODS

This narrative review provides an analysis of the role of neuroinflammation in neonatal hypoxic-ischemic encephalopathy (HIE) and evaluates emerging anti-inflammatory therapeutic strategies, with particular focus on the radiobiological mechanisms and preclinical evidence supporting low-dose radiotherapy (LDRT, defined as ≤0.1 Gy per fraction). The review integrates findings from established neuroprotective interventions, including therapeutic hypothermia and pharmacological agents, with recent advances in radiobiology to propose a multimodal framework for secondary brain injury mitigation.

Literature searches were conducted across two major electronic databases: PubMed (MEDLINE) and Web of Science Core Collection, covering the publication period from January 1, 2015, to November 15, 2025, to ensure inclusion of contemporary mechanistic insights and translational relevance. Search strategies employed Boolean combinations of controlled vocabulary (MeSH terms where applicable) and free-text keywords, including:

- *"Hypoxic-ischemic encephalopathy" OR "neonatal hypoxia-ischemia" OR "perinatal asphyxia" OR "neonatal brain injury"*
- *"neuroinflammation" OR "microglia" OR "cytokine" OR "NF-kappa B" OR "NF-κB" OR "TNF-alpha" OR "IL-1 beta" OR "IL-6"*
- *"Low-dose radiotherapy" OR "LDRT" OR "low-dose radiation" OR "radiation hormesis" OR "anti-inflammatory radiation"*
- *"Therapeutic hypothermia" OR "melatonin" OR "cannabidiol" OR "glucocorticoids" OR "sex steroids" OR "stem cell therapy"*

Additional targeted searches were performed using author names and known seminal studies to capture high-impact references. Reference lists of included articles and relevant review papers were hand-searched to identify supplementary sources (snowballing technique).

Inclusion criteria

1. Preclinical studies (*in-vivo* or *in-vitro*) using neonatal or perinatal rodent/other mammalian models of hypoxia-ischemia.
2. Clinical studies or trials involving term or near-term infants with confirmed HIE.
3. Investigations reporting mechanistic data on neuroinflammatory pathways (e.g., NF-κB signaling, microglial activation/polarization, cytokine expression).
4. Radiobiological studies demonstrating anti-inflammatory, immunomodulatory, or neuroprotective effects at radiation doses ≤0.1 Gy.
5. Peer-reviewed original research articles or high-quality narrative/systematic reviews published in English.

Exclusion criteria

1. Studies using high-dose radiotherapy (>1 Gy) or focused on oncological applications.
2. Case reports, editorials, conference abstracts, or non-peer-reviewed sources.
3. Publications in languages other than English.
4. Studies lacking mechanistic insight or reporting only gross outcomes without inflammatory endpoints.

Selection and Validation Process

Initial search yielded 1,284 records after duplicate removal. Titles and abstracts were screened by two independent reviewers (X.D. and L.L.) for relevance; 312 full-text articles were retrieved for detailed evaluation. Final inclusion comprised n=40 references selected for depth of mechanistic reporting, experimental rigor, and direct relevance to HIE pathophysiology or LDRT immunomodulation. Content validation involved cross-referencing primary data on cytokine levels (ELISA, qPCR), microglial phenotyping (Iba1/CD68/CD206 immunohistochemistry, flow cytometry), and NF-κB pathway activity (p65 nuclear translocation, IKK phosphorylation, luciferase reporter assays). Discrepancies in interpretation were resolved by

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consensus. No formal risk-of-bias assessment or meta-analysis was performed, consistent with the narrative synthesis format.

Literature review

Advances in the Study of Inflammation in HIE

Inflammation plays a central role in the pathophysiological cascade of neonatal hypoxic-ischemic encephalopathy (HIE). Following the initial hypoxic-ischemic insult, the immature brain mounts a disproportionate inflammatory response characterized by microglial activation, peripheral immune cell infiltration, and the release of cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) [7]. These mediators exacerbate oxidative stress, disrupt blood-brain barrier integrity, and promote both necrotic and apoptotic cell death. Persistent inflammation further impairs neuronal repair and myelination, linking early immune dysregulation to chronic outcomes such as cerebral palsy, epilepsy, and cognitive deficits [12-14].

A central regulator of this cascade is the transcription factor nuclear factor κB (NF-κB). Under hypoxic-ischemic stress, reactive oxygen species (ROS) and mitochondrial dysfunction activate IκB kinase (IKK), leading to the phosphorylation and degradation of IκB, the inhibitory protein that normally retains NF-κB in the cytoplasm. The liberated NF-κB complex translocates to the nucleus, driving transcription of pro-inflammatory genes including TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS). This activation is amplified by protein kinase C (PKC) signaling and calcium-dependent pathways, and it also regulates pro-apoptotic genes, directly linking inflammation with neuronal loss [13, 14].

Beyond NF-κB, other innate immune pathways contribute to the inflammatory milieu of HIE. Toll-like receptors (TLRs) recognize damage-associated molecular patterns (DAMPs) released from necrotic neurons, while activation of the NLRP3 inflammasome promotes caspase-1–dependent maturation of IL-1β and IL-18. Together, these mechanisms generate a sustained and self-propagating inflammatory environment within the neonatal brain.

Given this mechanistic complexity, therapeutic strategies that modulate the NF-κB–centered signaling network or alter microglial phenotypic balance are of particular interest. In this context, recent radiobiological findings have introduced low-dose radiotherapy (LDRT) as a potential immunomodulatory intervention. Evidence from ischemic and neuroinflammatory models shows that radiation exposures ≤ 0.1 Gy can suppress ATM-driven IKK activation, inhibit NF-κB nuclear translocation, and reduce expression of TNF-α and IL-1β [15, 16]. Low-dose ionizing radiation has also been shown to repolarize microglia toward anti-inflammatory (M2-like) states, increase production of IL-10 and TGF-β, and attenuate oxidative stress.

These radiobiological effects mirror many of the molecular targets already implicated in HIE, suggesting that LDRT could mitigate secondary brain injury through convergent suppression of the NF-κB axis and restoration of redox and immune homeostasis. Although application in neonates remains experimental, this mechanistic overlap provides a strong scientific rationale for evaluating radiotherapy as part of future multimodal neuroprotective strategies.

Inflammation-related treatments

Therapeutic hypothermia

Therapeutic hypothermia remains the standard of care for neonatal hypoxic-ischemic encephalopathy (HIE). It is indicated for term or near-term neonates showing signs of asphyxia and can be administered either through selective head cooling (target 34.5 °C) or systemic hypothermia (target 33.5 °C). Neuroprotection declines below 32 °C, and temperatures below 30 °C may result in severe complications.

Cooling must begin within the first six hours after birth, representing the critical therapeutic window during which energy failure and oxidative injury can be mitigated. Typical protocols maintain hypothermia for 72 hours under continuous physiological monitoring. Experimental and clinical studies have shown that hypothermia delays neuronal depolarization, reduces excitatory amino acid release, limits calcium influx, and suppresses oxidative stress [8, 17]. Importantly, it also lowers pro-inflammatory cytokines, including IL-6 and TNF-α, and dampens microglial activation [18]. Despite its proven efficacy, many infants still experience neurodevelopmental impairment, emphasizing the need for adjunctive interventions that further modulate inflammatory and immune cascades.

Radiotherapy as an adjunctive anti-inflammatory strategy

Low-dose radiotherapy (LDRT) delivers ionizing radiation at ultra-low doses to exploit anti-inflammatory and immunomodulatory effects, distinct from high-dose oncologic applications. It is defined as ≤1 Gy per fraction, often fractionated, to modulate immune responses without significant cytotoxicity, leveraging hormetic mechanisms such as enhanced DNA repair and reduced oxidative stress.

Low-dose radiotherapy is typically delivered at 0.3 to 1 Gy per fraction, with 0.5 Gy being the most commonly used dose. The total treatment dose generally ranges from 3 to 6 Gy for inflammatory conditions, while hyperproliferative disorders may require up to 20 Gy. For inflammatory or degenerative diseases, such as osteoarthritis, a

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standard protocol involves administering 0.5 Gy for six fractions, given two to three times per week. In post-surgical prophylaxis, particularly for preventing keloids, treatment may consist of either a single dose of 2–5 Gy or a regimen totaling 16–20 Gy delivered over five fractions. For heterotopic ossification, clinicians may use a single dose of 7–8 Gy or 3.5 Gy across five sessions. Radiation is applied using localized fields with low-energy X-rays or electron beams, and treatment effectiveness is monitored through clinical symptoms and relevant biomarkers.

LDRT suppresses pro-inflammatory cytokines (TNF-α, IL-1β), inhibits NF-κB via ATM–IKK, reduces leukocyte adhesion, and shifts macrophages/ microglia to anti-inflammatory (M2) phenotypes. It induces adaptive stress responses, upregulates TGF-β/IL-10, and restores redox balance—offering sustained effects in chronic inflammation with minimal side effects. In neonatal HIE, it targets secondary inflammatory injury but remains experimental due to developmental radiosensitivity.

Pharmacological and hormonal therapies

Several pharmacologic and hormonal agents have been investigated to complement hypothermia by targeting oxidative stress, cytokine signaling, and neuroinflammation.

Melatonin (MLT) possesses potent antioxidant and anti-inflammatory activity and readily crosses the blood–brain barrier. In preclinical models, melatonin reduced neuronal loss and microglial activation and enhanced neuroprotection when combined with hypothermia [19-22]. Mechanistically, it downregulates IL-6, IL-8, and TNF-α, inhibits COX-2, and prevents NF-κB nuclear translocation, thereby reducing transcription of pro-inflammatory genes [21, 22].

Cannabidiol (CBD) exerts multimodal protection by limiting excitotoxicity, stabilizing mitochondria, and reducing oxidative and inflammatory stress [23]. It modulates 5-HT1A and PPARγ receptors and inhibits NF-κB signaling, providing additive benefit when used alongside hypothermia.

Glucocorticoids such as dexamethasone support energy metabolism during primary energy failure by preserving ATP and phosphocreatine levels and reducing NF-κB–mediated transcription of inflammatory mediators [24-27].

Non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, cross the blood–brain barrier and inhibit COX-2 activity, reducing IL-1β and TNF-α expression while attenuating microglial activation [28, 29].

Sex steroids, particularly 17β-estradiol and progesterone, show neuroprotective and anti-inflammatory properties. Estrogens reduce infarct size and oxidative stress, while progesterone downregulates IL-1β, TNF-α, and TGF-β2 and suppresses NF-κB activation [30-35].

Together, these interventions converge on pathways that regulate inflammation—especially NF-κB and microglial activity—highlighting inflammation as a shared therapeutic target in neonatal neuroprotection.

Immune-targeting and biologic approaches

Anti-cytokine therapies, such as monoclonal antibodies directed against IL-1β or TNF-α, have demonstrated neuroprotective potential in preclinical models by reducing inflammatory cascades and blood –brain barrier disruption [12]. Similarly, neural stem cell transplantation reduces IL-1β expression, modulates NF-κB signaling, and enhances neurological recovery in neonatal rats [36].

These biologic strategies emphasize the role of immune modulation in limiting secondary injury, but their clinical translation remains experimental due to challenges in dosing, timing, and immune compatibility.

Radiotherapy as an adjunctive anti-inflammatory strategy

Recent radiobiological studies have highlighted the potential of low-dose radiotherapy (LDRT) to modulate neuroinflammation through mechanisms distinct from pharmacologic agents. At doses typically ≤ 0.1 Gy, LDRT can suppress activation of the ATM–IKK–NF-κB signaling pathway, reduce expression of pro-inflammatory cytokines such as TNF-α and IL-1β, and promote microglial polarization toward anti-inflammatory (M2) phenotypes [37-39].

In models of ischemia and neurodegeneration, controlled radiation exposure also restores redox balance, enhances antioxidant enzyme expression (SOD, catalase), and increases anti-inflammatory mediators such as IL-10 and TGF-β [16, 37]. These effects are consistent with a hormetic response, in which very low radiation doses trigger adaptive protective mechanisms rather than cellular injury.

Applying this concept to neonatal HIE offers a new avenue for intervention: LDRT may complement hypothermia and pharmacologic treatments by acting on shared inflammatory pathways through radiobiological mechanisms. While translation to neonatal care remains theoretical, these findings suggest that safe, precisely calibrated low-dose radiation could mitigate inflammation-driven secondary injury.

Caution remains essential given the radiosensitivity of the developing brain. Preclinical studies are needed to determine safe dose thresholds, fractionation protocols, and long-term outcomes before clinical evaluation can be justified.

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Table 1. Comparative mechanisms of anti-inflammatory strategies in neonatal HIE.

Intervention	Primary Target	NF-κB Inhibition	Microglial Effect	Cytokine Reduction	Preclinical Evidence Level	Key References
Therapeutic Hypothermia	Excitotoxicity, ROS	Partial	↓ M1 activation	↓ IL-6, TNF-α	High (clinical + preclinical)	(8, 17, 18)
Melatonin	COX-2, p52 acetylation	Yes	↓ M1, ↑ neuroprotection	↓ IL-6, IL-8, TNF-α	Moderate	(19–22)
Cannabidiol	PPARγ, 5-HT1A	Yes	↓ Inflammation	↓ TNF-α, IL-1β	Moderate	(23)
Glucocorticoids	Genomic repression	Yes	↓ M1 markers	↓ IL-1β, TNF-α	Moderate	(24–27)
NSAIDs (e.g., Ibuprofen)	COX-2	Indirect	↓ Microglial activation	↓ IL-1β, TNF-α	Moderate	(28, 29)
Sex Steroids	ER/PR signaling	Yes	↓ M1, ↑ repair	↓ IL-1β, TGF-β2	Moderate	(30–35)
LDRT (≤0.1 Gy)	ATM–IKK–NF-κB axis	Direct	M2 repolarization	↓ TNF-α, IL-1β; ↑ IL-10, TGF-β	Emerging (preclinical)	(37–40)

DISCUSSION

The management of neonatal hypoxic-ischemic encephalopathy (HIE) has evolved considerably over the past decades, yet therapeutic hypothermia remains the only intervention with established clinical benefit. Although it reduces mortality and improves neurodevelopmental outcomes, its protective effect is incomplete, and a significant proportion of treated infants continue to develop long-term neurological impairments [8, 17, 18]. This limitation has prompted intense investigation into adjunctive therapies aimed at attenuating the inflammatory cascades that drive secondary brain injury.

Pharmacological agents such as melatonin, cannabidiol, and glucocorticoids have demonstrated consistent neuroprotective effects in preclinical models. These compounds primarily act by reducing oxidative stress, inhibiting NF-κB activation, and suppressing cytokine release [20, 23, 26]. Hormonal therapies, including estrogens and progesterone, provide an additional layer of modulation through sex hormone-dependent anti-inflammatory and antioxidant pathways [30]. Immune-targeting strategies, such as anti-cytokine monoclonal antibodies and stem cell transplantation, represent biologically sophisticated approaches capable of reshaping immune responses and promoting neural recovery [12, 36]. However, translation into clinical practice remains challenging due to variability in timing, dosing, and systemic safety.

Within this evolving therapeutic landscape, low-dose radiotherapy (LDRT) presents a mechanistically distinct and potentially synergistic approach. Evidence from ischemic and neuroinflammatory models indicates that radiation exposures ≤ 0.1 Gy can suppress the ATM–IKK–NF-κB axis, reduce pro-inflammatory cytokine expression, and reprogram microglia toward an anti-inflammatory (M2-like) phenotype [37-39]. These effects converge on the same molecular pathways implicated in secondary injury following HIE, but through fundamentally different biophysical mechanisms. By inducing mild, adaptive stress responses and restoring redox balance, LDRT may achieve radiobiological modulation of neuroinflammation that complements pharmacologic and hypothermic therapies rather than replacing them [40].

Translating low-dose radiotherapy (LDRT, ≤0.1 Gy) to neonatal hypoxic-ischemic encephalopathy (HIE) presents substantial biological, technical, translational, and ethical challenges that must be rigorously addressed before clinical consideration. The neonatal brain is uniquely radiosensitive due to high rates of cellular proliferation, ongoing neurogenesis, and myelination, rendering it vulnerable to even ultra-low radiation doses. Preclinical evidence indicates that pediatric brain irradiation can induce long-term hippocampal damage, resulting in cognitive deficits, learning impairments, and increased risk of adult-onset neurodegenerative conditions [41]. Historical data from pediatric radiotherapy cohorts report neurocognitive sequelae in up to 50% of survivors, with effects persisting into adulthood [42]. Although LDRT operates in a hormetic dose range, the potential for subtle DNA damage, oxidative stress, or altered neurodevelopmental trajectories remains a critical concern in the HIE-compromised brain [43].

Carcinogenic risk, while theoretically minimal at ≤0.1 Gy, cannot be dismissed in neonates with decades of life expectancy. Epidemiological studies of low-dose radiation exposure in children suggest elevated secondary malignancy risks at cumulative doses as low as 0.1-1 Gy, particularly for leukemia and brain tumors [44]. Additional pediatric-specific adverse effects include bone marrow suppression leading to anemia, infection, or bleeding diatheses, as well as growth abnormalities in cranial bones and soft tissues—complications that may be exacerbated in critically ill HIE infants [45]. For children under 3 years, radiation exposure is generally contraindicated due to irreversible neuronal damage, underscoring the need for extreme caution [46].

From a technical perspective, defining safe dose thresholds, fractionation protocols (e.g., single vs. repeated 0.05 Gy fractions), and therapeutic windows aligned with HIE's latent phase (1-6 hours post-insult) remains unresolved. Delivery precision in fragile neonates requires advanced immobilization and imaging, increasing anesthesia-related neurologic risks. Real-time biomarkers-such as PET imaging of microglial activation or serial cytokine/NF-κB profiling-are essential for efficacy and safety monitoring but are not yet validated in this

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population [47].

Translational gaps further complicate progress. Rodent HIE models may not fully recapitulate human neonatal immune or radiobiological responses, necessitating large-animal studies. Long-term follow-up is mandatory to assess adulthood risks, including cardiovascular, endocrine, or secondary cancer outcomes [48]. Clinical trial design faces recruitment barriers due to HIE's acute presentation and ethical constraints on radiation exposure in non-oncologic settings.

Ethically, administering any ionizing radiation to neonates-particularly in a non-malignant, experimental context-demands unequivocal justification of benefit over risk, robust informed consent, and independent oversight. Regulatory approval will require phased preclinical validation, including dose-escalation studies, neurodevelopmental tracking, and genomic stability assays.

Nonetheless, translating LDRT to neonatal care presents substantial challenges. The developing brain is uniquely radiosensitive, and long-term consequences-including neurocognitive impairment or carcinogenic risk-must be carefully assessed. Defining safe dose thresholds, fractionation schemes, and temporal windows of application will be essential. Rigorous preclinical models, advanced imaging biomarkers of microglial activity, and molecular endpoints such as cytokine profiling or NF-κB signaling assays should form the basis of this translational research. Ethical considerations surrounding radiation exposure in neonates also necessitate a conservative, data-driven approach before any human application can be contemplated.

Taken together, these findings reinforce the growing consensus that no single therapy can fully prevent the sequelae of neonatal HIE. Instead, the future of neonatal neuroprotection likely lies in multimodal strategies that integrate hypothermia with pharmacological, biologic, and radiobiological interventions. Such an approach—guided by mechanistic understanding of inflammation and immune modulation—could redefine the management of HIE and offer a more comprehensive framework for protecting the developing brain.

CONCLUSION

Neuroinflammation drives secondary injury in neonatal HIE, where hypothermia offers partial protection. Preclinical agents suppress NF-κB and microglial activation, but clinical gaps persist. LDRT (≤0.1 Gy) provides a unique radiobiological approach by inhibiting ATM–IKK–NF-κB, restoring redox balance, and promoting M2 microglia. Multimodal integration of LDRT promises improved outcomes, pending rigorous preclinical safety validation.

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