Advances in the Mechanism of Ferroptosis in Neonatal Hypoxic-Ischemic Brain Injury (Post-print)

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Abstract

Neonatal hypoxic-ischemic brain damage (HIBD) represents one of the common causes of neurological injury during the neonatal period, associated with high rates of disability and mortality in neonates. Its pathogenesis is complex, and no specific therapeutic approaches are currently available clinically. Ferroptosis, a newly identified form of non-apoptotic cell death in recent years, has garnered extensive attention and emerged as a research focus. Investigations into the relationship between ferroptosis and neonatal HIBD have been increasing annually, with substantial evidence demonstrating that ferroptosis is intimately involved in the pathogenesis and progression of neonatal HIBD. Furthermore, research has indicated that vitamin K2, particularly menaquinone-4 (MK-4), may exert neuroprotective effects through the inhibition of ferroptosis. This review briefly summarizes the mechanisms of ferroptosis in neonatal HIBD and microglia, and explores the potential of vitamin K2, especially MK-4, to improve outcomes in neonatal HIBD by suppressing ferroptosis, thereby offering a more economical, safe, and targeted therapeutic strategy.

Full Text

Research Progress on the Mechanism of Ferroptosis in Neonatal Hypoxic-Ischemic Brain Damage

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Abstract

Neonatal hypoxic-ischemic brain damage (HIBD) is one of the common causes of neurological injury in the neonatal period, often leading to high rates of disability and mortality. Its pathogenesis is complex, and there are currently no specific clinical treatments. Ferroptosis, a newly discovered form of non-apoptotic cell death, has attracted widespread attention and gradually become a research hotspot. Studies on ferroptosis and neonatal HIBD have increased annually, with substantial evidence demonstrating that ferroptosis is closely associated with the occurrence and progression of neonatal HIBD. Moreover, research has indicated that vitamin K2, particularly menaquinone-4 (MK-4), can exert neuroprotective effects by inhibiting ferroptosis. This review summarizes the mechanisms of ferroptosis in neonatal HIBD and microglia, and explores the potential of vitamin K2, especially MK-4, to improve outcomes in neonatal HIBD by inhibiting ferroptosis, aiming to provide a more economical, safer, and targeted therapeutic approach.

Keywords: Brain injuries; Ferroptosis; Neonatal hypoxic-ischemic brain damage; Lipid peroxidation; MK-4; Microglia; Review

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Neonatal hypoxic-ischemic brain damage (HIBD) refers to brain injury in fetuses or newborns resulting from systemic hypoxemia and/or reduced cerebral blood flow caused by perinatal asphyxia. This condition often leads to irreversible central nervous system damage and white matter injury, seriously endangering neonatal health. The pathogenesis of neonatal HIBD is complex, and the lack of specific treatments makes it crucial to explore its underlying mechanisms in depth.

Ferroptosis is a novel mechanism of programmed cell death characterized by unrestricted lipid peroxidation and subsequent plasma membrane rupture. Its occurrence is closely related to glutathione (GSH) metabolism, abnormal accumulation of lipid peroxides, and iron metabolism disorders. Ferroptosis participates in the pathogenesis of various diseases, including cerebral ischemia-reperfusion injury, Alzheimer's disease, and acute lung injury. Recent studies have revealed that ferroptosis plays an important role in neonatal HIBD, and that neuroinflammation and iron accumulation in microglia can interact to jointly promote the progression of neuroinflammation.

This review focuses on the mechanisms of ferroptosis, its role in neonatal HIBD and microglia, and proposes the potential of menaquinones (vitamin K2), particularly menaquinone-4 (MK-4), to improve neonatal HIBD outcomes by inhibiting ferroptosis. We aim to provide new insights for preventing neonatal

HIBD and offer a basis for future research.

Literature Search Strategy: We systematically searched the CNKI, Wanfang Data, PubMed, and Web of Science databases from inception to 2024. Chinese search terms included: ferroptosis, neonatal hypoxic-ischemic brain damage, MK-4, lipid peroxidation, iron overload, microglia, treatment, and their combinations. English search terms included: ferroptosis, neonatal hypoxic-ischemic brain damage, MK-4, lipid peroxidation, iron overload, microglia, treat, and their combinations. Inclusion criteria were: (1) studies on ferroptosis in HIBD models; (2) randomized controlled trials, animal studies, or clinical studies related to the topic. Exclusion criteria were: insufficient data, duplicate publications, and low-quality studies.

Mechanisms of Ferroptosis

Iron-Related Metabolism Iron is an essential trace element crucial for biological survival. Under physiological conditions, plasma Fe^{3+} is tightly bound to transferrin (TF), which interacts with transferrin receptor 1 (TFR1) widely expressed on cell surfaces. The TF-Fe^{3+}-TFR1 complex is internalized via clathrin-mediated endocytosis to form endosomes. Within the cytoplasm, the low pH in endosomes releases Fe^{3+} from TFR1, which is then reduced to Fe^{2+} by the metalloreductase six-transmembrane epithelial antigen of prostate 3 (STEAP3) and transported into the cytoplasm via divalent metal transporter 1 (DMT1). Most Fe^{2+} is exported back to the circulatory system through the iron exporter ferroportin (FPN) on the cell membrane, while the remaining labile iron not involved in biological processes is stored in ferritin [encoded by ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL)], with the rest participating in cellular metabolic processes.

However, inappropriate low or high iron concentrations can cause disease. Improper iron accumulation in certain compartments (such as lysosomes) or ferritinophagy can increase redox-active iron in the labile iron pool, driving ferroptotic peroxidation. Severe TF deficiency can lead to tissue iron overload. Additionally, when plasma iron levels exceed the buffering capacity of TF, accumulation of loosely bound and toxic non-transferrin-bound iron (NTBI) can cause iron toxicity.

Generation of Lipid Peroxides Abnormal accumulation of lipid peroxides is the primary trigger of ferroptosis. The generation of intracellular lipid peroxides is regulated through complex and precise mechanisms involving two main pathways: enzyme-catalyzed lipid peroxidation and free Fe^{2+}-induced Fenton reactions.

First, polyunsaturated fatty acids (PUFAs) are converted into highly reactive lipid peroxides (phospholipid hydroperoxide, PL-PUFA-OOH) through a series of enzymatic reactions. PUFAs primarily derive from dietary sources, arachidonic acid (AA), and linoleic acid. PUFAs are first acylated to fatty acyl-

CoA esters (PUFA-CoA) by acyl-CoA synthetase long-chain family protein 4 (ACSL4). The activated lipid molecules then undergo esterification with phosphatidylcholine via lysophosphatidyltransferase 3 (LPCAT3) to generate polyunsaturated fatty acid-containing phospholipids (PUFA-PL), which subsequently undergo lipid peroxidation catalyzed by the lipoxygenase protein family (LOXs). ACSL4 serves as an important indicator protein in ferroptosis, while iron-containing LOXs, particularly LOX-15 and LOX-12, are key enzymes initiating lipid peroxidation and represent targets for many ferroptosis inducers. Under normal conditions, LOX-catalyzed reactions proceed mildly as part of lipid metabolism, but in pathological states, they can cooperate with Fenton reactions to trigger ferroptosis.

Second, free Fe^{2+} can induce lipid peroxidation through the Fenton reaction. Intracellular iron mainly exchanges through transfer proteins containing Fe^{3+}, entering cells via TFR. The acidic environment of endosomes releases Fe^{3+}, which is reduced to Fe^{2+} by iron reductases such as STEAP3. When Fe^{2+} mixes with peroxides, it becomes extremely oxidative, generating Fe^{3+} and peroxyl radicals. Once PUFA-PLs are incorporated into the membrane environment, these peroxyl radicals attack lipid molecules, oxidizing them to PL-PUFA-OOH. In normal cells, lipid peroxides remain in homeostasis due to controlled iron concentrations. However, sudden iron surges dramatically intensify Fenton reactions, causing excessive lipid peroxide accumulation and ultimately ferroptosis.

Clearance of Lipid Peroxides Cells have four main pathways to clear peroxidized PUFA-PLs: the GPX4/GSH axis, FSP1/CoQ10 axis, GTP cyclohydrolase 1/tetrahydrobiopterin (GCH1/BH4) axis, and DHODH/CoQ10 axis. The primary mechanism relies on GPX4, which uses GSH as a substrate to reduce lipid peroxides to normal phospholipid molecules. Cells also import cystine via the cystine-glutamate antiporter (system Xc^-) to produce intracellular cysteine, a crucial precursor for GSH synthesis. Thus, system Xc^- represents a central regulator of ferroptosis. Studies show that modulating system Xc^- can control ferroptosis progression. For instance, $CD8^+$ T cell-derived interferon-γ (IFN-γ) can trigger cancer cell ferroptosis by downregulating solute carrier family 7A member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2), the two genes encoding system Xc^-. The p53 tumor suppressor sensitizes cells to ferroptosis by inhibiting SLC7A11 transcription, while nuclear factor E2-related factor 2 (NRF2) prevents ferroptosis by upregulating SLC7A11.

Beyond the classic GPX4/GSH axis, researchers have identified additional antioxidant systems. The FSP1/CoQ10 axis operates independently of GPX4/GSH, with FSP1 regenerating reduced CoQ10 (ubiquinol, $CoQH_2$) from oxidized CoQ10, thereby inhibiting PL-PUFA-OOH formation. Similarly, the GCH1/BH4 axis suppresses lipid peroxidation through $CoQH_2$ generation and lipid remodeling, with GCH1 as the rate-limiting enzyme in BH4 biosynthesis. Recent studies also reveal that the DHODH/CoQ10 axis works in parallel with mitochondrial GPX4 but independently of cytosolic GPX4 or FSP1. DHODH,

a CoQ10-reducing flavoprotein similar to FSP1, inhibits ferroptosis in the mitochondrial inner membrane by reducing CoQ10 to $CoQH_2$ and modulating cellular sensitivity to the GPX4 inhibitor RSL3.

Ferroptosis and Neonatal HIBD

Neonatal HIBD refers to brain injury in fetuses or newborns caused by partial or complete hypoxia, reduced or suspended cerebral blood flow due to prenatal, intrapartum, and/or neonatal asphyxia. This condition strongly activates immune cells in the brain, primarily causing microglial activation and initiating inflammatory cascades. Activated microglia release excessive pro-inflammatory mediators including tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6, while chronic overactivation of neuroinflammation accelerates and even causes neurodegeneration.

Mechanisms of Ferroptosis in Neonatal HIBD Following HIBD, brain tissue exhibits iron overload. Three decades ago, Dietrich et al. observed through cranial MRI that severe hypoxic-ischemic injury resulted in obvious hemorrhagic lesions in periventricular white matter and iron deposition in basal ganglia. Subsequent work by Hu et al. in a 3-day-old rat HIBD model demonstrated that brain iron deposition varied temporally, peaking at 3 days post-hypoxia-ischemia. Hypoxia-ischemia activates hypoxia-inducible factor (HIF), which upregulates iron-regulatory genes and predisposes cells to ferroptosis, making HIF a key regulator of cellular iron concentration during hypoxia-ischemia. Additionally, hypoxia-ischemia and immature antioxidant systems cause accumulation of toxic NTBI in neonates, while elevated ROS levels release iron from ferritin and erythrocytes, increasing free iron concentration. Hypoxia also upregulates heme oxygenase-1 (HO-1), causing heme degradation and Fe^{2+} production that further increases iron levels. Beyond these intrinsic disruptions, hypoxia induces TFR expression, increasing iron uptake. As iron concentration rises, intense Fenton reactions generate radicals from NTBI and free Fe^{2+}, triggering lipid peroxidation and ferroptosis.

Second, hypoxia-ischemia causes excessive ROS production and oxidative stress. Under pathological conditions, impaired antioxidant systems fail to clear ROS promptly, leading to lipid peroxidation. Oxidative stress is widely recognized as closely related to neonatal brain injury. Studies using the free radical scavenger edaravone have shown it can inhibit lipid peroxidation in HIBD neonatal rats by suppressing oxidative stress. ROS-mediated lipid peroxidation is considered the main cause of oxidative stress. Research has found that in both HIBD neonatal rat brain tissue and umbilical cord blood of asphyxiated newborns, malondialdehyde (the end product of lipid peroxidation) gradually increases with brain injury duration, and its expression correlates closely with HIBD severity.

Clinical studies have found elevated glutamate concentrations in brain metabolites after HIBD. Glutamate is an excitatory neurotransmitter released from

presynaptic vesicles during hypoxic cell depolarization. In the brain, most glutamate transporter-1 (GLT1) is expressed in mature astrocytes. During hypoxia-ischemia, un-reuptaked glutamate accumulates extracellularly, damaging immature oligodendrocytes and neurons and causing basal ganglia and periventricular white matter injury. Additionally, SLC7A11 mediates exchange of extracellular cystine and intracellular glutamate to support GSH biosynthesis. Abnormal extracellular glutamate accumulation prevents adequate cystine uptake, reducing reduced GSH synthesis and impairing the antioxidant system. Yang et al. found that hypoxia activates HIF-1α, which enhances transcription of the membrane glutamate transporter gene solute carrier family 1 member 1 (SLC1A1), promoting SLC7A11-mediated cystine uptake by recycling extracellular glutamate into cells and increasing ferroptosis resistance. In HIBD rat brain tissue, glial cell proliferation, elevated ROS levels, and decreased SLC7A11, GSH, and GPX4 expression ultimately reduce antioxidant capacity, causing cortical lipid peroxidation. Zhu et al. found that hypoxia-ischemia significantly upregulates Toll-like receptor 4 (TLR4), which is widely distributed in neural cells and triggers inflammatory pathway activation. TLR4 inhibition can upregulate SLC7A11 and GPX4 expression in hippocampal tissue, and early TLR4 signaling inhibition may improve long-term outcomes in neonatal HIBD by reducing neuronal loss, decreasing glial activation, and improving synaptic plasticity.

Ferroptosis and Microglia Microglia are the primary immune cells of the brain, responsible for innate immunity and maintaining central nervous system homeostasis. Hypoxia-ischemia triggers brain inflammation, and excitotoxic-injured neurons can activate microglia, which produce excessive cytokines and ultimately cause neuronal death. Several new forms of cell death have been identified, and research on ferroptosis in microglia has increased annually. Studies show that neuroinflammation and microglial iron accumulation promote each other, and inhibiting microglial iron accumulation can prevent neuroinflammation. After hypoxia, microglial iron accumulation can lead to oligodendrocyte death and axonal swelling, accelerating neuronal death. Fernandez-Mendivil et al. found that inflammatory stimulation causes overexpressed HO-1 in microglia to alter iron metabolism proteins, promote iron accumulation, and induce ferroptosis. Cui et al. demonstrated that in early-stage brain ischemia, HIF-1α-mediated ACSL4 downregulation not only reduces lipid peroxidation but also inhibits pro-inflammatory cytokine production in microglia, with HIF-1α negatively regulating ACSL4 expression by binding to its promoter. Ryan et al. found that microglia may be more susceptible to ferroptosis than neurons and astrocytes, with only microglia showing upregulated FTH1 expression after ferroptotic stimulation. Microglia can be activated into pro-inflammatory M1 or anti-inflammatory M2 phenotypes under different stimuli, with M2 microglia being more sensitive to RSL3-induced ferroptosis than M1 microglia. Thus, microglial iron accumulation is closely related to neuroinflammation, suggesting that inhibiting microglial ferroptosis may represent a novel target for reducing neuroinflammation.

Ferroptosis-Targeted Therapy for Neonatal HIBD

Ferroptosis has been implicated in various neurological diseases including cerebral ischemia-reperfusion injury, periventricular leukomalacia, Parkinson's disease, and traumatic brain injury. Increasing evidence shows that ferroptosis mechanisms such as lipid peroxidation and mitochondrial dysfunction are closely related to neonatal HIBD, and inhibiting ferroptosis may improve brain injury severity. Microglia have high iron storage capacity, accumulate iron during disease, and show increased sensitivity to ferroptosis. Both antioxidant ferroptosis inhibitors (ferroptosis inhibitors-1, FER-1) and iron chelators such as deferoxamine (DFO) can partially reverse the additional neurotoxicity caused by microglia.

Gou et al. demonstrated that exogenous melatonin injection in a neonatal rat HIBD model effectively inhibited neuronal ferroptosis, promoted hippocampal neuron survival, and improved long-term learning and memory abilities, while GPX4 inhibitor RSL3 treatment abolished melatonin's protective effects. Additionally, glycyrrhizic acid has been shown to inhibit neuronal ferroptosis and oxidative stress, reduce mitochondrial damage, and alleviate neuroinflammation in HIBD via the HMGB1/GPX4 pathway. Li et al. found that ferroptosis in 7-day-old HIBD rats was mediated by the SIRT1/NRF2/GPX4 signaling pathway, and FER-1 administration effectively reduced hypoxia-ischemia-induced brain atrophy. Yang et al. showed that salidroside attenuated neuronal ferroptosis in glutamate-injured HT22 mouse hippocampal neurons by upregulating GPX4 and SLC7A11 expression through activation of the NRF2/HO-1 signaling pathway.

Vitamin K has long been reported to have antioxidant properties. Due to its structural similarity to CoQ, recent studies show that FSP1 can reduce vitamin K to vitamin K hydroquinone (VKH_2), which captures oxygen radicals to exert antioxidant effects and inhibit phospholipid peroxide generation. The primary form of vitamin K2 used in research is MK-4, indicating its close relationship with ferroptosis.

Conclusion and Future Perspectives

Neonatal HIBD remains a major cause of neonatal mortality. Due to unclear pathogenesis and lack of specific treatments, the resulting neurological sequelae severely impair patients' quality of life and impose unpredictable burdens on families and society. This review has summarized the mechanisms of ferroptosis, its role in neonatal HIBD and microglia, and the potential of MK-4 to improve neonatal HIBD outcomes by inhibiting ferroptosis, aiming to provide new preventive strategies and a basis for future research.

Clinical conditions in HIBD patients are often complex, and clinical trials face numerous uncertainties, making rigorous animal experiments indispensable for advancing clinical applications. Although existing animal studies suggest MK-4 is an effective ferroptosis inhibitor, many questions remain for future experi-

mental research and clinical application. For example, in hypoxic microglia, can MK-4 activate NRF2/HIF-1α to promote ferritin formation (particularly FTH1) and regulate the labile iron pool to reduce iron overload and ferroptosis damage? These questions warrant further investigation to provide sufficient experimental evidence that inhibiting ferroptosis can improve neonatal HIBD prognosis. If the hypothesis that targeted ferroptosis inhibition can improve neonatal HIBD proves viable, it would make treatment safer, more effective, and economical.

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