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Research Progress on Ferroptosis in Cardiac Ganglionated Plexi in the Pathogenesis of Bradyarrhythmias: A Review

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ABSTRACT

Bradyarrhythmias, characterized by abnormally slow heart rhythms, represent a common clinical cardiac arrhythmia with complex and not fully elucidated pathogenesis. The cardiac ganglionated plexi (GP), integral components of the intrinsic cardiac autonomic nervous system, have garnered increasing attention for their critical role in modulating cardiac rhythm and arrhythmogenesis. Ferroptosis, a recently identified form of programmed cell death driven by iron-dependent lipid peroxidation, has been implicated in the pathophysiology of various cardiovascular diseases. This review comprehensively summarizes the anatomical and functional characteristics of cardiac ganglionated plexi, the core molecular mechanisms underlying ferroptosis, and the regulatory networks of ferroptosis within the cardiac autonomic nervous system. We explore the intrinsic link between ferroptosis-mediated injury of ganglion cells and the development of bradyarrhythmias, highlighting how ferroptotic processes may disrupt autonomic regulation and contribute to arrhythmic manifestations. Furthermore, potential therapeutic strategies targeting ferroptosis pathways for the prevention and treatment of bradyarrhythmias are discussed, alongside future research directions aimed at elucidating the precise molecular interactions and clinical applications. This synthesis aims to provide a foundation for advancing understanding and management of bradyarrhythmias through the lens of ferroptosis in cardiac neural regulation.

Keywords: Cardiac Ganglionated Plexi; Ferroptosis; Bradyarrhythmias; Bradycardia; Lipid Peroxidation; Autonomic Nervous Regulation

Abbreviations: GP: Ganglionated Plexi; ICNS: Intrinsic Cardiac Nervous System; GPS: Ganglionated Plexi; GP: Ganglionated Plexus; AV: Atrioventricular; VACHT: Vesicular Acetylcholine Transporter; TH: Tyrosine Hydroxylase; SA: Sinoatria; 4-HNE: 4-Hydroxynonenal; MDA: Malondialdehyde; GSH: Glutathione; TFR1: Transferrin Receptor; OH: Hydroxyl Radicals ; DMT1: Divalent Metal Transporter 1 ; Fe^{2+}: Ferrous Iron ; H_2O_2: Hydrogen Peroxide ; PUFAS: Particularly Targeting Polyunsaturated Fatty Acids; AA: Arachidonic Acid; ADA: Adrenic Acid; ACSL4: Acyl-Coa Synthetase Long-Chain Family Member 4; LPCAT3: Lysophosphatidylcholine Acyltransferase 3; LOXS: Lipoxygenases; GPX4: Glutathione Peroxidase 4; FSP1: Ferroptosis Suppressor Protein 1; DHODH: Dihydroorotate Dehydrogenase; NRF2: Nuclear Factor Erythroid 2-Related Factor 2; HO-1: Heme Oxygenase-1; 4-HNE: 4-Hydroxynonenal ; GPX4: Glutathione Peroxidase 4 ; ACSL4: Acyl-Coa Synthetase Long-Chain Family Member 4; DAMPS: Damage-Associated Molecular Patterns; ROS: Reactive Oxygen Species; HMGB1: High-Mobility Group Box 1; TNF-A: Tumor Necrosis Factor-Alpha; IL-1B: Interleukin-1 Beta; LL-VNS: Low-Level Vagus Nerve Stimulation; SOD: Superoxide Dismutase; CMR: Cardiac Magnetic Resonance; HRV: Heart Rate Variability; ECG: Electrocardiogram; AAV: Adeno-Associated Virus

Introduction

Slow heart rhythm disorders, collectively termed bradyarrhythmias, are characterized by a heart rate below 60 beats per minute and encompass conditions such as sick sinus syndrome and atrioventricular conduction block. These disorders pose significant clinical challenges due to their potential to cause syncope, heart failure, and even sudden cardiac death. Despite advances in cardiac electrophysiology and device therapy, the underlying mechanisms driving bradyarrhythmias remain incompletely understood, limiting the development of targeted therapeutic strategies. The intrinsic cardiac nervous system (ICNS), often referred to as the heart's "little brain," has emerged as a critical regulator of cardiac function, integrating autonomic inputs and modulating heart rate, conduction, and contractility. This network of ganglionated plexi (GPs) and intracardiac neurons is embedded within epicardial fat pads and exhibits remarkable neurochemical and electrophysiological diversity, enabling fine-tuned beat-to-beat control of cardiac performance. The ICNS not only mediates parasympathetic and sympathetic efferent signals but also contains afferent and local circuit neurons, facilitating complex reflexes and plasticity that adapt cardiac responses to physiological and pathological stimuli [1] Dysfunction or remodeling of the ICNS has been implicated in various cardiac pathologies, including atrial fibrillation, heart failure, and sudden cardiac death, highlighting its pivotal role in maintaining cardiac homeostasis.

Recent advances in molecular and cellular profiling techniques, such as single-cell RNA sequencing and spatial transcriptomics, have unveiled the intricate cellular heterogeneity within the ICNS. These studies have identified distinct neuronal subtypes with specialized functions, including parasympathetic Npy^+ neurons that regulate coronary perfusion and heart rate, and sympathetic $Ddah1^+$ neurons essential for electrical stability under stress. Moreover, the ICNS exhibits a rich repertoire of neuromodulators and ion channels that govern neuronal excitability and synaptic transmission, which are critical for its regulatory capacity. Electrophysiological investigations have revealed diverse firing patterns among ICNS neurons, ranging from phasic to tonic activity, reflecting their functional specialization and adaptability. The anatomical organization of the ICNS is highly conserved across species and sexes, with distinct clusters of neurons localized in predictable patterns, providing a structural basis for targeted interventions [2] Importantly, pathological conditions such as cardiomyopathy and chemotherapeutic cardiotoxicity induce morphological and functional alterations in the ICNS, including neuronal loss, inflammation, and oxidative stress, which may contribute to autonomic imbalance and arrhythmogenesis .Iron-dependent regulated cell death, termed ferroptosis, has recently been recognized as a novel mechanism contributing to cardiovascular diseases.

Unlike apoptosis or necrosis, ferroptosis is characterized by iron-catalyzed lipid peroxidation leading to cell death, and has been implicated in myocardial ischemia-reperfusion injury, heart failure, and other cardiac pathologies [1] the susceptibility of cardiac cells, including cardiomyocytes and potentially neurons within the ICNS, to ferroptosis suggests a mechanistic link between iron metabolism dysregulation and cardiac dysfunction. Emerging evidence indicates that ferroptosis in the ICNS may disrupt the delicate autonomic balance by impairing neuronal viability and function, thereby reducing heart rate variability and conduction efficiency. This disruption can precipitate or exacerbate bradyarrhythmias by compromising the intrinsic neural control of cardiac rhythm [1] Understanding the molecular pathways governing ferroptosis in cardiac neurons, including the role of lipid peroxidation, iron homeostasis, and antioxidant defenses, is crucial for elucidating its contribution to slow heart rhythm disorders. Given the central role of the ICNS in cardiac autonomic regulation and the emerging importance of ferroptosis in cardiac pathology, investigating the intersection of these fields offers promising avenues for novel therapeutic strategies. Modulating ferroptotic pathways within the ICNS could restore autonomic balance and improve outcomes in patients with bradyarrhythmias.

This review systematically examines the anatomical and functional basis of the ICNS, the molecular mechanisms underlying ferroptosis, and the current evidence linking ferroptosis in cardiac ganglion neurons to the pathogenesis of slow heart rhythm disorders. Furthermore, we discuss potential interventions targeting ferroptosis and highlight future research directions aimed at translating these insights into clinical practice. By integrating multidisciplinary findings, this article aims to provide a comprehensive perspective that advances the understanding and management of bradyarrhythmias through the lens of cardiac neurobiology and regulated cell death.

Anatomical Structure and Physiological Function of the Cardiac Ganglionated Plexus

Distribution and Composition of the Cardiac Ganglionated Plexus

The cardiac ganglionated plexus (GP), a critical component of the intrinsic cardiac nervous system (ICNS), is anatomically distributed predominantly on the atrial surfaces, around the roots of major vessels, and within the atrioventricular (AV) grooves. It is classically subdivided into four major subplexi: the right superior, right inferior, left superior, and left inferior ganglionated plexi. These clusters of neurons form a complex network embedded within epicardial fat pads, serving as localized centers for autonomic regulation of cardiac function1 Each GP contains a heterogeneous population of neuronal cell bodies, glial cells, sympathetic and parasympathetic nerve fibers, and an extensive capillary network, collectively constituting a self-contained neural regulatory unit. Immunohistochemical and transcriptomic analyses have revealed that the majority of neurons within these plexi are cholinergic parasympathetic neurons, expressing markers such as vesicular acetylcholine transporter (VAChT), but

a smaller subset of adrenergic sympathetic neurons coexists, expressing tyrosine hydroxylase (TH) [3,4] This dual innervation allows for intricate local synaptic interactions and modulation of cardiac electrophysiology.

Notably, the neuronal populations demonstrate phenotypic plasticity, with some neurons co-expressing cholinergic and catecholaminergic markers, suggesting multipotential phenotypes that may underlie neuroplasticity and adaptive responses within the GP [3] Anatomical studies have also documented significant interindividual variability in GP distribution and density; however, the right atrium and posterior wall of the left atrium consistently exhibit a higher density of ganglia compared to ventricular surfaces. This anatomical predominance aligns with the critical regulatory roles of these regions in sinoatrial (SA) and atrioventricular nodal function, positioning the GP as a pivotal modulator of heart rate and conduction [1,2] Furthermore, advanced imaging and three-dimensional mapping techniques have elucidated the complex branching and synaptic architecture within the GP, revealing extensive neurite outgrowth and synaptic density that underpin the functional complexity of this intrinsic cardiac neural network [5] Collectively, the cardiac ganglionated plexus represents a sophisticated, anatomically specialized neural hub integrating sympathetic and parasympathetic inputs to finely tune cardiac function at the local level.

Regulatory Mechanisms of the Cardiac Ganglionated Plexus on Heart Rate

The cardiac ganglionated plexus exerts a fundamental influence on heart rate regulation through its dual autonomic innervation and local reflex circuits. Parasympathetic postganglionic neurons within the GP release acetylcholine, which activates muscarinic M2 receptors on sinoatrial nodal pacemaker cells, leading to hyperpolarization and a reduction in pacemaker firing rate. This cholinergic pathway constitutes the primary effector mechanism of vagally mediated bradycardia, serving as a critical intermediary between central vagal outflow and cardiac chronotropy [1,4] Conversely, sympathetic fibers within the GP release norepinephrine, which binds to β1-adrenergic receptors on pacemaker cells, enhancing the funny current (If) and L-type calcium currents, thereby increasing pacemaker depolarization rate and heart rate. The balance between these opposing autonomic influences within the GP establishes a dynamic equilibrium essential for physiological heart rate variability [1,6] Importantly, the GP contains intrinsic local reflex circuits capable of sensing atrial pressure and chemical milieu changes, enabling rapid, beat-to-beat modulation of cardiac function independent of central input. These short-loop reflexes involve afferent sensory neurons and interneurons within the GP, facilitating immediate adjustments in heart rate and conduction velocity in response to hemodynamic demands [7] Experimental evidence indicates that excessive activation of the GP, particularly parasympathetic components, can lead to augmented acetylcholine release, prolonging refractory periods in the sinoatrial and atrioventricular nodes and slowing conduction velocity.

This mechanism underlies vagally mediated bradyarrhythmias and may contribute to pathological conditions such as sinus node dysfunction and AV block [1,8] Moreover, electrophysiological studies have demonstrated that GP neurons exhibit diverse firing patterns and synaptic plasticity, which modulate their output and influence cardiac electrophysiology. Calcium imaging in hypertensive rat models has revealed enhanced cholinergic responsiveness and prolonged calcium transients in GP neurons, correlating with increased susceptibility to arrhythmias such as atrial fibrillation, highlighting the role of GP plasticity in disease states [9] Thus, the cardiac ganglionated plexus functions as a sophisticated integrative center, orchestrating autonomic inputs and local reflexes to maintain cardiac rhythm homeostasis.

Relationship Between Cardiac Ganglionated Plexus Dysfunction and Cardiac Arrhythmias

Dysfunction of the cardiac ganglionated plexus is increasingly recognized as a critical contributor to the pathogenesis of various cardiac arrhythmias, including atrial fibrillation, sinus bradycardia, and atrioventricular conduction block. Pathological alterations such as inflammatory infiltration, fibrosis, and neuronal degeneration within the GP disrupt the delicate autonomic balance, leading to autonomic dysregulation and arrhythmogenic substrate formation [10] In models of heart failure and myocardial ischemia, the GP undergoes significant neuroplastic remodeling characterized by nerve sprouting, altered neurotransmitter expression, and heterogeneous synaptic reorganization. This remodeling enhances parasympathetic efferent signaling, which can suppress sinoatrial node automaticity and slow AV nodal conduction, thereby promoting bradyarrhythmias and conduction disturbances [1,10] Clinical interventions targeting the GP, such as radiofrequency ablation or chemical denervation, have demonstrated therapeutic efficacy in patients with atrial fibrillation complicated by bradycardia, underscoring the pathogenic role of GP hyperactivity in these conditions [11,12] However, extensive ablation, particularly in the right atrium, may induce pan-atrial denervation and profound autonomic failure, manifesting as refractory hypotension and necessitating vasopressor support, illustrating the delicate balance required in modulating GP function therapeutically [12] Furthermore, GP dysfunction-related bradycardia often presents as paroxysmal episodes closely linked to fluctuations in vagal tone, with nocturnal or resting states exacerbating the phenomenon.

Mechanistically, this involves heightened excitability and synaptic transmission within GP neurons, as evidenced by electrophysiological studies showing increased firing rates and synaptic density in patients with atrial fibrillation [1,5] The interplay between neuroinflammation, fibrosis, and altered ion channel expression within the GP further compounds autonomic imbalance, fostering arrhythmogenesis [8,10] Collectively, these findings highlight the cardiac gangli-

onated plexus as a pivotal nexus in the genesis of arrhythmias, where structural and functional derangements disrupt autonomic regulation and cardiac electrophysiological stability. Understanding these mechanisms offers promising avenues for targeted neuromodulatory therapies aimed at restoring autonomic homeostasis and preventing arrhythmia recurrence.

Core Molecular Mechanisms and Regulatory Networks of Ferroptosis

Definition and Morphological Characteristics of Ferroptosis

Ferroptosis, first coined by Dixon et al. in 2012, represents a distinct form of regulated cell death that is iron-dependent and driven by the overwhelming accumulation of lipid peroxides, setting it apart morphologically and biochemically from apoptosis, necrosis, and autophagy. Morphologically, ferroptotic cells exhibit characteristic mitochondrial alterations observable under electron microscopy, including mitochondrial shrinkage, reduction or loss of mitochondrial cristae, and increased mitochondrial membrane density, while the nuclear morphology remains relatively intact without the formation of classical apoptotic bodies. These features underscore the unique subcellular damage pattern that differentiates ferroptosis from other cell death modalities. Biochemically, ferroptosis is hallmarked by elevated intracellular iron levels, significant accumulation of lipid peroxidation products such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), and depletion of the antioxidant glutathione (GSH). These biochemical markers serve as reliable indicators for the identification and quantification of ferroptosis in various experimental contexts. Unlike apoptosis, which relies on caspase activation, ferroptosis is executed primarily through the accumulation of phospholipid hydroperoxides that, upon reaching a critical threshold, induce plasma membrane rupture and release of intracellular contents, leading to cell death.

This lipid peroxide-driven membrane damage is a pivotal event in ferroptosis, highlighting the centrality of oxidative lipid damage in its execution. The distinct morphological and biochemical hallmarks of ferroptosis have been consistently observed across diverse cell types and pathological conditions, reinforcing its recognition as a unique programmed cell death pathway with significant implications in disease pathogenesis and therapy [13,14] Understanding these defining features is crucial for developing targeted interventions that modulate ferroptosis in clinical settings.

Role of Iron Metabolism and Lipid Peroxidation in Ferroptosis

The initiation and progression of ferroptosis critically depend on the intricate regulation of intracellular iron homeostasis and lipid peroxidation processes. Cellular iron balance is tightly controlled by a network of proteins including iron transporters such as transferrin receptor 1 (TfR1) and divalent metal transporter 1 (DMT1), iron storage proteins like ferritin heavy and light chains, and iron export proteins such as ferroportin. Dysregulation leading to iron overload is a prerequisite for ferroptosis, as excess ferrous iron (Fe^{2+}) catalyzes the Fenton reaction, generating highly reactive hydroxyl radicals (•OH) from hydrogen peroxide (H_2O_2). These radicals initiate and propagate chain reactions of lipid peroxidation, particularly targeting polyunsaturated fatty acids (PUFAs) esterified in membrane phospholipids, thereby compromising membrane integrity and cellular viability. The primary substrates for lipid peroxidation in ferroptosis are membrane phospholipids containing esterified arachidonic acid (AA) and adrenic acid (AdA), which are incorporated into phospholipids by the enzymatic actions of acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3). These enzymes facilitate the enrichment of peroxidation-susceptible PUFAs in membranes, sensitizing cells to ferroptotic death. Additionally, lipoxygenases (LOXs) and cytochrome P450 reductases contribute to the initiation and amplification of lipid peroxidation by enzymatically oxidizing PUFA-containing phospholipids.

Counteracting this oxidative cascade, the reduced form of coenzyme Q10 (ubiquinol) acts as an endogenous radical-trapping antioxidant, mitigating lipid peroxidation and thereby inhibiting ferroptosis. The balance between iron-mediated oxidative stress and antioxidant defenses determines the susceptibility of cells to ferroptosis, underscoring the pivotal roles of iron metabolism and lipid peroxidation in this cell death pathway. Therapeutic strategies targeting these processes, such as iron chelation or inhibition of lipid peroxidation enzymes, hold promise for modulating ferroptosis in various diseases [14-16].

Key Regulatory Pathways of Ferroptosis

Ferroptosis is governed by a complex regulatory network with several critical pathways modulating its induction and suppression. Central to ferroptosis inhibition is the system Xc^--GSH-GPX4 axis, where system Xc^-, a heterodimeric cystine/glutamate antiporter composed of SLC7A11 and SLC3A2 subunits, mediates cystine uptake essential for glutathione (GSH) biosynthesis. GSH serves as a substrate for glutathione peroxidase 4 (GPX4), a selenoenzyme that reduces toxic phospholipid hydroperoxides to non-toxic lipid alcohols, thereby preventing lipid peroxidation and ferroptotic cell death. Loss of GPX4 activity, whether by genetic deletion or pharmacological inhibition (e.g., RSL3), leads to unchecked lipid peroxide accumulation and ferroptosis, whereas GPX4 overexpression confers resistance. Parallel to this, ferroptosis suppressor protein 1 (FSP1, also known as AIFM2) constitutes a GPX4-independent defense mechanism by localizing to the plasma membrane and reducing coenzyme Q10 (CoQ10) via NAD(P)H, which acts as a lipophilic antioxidant to inhibit lipid peroxidation. Additionally, dihydroorotate dehydrogenase (DHODH) operates within the mitochondrial inner membrane to reduce CoQ10, providing mitochondrial-specific protection against ferroptosis. At the transcriptional level, nuclear factor erythroid 2-related factor 2

(Nrf2) orchestrates the expression of multiple antioxidant genes including SLC7A11, GPX4, and heme oxygenase-1 (HO-1), forming a transcriptional network that enhances cellular resistance to ferroptosis. Tumor suppressors such as p53 and BAP1 further modulate ferroptosis by repressing SLC7A11 expression or activating pro-ferroptotic genes like SAT1 and GLS2, thereby promoting ferroptotic cell death. This multilayered regulatory framework integrates metabolic, enzymatic, and transcriptional controls to finely tune ferroptosis sensitivity, offering multiple potential targets for therapeutic intervention in diseases where ferroptosis plays a pathogenic or protective role [17-19].

The Association Between Ferroptosis in the Cardiac Ganglionated Plexus and Bradyarrhythmias

Evidence of Ferroptosis Occurrence in Cardiac Ganglionated Plexus

Emerging experimental data from various animal models of cardiac pathology such as myocardial ischemia, heart failure, and diabetic cardiomyopathy provide compelling evidence for the occurrence of ferroptosis within the cardiac ganglionated plexus (GP). Immunohistochemical analyses consistently reveal significant accumulation of lipid peroxidation products, notably 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), localized specifically in the GP regions, indicating active lipid peroxidation processes within ganglion cells. These findings underscore the susceptibility of intrinsic cardiac neurons to oxidative damage mediated by iron-dependent lipid peroxidation, a hallmark of ferroptosis. Ultrastructural examination via transmission electron microscopy in bradycardic animal models further corroborates these observations by demonstrating classical ferroptotic morphological features in GP neurons, including mitochondrial shrinkage, loss of cristae, and membrane rupture. Complementary histochemical staining using Perls' Prussian Blue confirms increased iron deposition within these neurons, reinforcing the notion of iron overload as a critical trigger for ferroptosis in the cardiac autonomic nervous system. At the molecular level, protein expression profiling reveals a significant downregulation of glutathione peroxidase 4 (GPX4) and the cystine/glutamate antiporter subunit SLC7A11, both essential for cellular antioxidant defense against lipid peroxidation.

Concurrently, there is an upregulation of acyl-CoA synthetase long-chain family member 4 (ACSL4) and transferrin receptor 1 (TfR1), which facilitate lipid remodeling and iron uptake respectively, thereby promoting ferroptotic pathways. These molecular alterations collectively suggest an aberrant activation of ferroptosis signaling cascades within the cardiac GP under pathological conditions associated with bradyarrhythmias. Notably, glial cells within the cardiac GP exhibit heightened sensitivity to ferroptotic stimuli; their death leads to the release of pro-inflammatory cytokines and damage-associated molecular patterns (DAMPs), which exacerbate neuronal injury and disrupt autonomic regulation. This glial contribution to ferroptosis-induced neuroinflammation highlights a complex interplay between neuronal and non-neuronal cells in the pathogenesis of cardiac autonomic dysfunction. Taken together, these multi-level lines of evidence—from biochemical markers, ultrastructural changes, iron accumulation, to molecular signaling—strongly support the presence and pathological relevance of ferroptosis in the cardiac ganglionated plexus, implicating it as a pivotal mechanism underlying slow heart rhythm disorders [14,20,21].

Mechanisms by which Ferroptosis Leads to Cardiac Ganglionated Plexus Dysfunction

Ferroptosis-induced damage within the cardiac ganglionated plexus (GP) disrupts its functional integrity through several interrelated mechanisms that culminate in impaired autonomic regulation of cardiac rhythm. Central to this process is the iron-dependent lipid peroxidation that compromises neuronal plasma membrane integrity, particularly affecting the lipid bilayer essential for maintaining electrophysiological properties. The resultant membrane damage impairs the generation and propagation of action potentials, thereby reducing neuronal excitability and synaptic transmission efficiency within the GP. This electrophysiological disruption manifests as diminished ganglion cell responsiveness and impaired neurotransmitter release, notably acetylcholine, which is critical for parasympathetic modulation of heart rate. The depletion or inhibition of glutathione peroxidase 4 (GPX4), a key ferroptosis regulator, exacerbates this process by permitting unchecked lipid peroxidation and triggering mitochondrial dysfunction. Mitochondrial impairment is characterized by decreased membrane potential, reduced ATP synthesis, and increased reactive oxygen species (ROS) production, all of which compromise neuronal energy metabolism and neurotransmitter biosynthesis. Consequently, acetylcholine synthesis and release are directly affected, further attenuating parasympathetic output.

Additionally, ferroptotic cell death leads to the liberation of damage-associated molecular patterns (DAMPs) such as high-mobility group box 1 (HMGB1), extracellular ATP, and mitochondrial DNA. These molecules activate surrounding glial cells, inducing a pro-inflammatory milieu through secretion of cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β). This neuroinflammation amplifies neuronal injury via paracrine signaling, creating a vicious cycle of damage within the GP microenvironment. The cumulative effect of neuronal loss and functional decline disrupts the delicate balance between sympathetic and parasympathetic innervation, often resulting in parasympathetic predominance or impaired postganglionic signal conduction. This autonomic imbalance manifests clinically as reduced sinoatrial node pacing frequency and slowed atrioventricular conduction, hallmarks of bradyarrhythmias. Thus, ferroptosis not only causes direct neuronal death but also initiates secondary inflammatory and metabolic disturbances that collectively impair cardiac autonomic ganglion function, providing a mechanistic link between ferroptotic processes and the pathogenesis of slow heart rhythm disorders [14,20,21].

Evidence of Ferroptosis in Animal Models of Bradyarrhythmia

Experimental animal models of bradyarrhythmia have yielded robust evidence implicating ferroptosis as a key pathological mechanism within the cardiac ganglionated plexus (GP). In a widely used isoproterenol-induced myocardial injury model, mice exhibit significant bradycardia accompanied by elevated iron content and increased lipid peroxidation markers within the cardiac GP. Molecular analyses reveal downregulation of GPX4 and upregulation of ferroptosis-promoting proteins, confirming activation of ferroptotic pathways in this context. Similarly, high-fat diet-induced obesity models demonstrate sinus bradycardia concomitant with ferroptotic features in GP neurons, suggesting that metabolic dysregulation can precipitate autonomic dysfunction via ferroptosis. These findings highlight the susceptibility of cardiac autonomic neurons to ferroptotic injury under systemic metabolic stress. Functional studies using isolated Langendorff-perfused hearts further substantiate the causal role of ferroptosis: administration of the ferroptosis inducer Erastin leads to marked reductions in heart rate and prolongation of atrioventricular conduction time, effects that are reversed by the ferroptosis inhibitor Ferrostatin-1. This pharmacological evidence underscores the direct impact of ferroptosis on cardiac electrophysiology mediated through intrinsic cardiac autonomic pathways.

Moreover, aging mouse models reveal a progressive accumulation of ferroptotic damage within the cardiac GP correlating with the onset of age-related bradyarrhythmias, implicating ferroptosis as a contributor to autonomic decline in senescence. Collectively, these animal studies provide convergent biochemical, electrophysiological, and pharmacological data supporting ferroptosis as a mechanistic driver of cardiac autonomic ganglion injury and consequent slow heart rhythm disorders. This body of evidence not only elucidates the pathophysiological underpinnings of bradyarrhythmias but also identifies ferroptosis as a potential therapeutic target for intervention in autonomic-related cardiac dysfunction [14,20,21].

Strategies Targeting Cardiac Ganglionated Plexi Ferroptosis for the Prevention and Treatment of Bradyarrhythmias

Potential Application of Iron Chelators in Bradyarrhythmias

Iron chelators such as deferoxamine and deferiprone have demonstrated significant potential in mitigating bradyarrhythmias by targeting ferroptosis mechanisms within cardiac ganglionated plexi (GP). These agents effectively reduce intracellular labile iron pools, thereby inhibiting the Fenton reaction that catalyzes the generation of reactive oxygen species (ROS) and initiates lipid peroxidation—a hallmark of ferroptosis. Experimental evidence from cardiovascular disease models underscores the cardioprotective effects of iron chelation, where deferoxamine notably decreases 4-hydroxynonenal (4-HNE) levels, a lipid peroxidation biomarker, within the cardiac GP of bradycardia models. This reduction correlates with restoration of glutathione peroxidase 4 (GPX4) expression, a critical enzyme that detoxifies lipid hydroperoxides and suppresses ferroptosis, ultimately improving heart rate parameters and atrioventricular conduction function. The therapeutic efficacy of iron chelators exhibits a dose-dependent profile; however, excessive iron depletion risks impairing iron-dependent enzymes such as mitochondrial respiratory chain complexes, which are essential for cellular energy metabolism. Therefore, optimizing dosing regimens to achieve precise iron homeostasis without compromising mitochondrial function is paramount. Emerging oral iron chelators like deferasirox offer advantages over traditional agents due to superior bioavailability and enhanced tissue penetration, potentially enabling more effective targeting of cardiac GPs.

These properties suggest deferasirox and similar compounds could provide improved clinical outcomes in managing slow arrhythmias by attenuating ferroptosis-mediated neuronal injury within the cardiac autonomic nervous system. Nonetheless, clinical translation requires rigorous evaluation of safety, pharmacokinetics, and long-term effects on cardiac autonomic regulation. Overall, iron chelation represents a promising strategy to modulate iron-driven oxidative stress and ferroptosis in cardiac GPs, offering a novel avenue for therapeutic intervention in bradyarrhythmias associated with autonomic dysfunction [14,22,23].

GPX4 Activation and Lipid Peroxidation Inhibition Strategies

Targeting the execution phase of ferroptosis through activation of glutathione peroxidase 4 (GPX4) and suppression of lipid peroxidation offers a compelling approach to protect cardiac ganglionated plexi (GP) neurons from oxidative damage implicated in slow arrhythmogenesis. Lipophilic antioxidants such as Ferrostatin-1 and Liproxstatin-1 have been shown to effectively scavenge lipid peroxyl radicals, thereby halting the propagation of lipid peroxidation and ferroptotic cell death. Their cardioprotective effects have been validated in myocardial ischemia-reperfusion injury models, where they reduce infarct size and preserve cardiac function. Pharmacological enhancement of GPX4 expression or enzymatic activity, for instance via selenium supplementation, bolsters the intrinsic antioxidant defenses of GP neurons, restoring their resilience against ferroptosis-inducing stimuli. Vitamin E (α-tocopherol), a natural lipid-soluble antioxidant, integrates into cellular membranes to terminate lipid peroxidation chain reactions. In vitro studies using GP neuron cultures demonstrate that vitamin E effectively prevents Erastin-induced ferroptosis, underscoring its potential utility in maintaining GP neuronal integrity. Importantly, combinatorial therapy employing iron chelators alongside radical-trapping antioxidants may exert synergistic effects by concurrently inhibiting ferroptosis initiation and execution phases. This dual blockade could provide robust neuroprotection within cardiac GPs, thereby mitigating the development of bradyarrhythmias linked to autonomic dysregulation.

However, the clinical application of these strategies necessitates careful consideration of pharmacodynamics, tissue distribution, and potential off-target effects. Future research should focus on optimizing delivery systems to enhance bioavailability and targeting specificity to cardiac autonomic structures. Collectively, GPX4 activation and lipid peroxidation inhibition represent promising therapeutic modalities to counteract ferroptosis-mediated neuronal injury in the cardiac autonomic nervous system, with significant implications for managing slow heart rhythm disorders [14,22,24].

Combined Strategies of Autonomic Nervous Regulation and Ferroptosis Intervention

Integrating autonomic nervous system modulation with ferroptosis-targeted interventions constitutes a novel and multifaceted therapeutic paradigm for slow arrhythmias associated with cardiac ganglionated plexi (GP) dysfunction. Low-level vagus nerve stimulation (LL-VNS) has been demonstrated to attenuate inflammation and oxidative stress within cardiac GPs, potentially through upregulation of the nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathway, which orchestrates endogenous antioxidant responses and may indirectly suppress ferroptosis. This neuromodulatory approach offers a non-pharmacological means to restore autonomic balance and protect GP neurons from ferroptotic injury. Additionally, radiofrequency ablation of cardiac GPs has shown efficacy in improving heart rate control in patients with bradycardia complicated by atrial fibrillation, likely by eliminating hyperactive GP neurons. However, excessive ablation risks irreversible autonomic denervation, underscoring the need for precise targeting. Exercise training enhances intrinsic cardiac autonomic function by upregulating antioxidant enzymes such as GPX4 and superoxide dismutase (SOD), thereby reducing GP susceptibility to ferroptosis. This physiological intervention complements pharmacological strategies by reinforcing endogenous defense mechanisms. Cutting-edge targeted drug delivery systems, including nanoparticle carriers and GP-specific peptide conjugates, enable localized administration of ferroptosis inhibitors with high efficiency and minimal systemic toxicity.

Such precision medicine approaches hold promise for selectively mitigating ferroptotic damage within cardiac GPs while preserving overall autonomic function. Collectively, combining autonomic modulation techniques with ferroptosis inhibition strategies offers a synergistic framework to address the complex pathophysiology of slow arrhythmias, paving the way for innovative and personalized therapeutic options [22,25-27].

Interventions Targeting Upstream Signaling Pathways of Ferroptosis

Intervening at the upstream regulatory nodes of ferroptosis signaling pathways presents a strategic opportunity to prevent cardiac ganglionated plexi (GP) neuronal death and consequent slow arrhythmias. Activation of the Nrf2 pathway, achievable through agents such as sulforaphane and dimethyl fumarate, induces transcriptional upregulation of key ferroptosis defense genes including GPX4, SLC7A11, and heme oxygenase-1 (HO-1). This enhances the intrinsic antioxidative capacity of GP neurons, fortifying them against iron-catalyzed lipid peroxidation. Modulation of the tumor suppressor p53 pathway offers another layer of control; inhibiting p53's pro-ferroptotic functions or promoting transcription of its anti-ferroptotic targets can recalibrate ferroptosis susceptibility. Several small molecules targeting this axis are currently under preclinical evaluation, highlighting translational potential. Regulating acyl-CoA synthetase long-chain family member 4 (ACSL4) expression or activity reduces the incorporation of polyunsaturated fatty acids into membrane phospholipids, thereby limiting substrates for lipid peroxidation. ACSL4-specific inhibitors like Triacsin C have demonstrated efficacy in ferroptosis suppression, suggesting applicability in cardiac GP protection. Furthermore, mitochondria-targeted antioxidants such as MitoQ and MitoTEMPO selectively scavenge mitochondrial reactive oxygen species (ROS), preserving mitochondrial integrity and disrupting the positive feedback loop between mitochondrial dysfunction and ferroptosis. By safeguarding mitochondrial function, these agents mitigate a critical source of oxidative stress within GP neurons. Collectively, targeting these upstream signaling pathways offers a comprehensive approach to modulate ferroptosis at multiple regulatory checkpoints, thereby preserving cardiac autonomic neuronal function and preventing bradyarrhythmogenic remodeling [14,28,29].

Research Prospects and Future Directions

Discovery and Validation of Cardiac Ganglionated Plexus Ferroptosis-Specific Biomarkers

Currently, there is a significant gap in the identification of specific biomarkers that accurately reflect ferroptosis within the cardiac ganglionated plexus (GP). Traditional systemic or tissue markers such as serum or tissue levels of 4-hydroxynonenal (4-HNE), malondialdehyde (MDA), and ferritin, while indicative of oxidative stress and iron metabolism, lack the spatial specificity to precisely quantify ferroptotic activity localized to the GP. This limitation underscores the urgent need to develop GP tissue-specific ferroptosis detection indices to enable early and accurate assessment of ferroptosis in this critical autonomic cardiac structure. Cutting-edge single-cell transcriptomics and spatial transcriptomics technologies offer promising avenues to dissect the heterogeneity of cellular responses within the GP, which comprises neurons, glial cells, and vascular endothelial cells. These approaches can unravel cell type-specific ferroptosis regulatory molecules and pathways, thereby facilitating the discovery of novel biomarkers with high specificity to GP ferroptosis. Moreover, proteomic and lipidomic analyses of GP tissue hold potential for identifying functionally relevant ferroptosis markers, such as unique oxidized phospholipid species that are pivotal in lipid peroxidation-driven cell death. These molecular signatures could serve as sensitive tools for early detection and dynamic monitoring of ferroptosis progression in the GP.

The integration of these multi-omics strategies will not only enhance our understanding of ferroptosis at the cellular and molecular levels within the GP but also provide a molecular toolkit for translational applications, including diagnostic biomarker development and therapeutic target identification. Ultimately, the establishment of GP-specific ferroptosis biomarkers will be instrumental in advancing precision medicine approaches for slow-onset cardiac arrhythmias linked to autonomic dysfunction mediated by GP ferroptosis [14,30,31].

Translational Research on Cardiac Ganglionated Plexus Ferroptosis and Clinical Bradyarrhythmias

The current evidence linking ferroptosis within the cardiac ganglionated plexus (GP) to slow-onset bradyarrhythmias predominantly stems from in vitro cellular and in vivo animal models, necessitating robust validation in large-scale clinical cohorts. To bridge this translational gap, it is imperative to correlate GP ferroptosis-associated biomarkers with clinical parameters such as the severity of bradycardia and patient prognosis. Non-invasive imaging modalities, particularly cardiac magnetic resonance (CMR) T2* imaging, offer a promising approach to quantify myocardial and GP iron deposition, providing an imaging biomarker for iron overload-related arrhythmogenic substrates. This technique could facilitate early diagnosis and risk stratification of patients predisposed to ferroptosis-mediated bradyarrhythmias. Complementarily, electrocardiographic analyses, including heart rate variability (HRV) and electrocardiogram (ECG) variability metrics, serve as indirect indicators of cardiac autonomic nervous system function. When integrated with biochemical assays measuring iron metabolism and oxidative stress markers, these parameters could form a multidimensional risk prediction model for bradycardia. Furthermore, retrospective and prospective clinical studies evaluating the efficacy of iron chelators and antioxidants in modulating heart rate recovery and clinical outcomes in patients with slow arrhythmias are critical. Such investigations will provide evidence-based guidance for therapeutic interventions targeting ferroptosis pathways within the GP. This translational research framework, combining advanced imaging, electrophysiological assessment, molecular biomarker evaluation, and clinical trials, is essential to validate the pathogenic role of GP ferroptosis in human bradyarrhythmias and to develop targeted treatment strategies [14,32,33].

Novel Drug Development and Delivery Strategies Targeting GP Ferroptosis

Given the localized nature of ferroptosis within the cardiac ganglionated plexus (GP), innovative drug delivery systems that achieve high local drug concentrations while minimizing systemic exposure are critical. Targeted delivery platforms such as epicardial sustained-release patches and ultrasound-targeted microbubble-mediated delivery offer promising strategies to concentrate ferroptosis inhibitors or modulators directly within the GP region. These approaches could enhance therapeutic efficacy and reduce off-target toxicities. Gene therapy modalities, including adeno-associated virus (AAV)-mediated overexpression of key ferroptosis regulators like glutathione peroxidase 4 (GPX4) or nuclear factor erythroid 2-related factor 2 (Nrf2), hold potential for long-term and stable GP-specific anti-ferroptotic effects. Such strategies are particularly promising in genetic models of bradyarrhythmia where ferroptosis contributes to pathogenesis. High-throughput small molecule screening platforms enable the identification of novel ferroptosis inhibitors with multi-target capabilities, potentially allowing simultaneous modulation of multiple ferroptotic signaling pathways to enhance therapeutic outcomes and overcome drug resistance. Additionally, advances in organoid and organ-on-chip technologies incorporating human GP neurons provide physiologically relevant in vitro models to accelerate drug screening and improve the predictive accuracy of clinical efficacy. These integrated drug development and delivery innovations are poised to transform the therapeutic landscape for GP ferroptosis-related slow arrhythmias by enabling precise, effective, and personalized interventions [30,31].

Multidisciplinary Research to Deepen Understanding of GP Ferroptosis Mechanisms

The intricate interplay between neural biology and iron metabolism within the cardiac ganglionated plexus (GP) necessitates a multidisciplinary research approach to elucidate the unique characteristics of GP neuronal iron handling and their differential susceptibility to ferroptosis. Integrating computational biology and systems biology methodologies can facilitate the construction of high-throughput network models of GP ferroptosis signaling pathways, enabling simulation of dynamic responses under various therapeutic interventions and guiding mechanistic studies and drug target identification. Bioinformatics analyses that integrate multi-omics datasets—including genomics, epigenomics, transcriptomics, and metabolomics—with clinical phenotypes can uncover genetic predispositions and regulatory modules driving GP ferroptosis. Furthermore, aging biology research highlights that dysregulated iron metabolism and ferroptosis accumulation are central features of tissue senescence. Investigating the crosstalk between GP ferroptosis and cardiac aging processes may reveal shared mechanisms underlying age-related bradyarrhythmias, providing insights into comorbidities in elderly populations. This multidisciplinary convergence will not only deepen mechanistic understanding but also foster the development of innovative diagnostic and therapeutic strategies targeting GP ferroptosis in the context of cardiac autonomic dysfunction and aging [14,34,35].

Interactions Between Ferroptosis and Other Cell Death Modalities in the Cardiac Ganglionated Plexus

Within the pathological milieu of the cardiac ganglionated plexus (GP), neurons may concurrently undergo multiple forms of regulated cell death, including ferroptosis, apoptosis, necroptosis, and pyroptosis, with complex crosstalk and regulatory interplay among these pathways. Lipid peroxidation products generated during ferroptosis

can activate the NLRP3 inflammasome, triggering pyroptosis and the release of pro-inflammatory cytokines, which in turn exacerbate ferroptotic damage, establishing a deleterious positive feedback loop. Autophagy plays a dual role in GP neuronal ferroptosis; moderate autophagic activity facilitates the clearance of damaged mitochondria and ferritin, thereby mitigating ferroptosis, whereas excessive autophagy leads to organelle depletion and cell death. Understanding the molecular switches and conversion mechanisms governing the balance and transitions between these cell death pathways is critical. Such insights will inform the rational design of combinatorial therapeutic strategies that simultaneously target multiple death modalities, offering comprehensive protection against GP neuronal injury and dysfunction. This integrated approach holds promise for effective prevention and treatment of GP-related slow arrhythmias by addressing the multifaceted nature of neuronal cell death [14,36,37].

Conclusion

The intricate role of the cardiac ganglionated plexus (GP) as a pivotal hub in autonomic regulation of heart rate underscores its critical importance in maintaining cardiac rhythm stability. From an expert perspective, the emerging recognition of ferroptosis—a regulated form of cell death characterized by iron accumulation, lipid peroxidation, and GPX4 inactivation—as a central mechanism driving GP neuronal injury represents a significant paradigm shift in understanding the pathogenesis of bradyarrhythmias. This novel insight bridges previously disparate pathological conditions such as ischemia, inflammation, metabolic disturbances, and aging, all of which converge on the activation of ferroptotic pathways within the cardiac autonomic nervous system, culminating in autonomic imbalance and heart rate reduction. Balancing the diverse research perspectives, it is evident that ferroptosis does not act in isolation but rather interacts intricately with other cell death modalities and molecular signaling networks. This complexity necessitates a nuanced approach to interpreting experimental findings, where ferroptosis is viewed as a common pathological denominator that integrates multiple upstream stressors affecting GP neurons. The therapeutic implications are profound: targeting ferroptosis through iron chelation, GPX4 activation, lipid peroxidation inhibition, and modulation of the Nrf2 antioxidant pathway has demonstrated promising efficacy in preclinical models, offering a compelling avenue for intervention in slow heart rate disorders.

However, translating these findings into clinical practice requires careful consideration of the specificity and sensitivity of ferroptosis biomarkers, the heterogeneity of patient populations, and the potential off-target effects of ferroptosis modulators. Future research must prioritize the identification of precise molecular signatures of GP ferroptosis to enable early diagnosis and targeted therapy. Moreover, the development of advanced drug delivery systems capable of selectively modulating ferroptotic pathways within the cardiac autonomic nervous system will be crucial for maximizing therapeutic benefit while minimizing systemic toxicity.

Interdisciplinary collaboration will be instrumental in advancing this field, integrating insights from molecular biology, cardiology, neurology, pharmacology, and bioengineering to construct a comprehensive framework for understanding and manipulating ferroptosis in cardiac autonomic regulation. Such synergy will facilitate the refinement of clinical intervention strategies, potentially transforming the management of bradyarrhythmias from symptomatic treatment to mechanism-based precision medicine. In conclusion, the elucidation of ferroptosis as a key driver of GP neuronal injury and subsequent bradyarrhythmia represents a transformative development in cardiovascular neuroscience. By harmonizing diverse research findings and embracing a multidisciplinary approach, the field is poised to develop innovative diagnostic and therapeutic modalities that address the root causes of slow heart rate disorders. This progress holds promise not only for improving patient outcomes and quality of life but also for establishing a new standard of care grounded in the molecular underpinnings of cardiac autonomic dysfunction.

Ethics Approval and Informed Consent

Not applicable.

Consent for Publication

The authors confirm that patient consent is not applicable to this article.

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Disclosures

The authors declare no conflict of interest.

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