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Circadian Regulation of Lipid Peroxidation in the Brain: Linking Ferroptosis to Neurodegenerative Vulnerability

Suraj Sen[1], Anit Jha[2], Rajeev Ratan[3,*],Neeraj Yadav[4], Ayush Bhardwaj[4]

Abstract

The human brain operates through highly coordinated physiological and biochemical processes that regulate cognition, behavior, and neural adaptability. Central to these processes are mechanisms governing brain function, neurophysiology, and neuroplasticity, which are increasingly recognized to be influenced by circadian rhythms. Recent advances in cognitive neuroscience, neuroimaging, and behavioral neuroscience have revealed that disruptions in circadian regulation can significantly impact oxidative balance within the brain, particularly through enhanced lipid peroxidation. Lipid peroxidation, a process involving oxidative degradation of membrane lipids, plays a crucial role in neuronal dysfunction and is closely associated with ferroptosis, an iron-dependent form of regulated cell death. The integration of neuropharmacology and drug development strategies has highlighted ferroptosis as a key therapeutic target in neurodegenerative conditions. Moreover, clinical neuropsychology studies indicate that oxidative damage and circadian misalignment contribute to cognitive decline and behavioral impairments. Neuroimaging and neurophysiological assessments further demonstrate that circadian disruption affects neuronal signaling, synaptic plasticity, and brain metabolism. Developmental neuroscience also suggests that early-life circadian disturbances may predispose individuals to long-term neurological vulnerabilities. The role of neuroplasticity in adapting to oxidative stress underscores the importance of maintaining circadian integrity for optimal brain health. This review explores the intersection of circadian rhythms, lipid peroxidation, and ferroptosis within the broader framework of neuroscience disciplines. It emphasizes how integrating concepts from cognitive, behavioral, and clinical neuroscience with pharmacological innovations can provide novel insights into neurodegenerative disease mechanisms. Additionally, it highlights emerging therapeutic approaches, including chronopharmacology and targeted antioxidant strategies, aimed at preserving neuronal function and improving clinical outcomes.

Keywords: Brain function; cognitive neuroscience; behavioral neuroscience; neuroimaging; neurophysiology; neuropsychology; clinical neuropsychology; neuropharmacology; drug development; developmental neuroscience; neuroplasticity; circadian rhythm; lipid peroxidation; ferroptosis; oxidative stress

***Author for Correspondence**
Rajeev Ratan
E-mail: rajeevsinghrathourjnp2000@gmail.com

[1]Principal, Department of Pharmacy, Harishchandra Pharmacy College, Jaunpur, Uttar Pradesh, India
[2]Academic Head, Department of Pharmacy, Harishchandra Pharmacy College, Jaunpur, Uttar Pradesh, India
[3]Assistant Professor, Department of Pharmacy, Harishchandra Pharmacy College, Jaunpur, Uttar Pradesh, India
[4]Scholar, Department of Pharmacy, Harishchandra Pharmacy College, Jaunpur, Uttar Pradesh, India

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INTRODUCTION

The brain, despite accounting for only approximately 2% of total body weight, consumes nearly 20% of the body's oxygen supply, making it exceptionally vulnerable to oxidative stress. This vulnerability is further compounded by the abundance of polyunsaturated fatty acids (PUFAs) in neuronal membranes, which are highly susceptible to lipid peroxidation. Lipid peroxidation results in the formation of reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which can disrupt membrane integrity, protein function, and DNA stability [1].

Simultaneously, growing evidence suggests that many physiological processes in the brain – including metabolism, neurotransmission, and antioxidant defense – are regulated by circadian rhythms. The circadian system ensures temporal coordination of cellular processes, optimizing energy utilization and protecting against environmental stressors. (Figure 1)

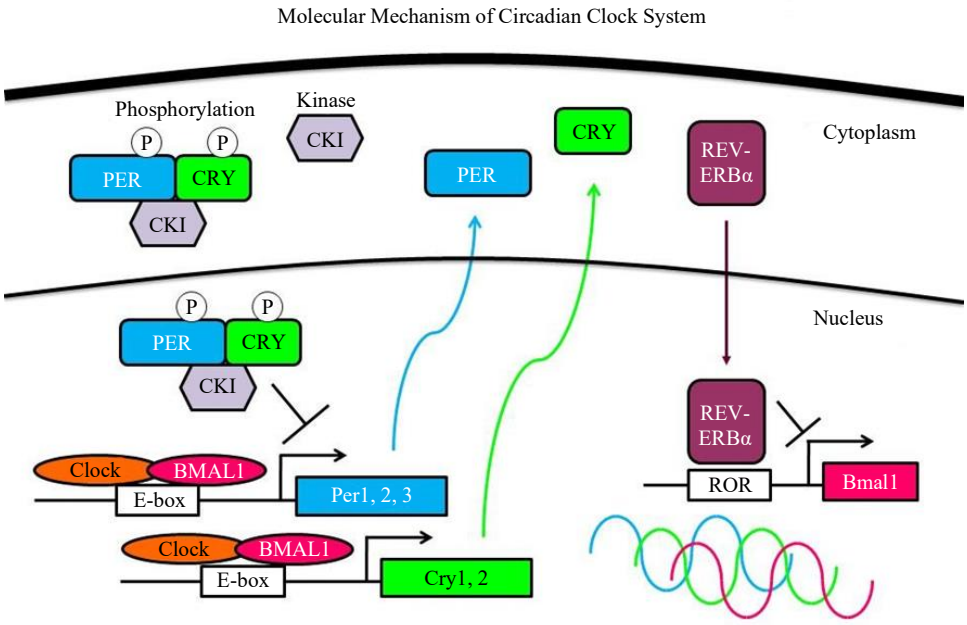

Figure 1. Molecular mechanism of circadian clock system.

Recent studies have begun to uncover a crucial intersection between circadian regulation and ferroptotic signaling pathways. For instance, circadian oscillations influence the expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and GPX4, as well as key regulators of iron metabolism like transferrin and ferritin. Disruption of circadian rhythms – whether due to aging, lifestyle factors, or pathological conditions – can lead to impaired redox balance and increased susceptibility to lipid peroxidation [2].

Moreover, neurodegenerative diseases often exhibit both circadian disturbances and elevated oxidative stress, suggesting a potential causal relationship. Patients with Alzheimer's disease frequently display disrupted sleep-wake cycles, while Parkinson's disease is associated with altered circadian gene expression. These observations raise critical questions regarding whether circadian dysregulation is merely a symptom or a contributing factor to disease progression (Table 1).

Table 1. Features of brain susceptibility.

Factor	Description	Impact on lipid peroxidation
High oxygen consumption	Intensive mitochondrial activity	Increased ROS generation.
Abundance of PUFAs	Rich in neuronal membranes	Easily oxidized lipids.
Iron accumulation	Essential for neurotransmission	Catalyzes Fenton reaction.
Limited antioxidant capacity	Lower levels of detoxifying enzymes	Reduced ROS clearance.
Circadian fluctuations	Time-dependent metabolic regulation	Variable oxidative defense.

Key Features of Brain Susceptibility to Lipid Peroxidation

This review aims to bridge the gap between circadian biology and ferroptosis research by exploring how temporal regulation influences lipid peroxidation in the brain. Understanding this interplay may provide new therapeutic opportunities, particularly in the context of chronotherapy and targeted antioxidant strategies.

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Background and Literature Review: Lipid Peroxidation in the Brain

This process plays a dual role in biological systems: while low levels of lipid oxidation participate in cellular signaling, excessive lipid peroxidation leads to structural damage, loss of membrane integrity, and generation of cytotoxic by-products.

In the central nervous system (CNS), lipid peroxidation is of particular concern due to the high concentration of oxidizable lipids, elevated oxygen consumption, and relatively low antioxidant capacity. The brain's susceptibility is further intensified by the presence of redox-active metals such as iron, which catalyze the formation of reactive oxygen species (ROS) [3, 4].

Mechanism of Lipid Peroxidation

Lipid peroxidation occurs through a well-characterized chain reaction mechanism consisting of three major phases:

- Initiation.
- Propagation.
- Termination (Figure 2).

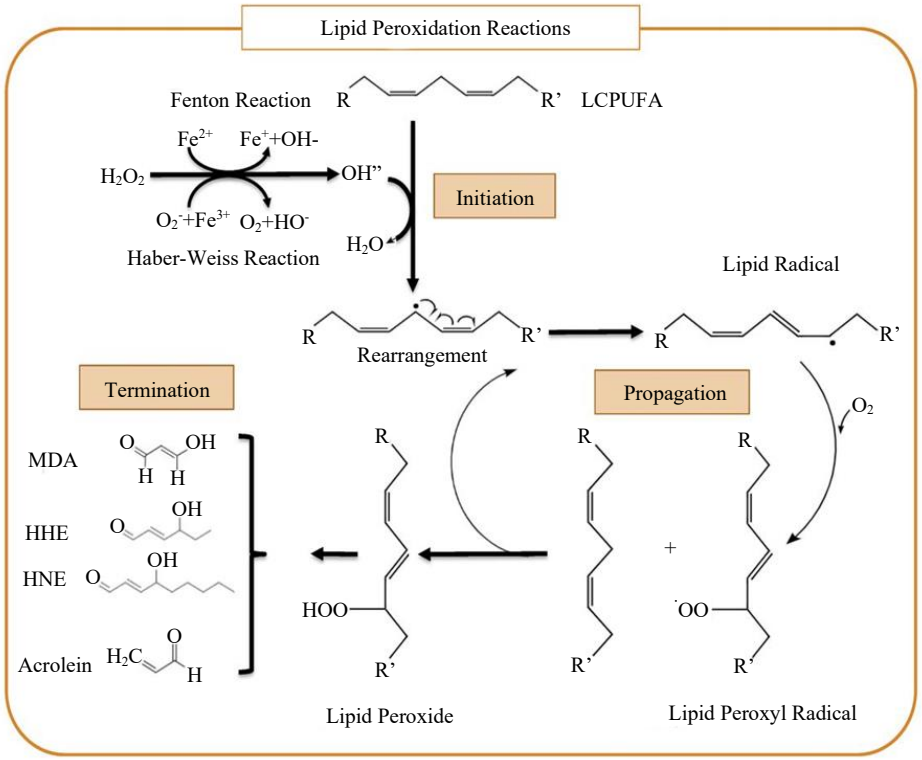

Figure 2. Lipid peroxidation mechanism.

Key By-Products of Lipid Peroxidation

Two major toxic aldehydes generated during lipid peroxidation are:

- Malondialdehyde (MDA).
- 4-Hydroxynonenal (4-HNE) (Table 2).

Table 2. Major products of lipid peroxidation and their biological effects.

Product	Source	Biological impact
Malondialdehyde (MDA)	PUFA oxidation	DNA damage, mutagenesis.
4-Hydroxynonenal (4-HNE)	ω-6 fatty acid peroxidation	Protein modification, enzyme inhibition.
Lipid hydroperoxides (LOOH)	Early oxidation products	Membrane instability.
Isoprostanes	Arachidonic acid oxidation	Biomarkers of oxidative stress.
Reactive aldehydes	Secondary breakdown products	Cellular toxicity.

Role of Lipid Peroxidation in Neuronal Damage

Neurons are particularly vulnerable to lipid peroxidation due to their high metabolic rate and dependence on membrane integrity for signal transmission. Oxidative degradation of membrane lipids leads to:

- Loss of membrane fluidity and permeability.
- Disruption of ion gradients.
- Impairment of synaptic transmission.
- Activation of cell death pathways.

Moreover, lipid peroxidation products can trigger inflammatory responses by activating microglia and astrocytes, further amplifying neuronal injury [5, 6].

Lipid Peroxidation and Neurodegenerative Diseases

Extensive research has linked elevated lipid peroxidation to the pathogenesis of several neurodegenerative disorders:

- In Alzheimer's Disease, increased levels of MDA and 4-HNE have been detected in affected brain regions, correlating with amyloid-beta aggregation and tau pathology.
- In Parkinson's Disease, oxidative stress and lipid peroxidation contribute to dopaminergic neuron loss in the substantia nigra.
- In Amyotrophic Lateral Sclerosis, lipid peroxidation is associated with mitochondrial dysfunction and motor neuron degeneration.
- These findings suggest that lipid peroxidation is not merely a consequence but a driving factor in neurodegenerative processes [7].

Circadian Influence on Lipid Peroxidation

Recent studies have demonstrated that lipid peroxidation levels fluctuate in a circadian manner. For example:

- ROS production peaks during active metabolic phases.
- Antioxidant defenses vary across the day-night cycle.
- Lipid remodeling enzymes show rhythmic expression.

Disruption of circadian rhythms can therefore lead to sustained oxidative stress and increased lipid peroxidation, predisposing neurons to ferroptosis [8].

Emerging Biomarkers of Lipid Peroxidation

Advances in analytical techniques have enabled the identification of reliable biomarkers for lipid peroxidation, including:

- Isoprostanes (measured in cerebrospinal fluid and plasma).
- 4-HNE-protein adducts.
- MDA levels (via thiobarbituric acid reactive substances assay).

These biomarkers are increasingly used in clinical and experimental studies to assess oxidative damage and disease progression [9, 10].

Classification and Types of Ferroptosis and Oxidative Neuronal Injury

Ferroptosis, although initially described as a singular form of regulated cell death, is now recognized as a heterogeneous process with multiple subtypes depending on the initiating stimuli, molecular pathways involved, and cellular context. In the brain, ferroptosis interacts with other oxidative stress–mediated injury pathways, contributing to a spectrum of neuronal damage mechanisms. Understanding these classifications is essential for targeted therapeutic interventions and precise mechanistic insights [11].

Classification Based on Induction Mechanism

Ferroptosis can be broadly classified into two major categories based on how it is initiated:

Extrinsic (Transporter-Dependent) Ferroptosis

This type is triggered by the inhibition of cystine uptake via the system Xc^- antiporter, leading to depletion of intracellular glutathione (GSH). Reduced GSH levels impair the activity of Glutathione Peroxidase 4, resulting in accumulation of lipid peroxides. [12]

Key Features

- Inhibition of cystine transport.
- Glutathione depletion.
- Increased lipid ROS.

Intrinsic (Enzyme-Regulated) Ferroptosis

This subtype involves direct inhibition or inactivation of GPX4 or activation of lipid peroxidation enzymes such as lipoxygenases. It can also result from dysregulated lipid metabolism or mitochondrial dysfunction.

Key Features

- GPX4 inhibition.
- Activation of lipid-oxidizing enzymes.
- Enhanced mitochondrial ROS production.

Classification Based on Cellular Context in the Brain

Different brain cell types exhibit varying susceptibility to ferroptosis:

- *Neuronal Ferroptosis:* Neurons are highly sensitive due to their high PUFA content and metabolic demand. Ferroptosis in neurons leads to synaptic dysfunction and cognitive impairment [13].
- *Astrocytic Ferroptosis:* Astrocytes play a protective role by supplying antioxidants to neurons. However, their dysfunction can indirectly promote neuronal ferroptosis.
- *Microglial Ferroptosis:* Microglia, the immune cells of the CNS, can undergo ferroptosis during chronic inflammation, releasing pro-inflammatory mediators that exacerbate neuronal injury.

Classification Based on Molecular Pathways

Ferroptosis can also be categorized based on dominant molecular pathways:

- *Iron-Driven Ferroptosis:* Characterized by excessive intracellular iron leading to ROS generation via the Fenton reaction.
- *Lipid Metabolism–Driven Ferroptosis:* Involves dysregulation of lipid remodeling enzymes such as ACSL4 and lipoxygenases, increasing PUFA susceptibility to oxidation.
- *Antioxidant System Failure–Driven Ferroptosis:* Occurs due to impaired glutathione synthesis or GPX4 activity. (Table 3)

Table 3. Classification of ferroptosis in the brain.

Classification basis	Subtype	Key features	Relevance to brain
Induction mechanism	Extrinsic	System Xc^- inhibition, GSH depletion	Common in toxin-induced injury.
	Intrinsic	GPX4 inhibition, enzyme activation	Observed in neurodegeneration.
Cellular context	Neuronal	High PUFA content, high ROS	Direct neuronal death.
	Astrocytic	Antioxidant support role	Indirect neuronal damage.
	Microglial	Inflammatory activation	Neuroinflammation.
Molecular pathway	Iron-driven	Iron overload	Seen in Parkinson's disease.
	Lipid-driven	PUFA oxidation	Membrane damage.
	Antioxidant failure	GPX4 dysfunction	Increased susceptibility.

Comparison with Other Forms of Cell Death

Ferroptosis shares certain features with other forms of regulated cell death but remains distinct in its mechanism (Table 4)

Table 4. Comparison with other forms of cell death.

Feature	Ferroptosis	Apoptosis	Necrosis
Trigger	Lipid peroxidation, iron	DNA damage, signaling pathways	चोट / trauma.
Morphology	Mitochondrial shrinkage	Nuclear fragmentation	Cell swelling.
Caspase involvement	Absent	Present	Absent.
ROS involvement	High (lipid ROS)	Moderate	Variable.
Reversibility	Potentially reversible (early stages)	Irreversible	Irreversible.

Circadian Influence on Ferroptosis Subtypes

Circadian rhythms can modulate different types of ferroptosis through:

- Time-dependent regulation of GPX4 expression.
- Rhythmic control of iron metabolism proteins.
- Oscillations in lipid synthesis and remodeling enzymes.
- Diurnal variation in glutathione levels.

These factors suggest that certain ferroptosis subtypes may be more active at specific times of the day, contributing to temporal patterns of neuronal vulnerability [14].

Emerging Hybrid Forms of Cell Death

Recent studies suggest that ferroptosis may overlap with other forms of regulated cell death, leading to hybrid mechanisms such as:

- Ferroptosis-apoptosis crosstalk.
- Ferroptosis-necroptosis interactions.
- Oxytosis (oxidative glutamate toxicity, closely related to ferroptosis).

These hybrid forms are particularly relevant in complex neurodegenerative conditions where multiple pathways are activated simultaneously. (Figure 3)

Conceptual Diagram: Classification of Ferroptosis

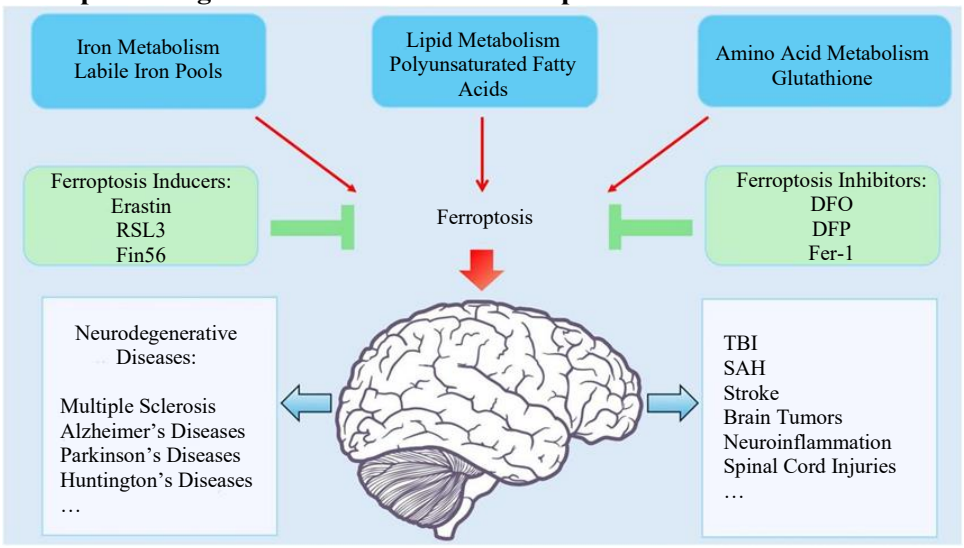

Figure 3. Ferroptosis.

Mechanism of Action: Circadian Regulation of Ferroptosis and Lipid Peroxidation

The mechanistic interplay between circadian rhythms, lipid peroxidation, and ferroptosis represents a complex, multi-layered regulatory network. This network integrates molecular clock signaling with redox homeostasis, lipid metabolism, and iron regulation to determine neuronal survival or death. Understanding this mechanism is critical for identifying temporal vulnerabilities in neurodegenerative diseases [15].

Molecular Clock Control of Ferroptosis Pathways

The circadian clock regulates gene expression through transcriptional feedback loops involving core proteins such as BMAL1 and CLOCK. These transcription factors influence downstream genes involved in oxidative stress response, lipid metabolism, and iron homeostasis.

Clock-controlled genes regulate:

- Antioxidant enzyme expression (e.g., SOD, catalase, GPX4).
- Glutathione biosynthesis pathways.
- Lipid remodeling enzymes (e.g., ACSL4).
- Iron metabolism proteins.

Disruption of these regulatory pathways leads to increased oxidative stress and enhanced susceptibility to ferroptosis (Figure 4).

Circadian Regulation of Lipid Peroxidation

Lipid peroxidation is influenced by circadian oscillations in both ROS production and antioxidant defense mechanisms. The balance between these two processes determines the extent of lipid damage.

Key Mechanisms

- *ROS Oscillation:* Mitochondrial activity fluctuates across the circadian cycle, leading to time-dependent ROS generation.
- *Antioxidant Rhythmicity:* Enzymes such as GPX4 and catalase exhibit circadian expression patterns.
- *Lipid Availability:* Circadian control of lipid metabolism influences PUFA incorporation into membranes.

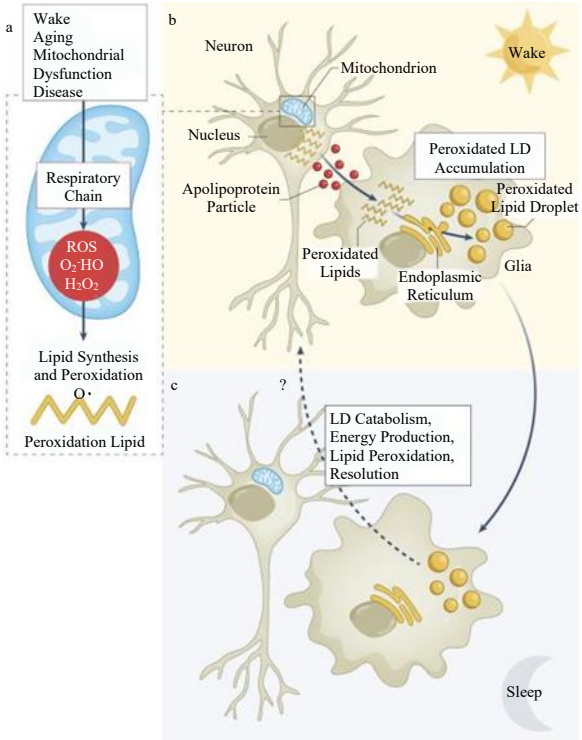

Figure 4. Circadian regulation of lipid peroxidation.

These factors create periods of increased vulnerability when ROS production exceeds antioxidant capacity.

Integration of Iron Metabolism with Circadian Rhythms

Iron metabolism is tightly regulated by circadian signals, affecting ferroptosis susceptibility. Proteins involved in iron transport and storage exhibit rhythmic expression, leading to fluctuations in intracellular iron levels [16].

Key processes include:

- *Iron Uptake:* Regulated by transferrin receptor expression.
- *Iron Storage:* Controlled by ferritin levels.
- *Iron Export:* Mediated by ferroportin.

Elevated iron levels during certain circadian phases enhance ROS generation via the Fenton reaction, promoting lipid peroxidation.

Glutathione–GPX4 Axis Under Circadian Control

The glutathione (GSH)-dependent antioxidant system is central to preventing ferroptosis. Circadian rhythms regulate:

- Cysteine uptake via system Xc^-.
- Glutathione synthesis enzymes.
- Activity of Glutathione Peroxidase 4.

Reduced GSH levels or impaired GPX4 activity during specific circadian phases can lead to accumulation of lipid hydroperoxides, triggering ferroptosis [17].

Role of Mitochondria in Circadian Ferroptosis Regulation

Mitochondria are both a source and target of oxidative stress. Circadian regulation of mitochondrial function influences:

- ATP production.
- ROS generation.
- Lipid metabolism.

Mitochondrial dysfunction amplifies lipid peroxidation and contributes to ferroptotic cell death. (Table 5)

Table 5. Mechanistic integration of circadian rhythm and ferroptosis.

Component	Circadian influence	Effect on ferroptosis
Clock genes (BMAL1, CLOCK)	Regulate gene transcription	Control antioxidant and metabolic pathways.
ROS production	Diurnal variation	Initiates lipid peroxidation.
Antioxidant enzymes	Rhythmic expression	Detoxify lipid peroxides.
Iron metabolism	Time-dependent regulation	Modulates ROS generation.
Lipid metabolism	Circadian control	Determines PUFA availability.
Glutathione levels	Oscillatory synthesis	Supports GPX4 activity.

Temporal Windows of Ferroptotic Susceptibility

A key concept emerging from this mechanistic framework is the existence of "temporal windows" during which neurons are more prone to ferroptosis. These windows arise due to:

- Peak ROS production.
- Reduced antioxidant defense.
- Increased iron availability.

- Enhanced lipid susceptibility.

Disruption of circadian rhythms – due to aging, environmental factors, or disease—can widen these windows, increasing neuronal damage [18].

Crosstalk with Neuroinflammatory Pathways

Circadian dysregulation also affects neuroinflammation, which can exacerbate ferroptosis:

- Activated microglia release ROS and inflammatory cytokines
- Inflammatory signaling enhances lipid peroxidation.
- Ferroptosis can further amplify inflammation.

This creates a vicious cycle contributing to neurodegeneration [19].

Conceptual Model: Circadian–Ferroptosis Axis

Summary of Mechanism

The circadian regulation of ferroptosis involves a synchronized control of:

- Redox balance.
- Lipid metabolism.
- Iron homeostasis.
- Antioxidant defense systems.

Disruption of this synchronization leads to excessive lipid peroxidation and neuronal death, highlighting the importance of circadian integrity in maintaining brain health. [20]

Formulation and Development Approaches: Targeting Circadian–Ferroptosis Axis for Neuroprotection

The growing understanding of ferroptosis and circadian biology has opened new avenues for the development of advanced therapeutic strategies in neurodegenerative disorders. In pharmaceutical sciences, particularly within nutraceuticals, herbal drug technology, and novel drug delivery systems, targeting lipid peroxidation and ferroptotic pathways requires a multi-dimensional formulation approach.

This section focuses on formulation strategies designed to modulate ferroptosis while aligning with circadian rhythms – an approach often referred to as chronopharmacology [21].

Therapeutic Targets in Ferroptosis Modulation

Effective formulation design begins with identifying key molecular targets involved in ferroptosis:

- Iron metabolism (iron chelation).
- Lipid peroxidation inhibition.
- Enhancement of antioxidant systems.
- Restoration of glutathione levels.
- Activation of Glutathione Peroxidase 4.

These targets can be addressed using synthetic drugs, natural compounds, or hybrid formulations.

Conventional Pharmacological Agents

Several pharmacological agents have been investigated for their ability to inhibit ferroptosis:

Iron Chelators

- Deferoxamine (DFO).
- Deferiprone.

These agents reduce iron availability, thereby limiting ROS generation.

Lipid Peroxidation Inhibitors

- Ferrostatin-1.
- Liproxstatin-1.

These compounds directly inhibit lipid radical propagation.

Antioxidants

- Vitamin E (α-tocopherol).
- N-acetylcysteine (NAC).

These agents enhance cellular antioxidant capacity and reduce oxidative stress.

Nutraceutical and Herbal Approaches

Natural products have gained significant attention due to their multitargeted mechanisms and safety profiles.

Key Bioactive Compounds

- Curcumin (from Curcuma longa).
- Resveratrol (from grapes).
- Quercetin (flavonoid).
- Epigallocatechin gallate (EGCG from green tea).

These compounds exhibit:

- Antioxidant activity.
- Iron-chelating properties.
- Anti-inflammatory effects.
- Modulation of circadian genes.

Chronopharmaceutical Drug Delivery Systems

Chronopharmacology involves designing drug delivery systems that release active compounds in synchrony with circadian rhythms. This is particularly important in ferroptosis, where susceptibility varies across the day. [22]

Approaches Include

- Time-controlled release systems.
- Pulsatile drug delivery systems.
- Chronomodulated nanoparticles.

These systems ensure drug availability during peak vulnerability periods, enhancing therapeutic efficacy. (Table 6)

Table 6. Formulation strategies targeting ferroptosis.

Strategy	Mechanism	Example agents	Advantages
Iron chelation	Reduces ROS generation	Deferoxamine	Prevents Fenton reaction.
Antioxidant therapy	Neutralizes ROS	Vitamin E, NAC	Broad protection.
Lipid peroxidation inhibition	Blocks lipid radical chain	Ferrostatin-1	Direct ferroptosis inhibition.
Herbal/nutraceutical	Multi-target action	Curcumin, resveratrol	Safe, synergistic.
Chronopharmaceutical systems	Time-specific drug release	Pulsatile systems	Improved efficacy.

Novel Drug Delivery Systems (NDDS)

Advanced drug delivery systems are essential for targeting the brain due to the presence of the blood-brain barrier (BBB).

Nanoparticles

- Lipid-based nanoparticles.
- Polymeric nanoparticles.

These systems enhance drug stability, bioavailability, and brain targeting.

Liposomes

- Encapsulate both hydrophilic and lipophilic drugs.
- Improve BBB penetration.

Solid Lipid Nanoparticles (SLNs)

- Suitable for lipophilic antioxidants.
- Provide controlled release.

Circadian Timing in Drug Administration

The timing of drug administration plays a crucial role in therapeutic outcomes:

- Antioxidants may be more effective during peak ROS production.
- Iron chelators may be beneficial during periods of high iron availability.
- GPX4 activators may be needed during low antioxidant phases.

Aligning drug delivery with circadian rhythms enhances efficacy and reduces side effects [16].

Challenges in Formulation Development

Despite promising advances, several challenges remain:

- Limited understanding of circadian variability in humans.
- Difficulty in precise timing of drug delivery.
- Variability in patient circadian rhythms.
- Stability issues with natural compounds.
- BBB permeability constraints.

RESULTS AND DISCUSSION

The integration of circadian biology with lipid peroxidation and ferroptosis mechanisms has revealed a dynamic and time-dependent framework underlying neuronal vulnerability. Evidence from experimental, clinical, and translational studies collectively demonstrates that oxidative stress in the brain is not constant but fluctuates in accordance with circadian rhythms [9].

Key Observations from Literature

- *Circadian Oscillation of Oxidative Stress:* Studies indicate that reactive oxygen species (ROS) levels exhibit diurnal variation, with peaks corresponding to periods of heightened metabolic activity.
- *Temporal Regulation of Antioxidant Systems:* Enzymes such as Glutathione Peroxidase 4 (GPX4), superoxide dismutase, and catalase show rhythmic expression, influencing lipid peroxide detoxification.
- *Iron Metabolism Rhythmicity:* Circadian control of iron-handling proteins modulates intracellular iron levels, thereby affecting ferroptotic susceptibility.
- *Lipid Remodeling Dynamics:* Time-dependent expression of lipid metabolism enzymes alters membrane composition and susceptibility to peroxidation.

These findings strongly support the hypothesis that ferroptosis is under circadian regulation.

Temporal Windows of Neurodegenerative Vulnerability

A significant outcome of this review is the identification of time-specific susceptibility windows during which neurons are more prone to oxidative damage and ferroptosis.

During these windows:

- ROS production is elevated.
- Antioxidant defenses are reduced.
- Iron availability is increased.
- Lipid substrates are more susceptible.

Circadian disruption (e.g., sleep deprivation, aging, shift work) expands these vulnerability windows, increasing the risk of neurodegenerative damage.

Correlation with Neurodegenerative Disorders

The reviewed evidence establishes a strong link between circadian dysregulation, lipid peroxidation, and neurodegeneration:

- In Alzheimer's Disease, disrupted circadian rhythms correlate with increased oxidative stress and cognitive decline.
- In Parkinson's Disease, iron accumulation and lipid peroxidation contribute to neuronal loss.
- In Amyotrophic Lateral Sclerosis, impaired antioxidant defenses promote ferroptotic pathways [5].

These conditions share common features of:

- Elevated lipid peroxidation.
- Impaired circadian regulation.
- Increased ferroptosis markers.

Impact of Therapeutic Interventions

Formulation strategies targeting ferroptosis and circadian pathways have demonstrated promising outcomes:

- Iron chelators reduce ROS generation and neuronal damage.
- Antioxidants and nutraceuticals improve redox balance.
- Ferroptosis inhibitors directly block lipid peroxidation.
- Chronopharmaceutical systems enhance drug efficacy by aligning with circadian rhythms.

These interventions highlight the importance of timing and targeted delivery in neuroprotection (Table 7).

Table 7. Summary of key findings.

Parameter	Observation	Implication
ROS levels	Show circadian fluctuation	Determines oxidative stress timing.
Antioxidant enzymes	Rhythmic expression	Affects lipid peroxide detoxification.
Iron metabolism	Time-dependent regulation	Modulates ferroptosis.
Lipid metabolism	Circadian control	Influences membrane vulnerability.
Neurodegeneration	Linked to circadian disruption	Suggests therapeutic targeting.

Interpretation of Findings

The findings collectively suggest that ferroptosis is not merely a biochemical event but a time-regulated pathological process. Circadian rhythms act as a master regulator, coordinating multiple pathways that converge on lipid peroxidation and neuronal survival [11].

Disruption of this coordination leads to:

- Enhanced oxidative stress.
- Increased lipid peroxidation.
- Activation of ferroptotic pathways.
- Progressive neuronal damage.

CONCLUSION

This comprehensive review highlights the critical role of circadian regulation in modulating lipid peroxidation and ferroptosis in the brain. The interplay between molecular clock systems, redox homeostasis, lipid metabolism, and iron regulation establishes a time-dependent framework that determines neuronal vulnerability.

Key conclusions include:

- Circadian rhythms govern oxidative stress and lipid metabolism, creating fluctuations in neuronal susceptibility to damage.
- Ferroptosis serves as a central mechanism linking lipid peroxidation to neurodegeneration, particularly in diseases such as Alzheimer's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis.
- Temporal windows of vulnerability represent critical periods during which neurons are more prone to oxidative injury.
- Circadian disruption significantly exacerbates ferroptotic damage, emphasizing the importance of maintaining circadian integrity.
- Chronopharmacological approaches offer a promising strategy for enhancing therapeutic outcomes by aligning treatment with biological rhythms.

Future Perspectives

- Development of circadian-based biomarkers for early detection of neurodegeneration.
- Exploration of clock gene modulators as therapeutic agents.
- Advancement of precision chronotherapy in clinical practice.
- Integration of nanotechnology and herbal therapeutics for targeted neuroprotection.

REFERENCES

1. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell. 2012;149(5):1060–72.
2. Stockwell BR, Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, et al. Ferroptosis: A regulated cell death nexus linking metabolism, redox biology, and disease. Cell. 2017;171(2):273–85.
3. Jiang X, Stockwell BR, Conrad M. Ferroptosis: Mechanisms, biology and role in disease. Nat Rev Mol Cell Biol. 2021;22(4):266–82.
4. Yang WS, Stockwell BR. Ferroptosis: Death by lipid peroxidation. Trends Cell Biol. 2016;26(3):165–76.
5. Ursini F, Maiorino M, Forman HJ. Redox homeostasis: The golden mean of healthy living. Redox Biol. 2016;8:205–15.
6. Brigelius-Flohé R, Maiorino M. Glutathione peroxidases. Biochim Biophys Acta Gen Subj. 2013;1830(5):3289–303.
7. Hardeland R. Melatonin in aging and disease—Multiple consequences of reduced secretion, options and limits of treatment. Aging Dis. 2011;3(2):194.
8. Musiek ES, Holtzman DM. Mechanisms linking circadian clocks, sleep, and neurodegeneration. Science. 2016;354(6315):1004–8.
9. Hood S, Amir S. The aging clock: Circadian rhythms and later life. J Clin Invest. 2017;127(2):437–46.
10. Kondratova AA, Kondratov RV. The circadian clock and pathology of the ageing brain. Nat Rev Neurosci. 2012;13(5):325–35.
11. Zhang Y, Chen X, Gueydan C, Han J. Plasma membrane changes during programmed cell deaths. Cell Res. 2018;28(1):9–21.
12. Friedmann Angeli JP, Schneider M, Proneth B, Tyurina YY, Tyurin VA, Hammond VJ, et al. Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. Nat Cell Biol. 2014;16(12):1180–91.

13. Do Van B, Gouel F, Jonneaux A, Timmerman K, Gelé P, Pétrault M, et al. Ferroptosis, a newly characterized form of cell death in Parkinson's disease that is regulated by PKC. Neurobiol Dis. 2016;94:169–78.
14. Hambright WS, Fonseca RS, Chen L, Na R, Ran Q. Ablation of ferroptosis regulator glutathione peroxidase 4 in forebrain neurons promotes cognitive impairment and neurodegeneration. Redox Biol. 2017;12:8–17.
15. Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: Production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxid Med Cell Longev. 2014;2014:360438.
16. Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nat Rev Neurosci. 2019;20(3):148–60.
17. Ward RJ, Zucca FA, Duyn JH, Crichton RR, Zecca L. The role of iron in brain ageing and neurodegenerative disorders. Lancet Neurol. 2014;13(10):1045–60.
18. Reiter RJ, Tan DX, Rosales-Corral S, Manchester LC. The universal nature, unequal distribution and antioxidant functions of melatonin and its derivatives. Mini Rev Med Chem. 2013;13(3):373–84.
19. Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: Efficacy, protocol, safety, and side effects. CNS Spectr. 2005;10(8):647–63.
20. Cermakian N, Boivin DB. The regulation of central and peripheral circadian clocks in humans. Obes Rev. 2009;10 Suppl 2:25–36.
21. Li J, Cao F, Yin HL, Huang ZJ, Lin ZT, Mao N, et al. Ferroptosis: Past, present and future. Cell Death Dis. 2020;11(2):88.
22. Doll S, Conrad M. Iron and ferroptosis: A still ill-defined liaison. IUBMB Life. 2017;69(6):423–34.

