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Research Progress on the Mechanism of PRDX3 Regulating Ferroptosis and Cardiac Ganglion Plexus Dysfunction in Bradyarrhythmias

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ABSTRACT

Bradyarrhythmias, characterized by abnormally slow heart rates, involve complex dysfunction of the cardiac pacing and conduction system. The cardiac ganglion plexus, a key hub of cardiac autonomic regulation, is increasingly recognized for its crucial role in maintaining normal rhythm through its structural and functional integrity. Concurrently, the roles of oxidative stress and ferroptosis, a novel form of regulated cell death, in cardiovascular diseases are being elucidated. Peroxiredoxin 3 (PRDX3), a key mitochondrial antioxidant enzyme, plays a vital role in regulating cellular redox balance and inhibiting ferroptosis. This review systematically elaborates on the role of cardiac ganglion plexus dysfunction in the pathogenesis of bradyarrhythmias and explores how PRDX3 influences the survival and function of ganglion plexus cells by modulating the ferroptosis pathway. It aims to provide a new perspective for understanding the pathophysiological mechanisms of bradyarrhythmias and to establish a theoretical foundation for developing therapeutic strategies targeting the PRDX3-ferroptosis axis.

Keywords: Bradyarrhythmia; Cardiac Ganglion Plexus; Peroxiredoxin 3; Ferroptosis; Oxidative Stress; Autonomic Regulation

Abbreviations: PRDX3: Peroxiredoxin 3; GP: Ganglionated Plexi; ROS: Reactive Oxygen Species; AV: Atrioventricular; SA: Sinoatrial; ANS: Autonomic Nervous System; GPs: Ganglionated Plexi; ICNS: Intrinsic Cardiac Nervous System; DCAN: Diabetic Cardiac Autonomic Neuropathyl; SGCs: Satellite Glial Cells; NGF: Nerve Growth Factor; CAN: Cardioneuroablation; GSH: Glutathione; CVDs: Cardiovascular Diseases; ICG: Intracardiac Ganglia

Introduction

Bradyarrhythmias, including sick sinus syndrome and atrioventricular block, are common clinical arrhythmias whose prevalence increases with age, significantly impacting patients' quality of life and elevating cardiovascular risk [1]. The traditional pathophysiological understanding has centered on degenerative changes or fibrosis within the sinoatrial node, atrioventricular node, and the specialized cardiac conduction system [2]. However, emerging evidence underscores the critical role of the intrinsic cardiac autonomic nervous system, particularly the cardiac ganglionated plexi (GP) distributed around the atria and great vessel roots, in the fine-tuning of cardiac pacing and conduction [3,4]. Dysfunction or imbalance within these neural clusters, involving both neurons and glial cells, can lead to

aberrant autonomic tone output, potentially initiating or exacerbating bradyarrhythmias [5]. Concurrently, research into regulated cell death mechanisms offers a novel lens through which to view tissue injury. Ferroptosis, an iron-dependent form of cell death characterized by lethal lipid peroxidation, is increasingly implicated in the pathogenesis of various cardiovascular diseases [3,4]. Peroxiredoxin 3 (PRDX3), a mitochondrial thioredoxin-dependent peroxidase, is a core molecule responsible for scavenging mitochondrial reactive oxygen species (ROS) and maintaining cellular redox homeostasis.

Recent studies suggest that the functional state of PRDX3 may directly influence cellular susceptibility to ferroptosis, thereby participating in the survival regulation of both neuronal and cardiac cells. Therefore, a deep investigation into the role of PRDX3 in ferroptosis within cardiac GP cells and elucidation of its connection to the development of bradyarrhythmias holds significant scientific and clinical value. This review will explore this theme, progressing from the established pathophysiology of bradyarrhythmias and the anatomy of the cardiac neural axis to the mechanisms of ferroptosis and the specific protective functions of PRDX3, ultimately integrating these concepts into a coherent hypothesis linking PRDX3-ferroptosis axis dysregulation to GP dysfunction and bradyarrhythmogenesis.

Pathophysiological Basis of Bradyarrhythmias: From Traditional Mechanisms to Neuromodulation Perspectives

Structural and Functional Abnormalities of the Sinoatrial Node and Conduction System

The sinoatrial (SA) node serves as the heart's primary pacemaker, and its dysfunction is a core mechanism underlying bradyarrhythmias such as sinus bradycardia and sinus arrest. Structural abnormalities, including degenerative fibrosis or ischemic damage, can directly impair automaticity and impulse generation. Furthermore, dysfunction within the atrioventricular (AV) node or the His-Purkinje system leads to various degrees of heart block, ranging from asymptomatic conduction delays to complete AV block [6]. These conduction disturbances are often progressive and can be influenced by underlying systemic diseases, electrolyte imbalances, or inflammatory processes affecting the cardiac tissue. The evaluation of such structural and functional impairments is crucial for risk stratification and determining the need for intervention, such as permanent pacemaker implantation, particularly when they herald future symptomatic disease [6].

Anatomy and Functional Overview of the Cardiac Autonomic Nervous System

The cardiac autonomic nervous system (ANS) is a complex network that provides fine, beat-to-beat regulation of heart rate and contractility, maintaining cardiovascular homeostasis. It comprises the sympathetic and parasympathetic divisions, which exert opposing influences. The sympathetic nervous system, via neurotransmitters like norepinephrine, increases heart rate and conduction velocity, while the parasympathetic nervous system, primarily through vagal efferents and acetylcholine, decreases heart rate and slows AV nodal conduction [7]. This intricate balance is essential for normal cardiac function, and its dysregulation is a fundamental pathophysiological component in many cardiovascular diseases, including arrhythmias. The ANS integrates signals from higher brain centers, peripheral receptors, and the heart itself to modulate cardiac performance dynamically [8].

Central Role of Cardiac Ganglionated Plexi in Rhythm Regulation

Cardiac ganglionated plexi (GPs) are clusters of autonomic neurons and ganglia located within the epicardial fat pads, forming a key part of the intrinsic cardiac nervous system (ICNS). This distributed neural network acts as an integration center, processing inputs from the central nervous system and local cardiac sensory signals to modulate regional electrophysiology. The GPs play a pivotal role in the neural control of the SA and AV nodes, influencing pacemaker activity and conduction [9]. Remodeling within these plexi, involving neuroinflammation, fibrosis, and altered neuron-glia signaling, can lead to autonomic imbalance. Such neurofibrotic changes within the ICNS are increasingly recognized as contributors to arrhythmogenesis by disrupting the precise neural control necessary for stable rhythm [9].

Evidence for Neurogenic Factors in the Pathogenesis of Bradyarrhythmias

Substantial evidence implicates neurogenic mechanisms in the development of bradyarrhythmias. Conditions like diabetic cardiac autonomic neuropathy (DCAN) demonstrate how pathological processes targeting autonomic ganglia can lead to bradyarrhythmias. Studies show that inflammation and ferroptosis in stellate or superior cervical ganglia, mediated by receptors like P2Y12 and P2Y14, disrupt sympathetic and parasympathetic tone, resulting in abnormal heart rate variability and bradycardia [3,4]. Furthermore, vagally-mediated bradyarrhythmias (VMB), such as those seen in vasovagal syncope or functional AV block, occur due to paroxysmal reflex activation of the parasympathetic system, often in individuals with structurally normal hearts [10]. This highlights that bradyarrhythmias can originate from primary neural dysfunction without significant structural heart disease, supporting neuromodulation strategies like cardioneuroablation as potential therapeutic options [10].

Structure, Function, and Role of Cardiac Ganglionated Plexus in Arrhythmias

Anatomical Distribution and Cellular Composition of Cardiac Ganglionated Plexus

The intrinsic cardiac ganglionated plexus (GP) constitutes a complex network of neurons and glial cells primarily located on the epicardial surface of the atria, with key clusters found near the pulmo-

nary veins, superior vena cava, and coronary sinus ostium [11]. These ganglia serve as the final integration hubs for autonomic control, receiving inputs from both extrinsic sympathetic and parasympathetic nerves while modulating local cardiac electrophysiology. Structurally, the GP is composed of heterogeneous neuronal populations, including cholinergic and adrenergic neurons, which are intimately associated with satellite glial cells (SGCs) [12]. Early pathological conditions, such as hypertension, can induce significant structural alterations within the GP, including a reduction in neuronal number, decreased axonal diameters, and neuropathic changes in cardiac glial cells, indicating that the plexus is susceptible to remodeling from cardiovascular stressors [13].

Interaction Between Ganglionic Neurons and Glial Cells

Neurons and satellite glial cells (SGCs) within the cardiac ganglia engage in bidirectional, contact-mediated communication critical for maintaining ganglionic homeostasis and function. SGCs closely envelop neuronal somata, creating a unique microenvironment. This interaction is regulated by retrograde signaling, such as target-derived nerve growth factor (NGF), which influences neuronal expression of proteins like DNER that are essential for establishing proper neuron-SGC contacts and subsequent neuronal morphology and activity [14]. Functional studies reveal that activation of purinergic receptors, particularly P2X7 on SGCs, can trigger paracrine ATP release, which then activates neuronal P2X3 receptors, thereby modulating neuronal excitability [15]. This glial-neuronal crosstalk is a dynamic process, and its dysregulation, evidenced by increased synaptic terminal density and altered postsynaptic receptor profiles in disease states, contributes to enhanced intracardiac nervous system excitability [12].

Etiology and Manifestations of Cardiac Ganglionated Plexus Dysfunction

Dysfunction of the cardiac GP can be triggered by various factors, including systemic hypertension, myocardial ischemia, and inflammatory processes. In hypertension, the GP undergoes significant synaptic and electrophysiological plasticity, characterized by increased spontaneous postsynaptic current frequency in neurons, decreased action potential amplitude, and a shift in neuronal and glial cell populations [12]. Myocardial infarction can lead to ischemia of the epicardial nerves and ganglia, disturbing their microcirculation and resulting in chronic sympathetic activation, which forms a substrate for atrial and ventricular arrhythmias [16]. Furthermore, inflammatory conditions, such as ganglionitis evidenced by lymphocytic aggregates in the stellate ganglia, are highly prevalent in cases of sudden cardiac death, suggesting that inflammation can trigger sympathetic storms and GP dysfunction [17].

Potential Pathways of Ganglionated Plexus Dysfunction Leading to Bradyarrhythmias

Excessive vagal tone mediated by hyperactive GP neurons is a key mechanism underlying symptomatic bradyarrhythmias, such as sinus node dysfunction. The intrinsic cardiac autonomic nervous system, including the GP, directly modulates the pacemaker activity of the sinoatrial and atrioventricular nodes [11]. Dysfunction can manifest as abnormal automaticity or excessive parasympathetic inhibition of nodal cells. Cardioneuroablation (CNA), which targets the fractionated electrograms of specific GPs, has emerged as a therapeutic strategy to ameliorate bradycardia by selectively attenuating this excessive parasympathetic input. Successful application of CNA in a pediatric patient with functional sinoatrial node dysfunction, targeting GPs around the pulmonary veins and great vessels, resulted in the restoration of sinus rhythm, demonstrating a direct pathway where GP modulation can reverse bradyarrhythmic manifestations [18]. This aligns with the understanding that the GP acts as a common regulator, and its ablation can disrupt the arrhythmogenic autonomic circuitry [19].

Ferroptosis: Mechanisms, Regulation, and its Significance in Cardiovascular Diseases

Core Biochemical Characteristics and Key Regulatory Pathways (GPX4, System Xc-)

Ferroptosis is a distinct form of iron-dependent regulated cell death, characterized morphologically and mechanistically by the lethal accumulation of lipid peroxides and redox imbalance, setting it apart from apoptosis, necrosis, and autophagy [20]. The core biochemical process involves an imbalance between lipid peroxidation and its reduction, primarily regulated by the glutathione (GSH)-glutathione peroxidase 4 (GPX4) axis. System Xc-, a cystine/glutamate antiporter, is crucial for importing cystine, which is subsequently reduced to cysteine for GSH synthesis. Depletion of GSH leads to the inactivation of GPX4, the key enzyme that reduces toxic lipid hydroperoxides to harmless lipid alcohols, thereby executing ferroptosis [21]. Dysregulation of this antioxidant pathway, alongside other systems like the tetrahydrobiopterin/coenzyme Q10 system, is central to the ferroptotic process [22].

Iron Metabolism, Lipid Peroxidation, and the Execution of Ferroptosis

The execution of ferroptosis hinges on the interplay between iron metabolism and lipid peroxidation. Intracellular iron overload, often involving dysregulated homeostasis, provides the catalytic engine for ferroptosis through the Fenton reaction, which generates reactive oxygen species (ROS) [23]. These ROS, particularly in the presence of polyunsaturated fatty acids (PUFAs) in membrane phospholipids, drive iron-dependent lipid peroxidation. The accumulation of these peroxidized lipids, especially phospholipid hydroperoxides, disrupts cellular membrane integrity and mitochondrial function, ultimately leading to cell death [24]. This process represents the second stage of ferroptosis, following the initial iron overload, and is marked by the failure of cellular antioxidant systems to counteract the peroxidative damage [23].

The Role of Ferroptosis in Cardiomyocyte Death

Emerging evidence strongly implicates ferroptosis as a significant contributor to cardiomyocyte death across various cardiovascular diseases (CVDs). While apoptosis was long considered primary, ferroptosis has been shown to play a major role in pathological conditions affecting the heart [25]. The process is involved in the pathogenesis of diverse CVDs, including ischemic heart disease, myocardial infarction, ischemia/reperfusion (I/R) injury, cardiomyopathy, and heart failure [26]. The susceptibility of cardiomyocytes to ferroptosis is linked to their high metabolic demand and potential for iron dysregulation and oxidative stress. Ferroptosis contributes to the progressive deterioration of cardiac structure and function, establishing it as a critical pathological mechanism in the cardiovascular system [27].

Exploring Targeting Ferroptosis in Cardiovascular Disease Therapy

Given its pathogenic role, targeting ferroptosis presents a promising therapeutic strategy for CVDs. Pharmacological inhibition of ferroptosis, using compounds such as iron chelators, lipophilic antioxidants (e.g., ferrostatin-1, liproxstatin-1), and other specific inhibitors, has demonstrated protective effects in experimental models of cardiac I/R injury, cardiomyopathy, and heart failure [28]. These modulators aim to restore redox balance by targeting key nodes like iron metabolism, the System Xc-/GSH/GPX4 axis, and lipid peroxidation pathways. However, translating these potential therapies from preclinical research to clinical practice faces challenges, including the need for safer, more effective, and specific agents [29]. Ongoing research focuses on identifying novel ferroptosis-related genes and developing targeted compounds to harness this cell death pathway for therapeutic benefit in CVD management [29].

Biological Functions of PRDX3 and Its Role in Cellular Protection

Molecular Structure, Expression, and Enzymatic Properties of PRDX3

PRDX3 is a mitochondrial-specific member of the peroxiredoxin family, functioning as a key peroxidase that scavenges hydrogen peroxide (H_2O_2) within the organelle. Its exclusive mitochondrial localization positions it as a primary defender against reactive oxygen species (ROS) generated during oxidative phosphorylation. The enzyme's activity is critically regulated by post-translational modifications; for instance, deacetylation by SIRT3 at lysine residues enhances its antioxidant function, while hyperoxidation of its catalytic cysteine to sulfinic or sulfonic acid (forming $SO_2/_3$-PRDX3) can lead to its functional inactivation and aberrant translocation [30]. This structural plasticity allows PRDX3 to act not only as an antioxidant enzyme but also as a redox sensor, with its modification state serving as a specific molecular marker for cellular stress conditions such as ferroptosis [31].

The Central Role of PRDX3 in Defending Against Mitochondrial Oxidative Stress

As the main enzymatic sink for mitochondrial H_2O_2, PRDX3 occupies a central position in preserving redox homeostasis and preventing oxidative damage to mitochondrial components, including DNA, lipids, and proteins. Its protective role is fundamental for maintaining mitochondrial integrity and function. Genetic ablation of PRDX3 in various models leads to severe mitochondrial dysfunction, characterized by increased ROS levels, loss of membrane potential, and impaired respiratory capacity [32]. Conversely, enhancing PRDX3 expression or activity, such as through SIRT3-mediated deacetylation, strengthens cellular defenses, mitigates oxidative stress, and preserves mitochondrial quality control mechanisms, including dynamics and mitophagy [33]. This underscores its non-redundant role as a guardian of mitochondrial health.

Interplay Between PRDX3 and Cell Death Pathways: Apoptosis, Autophagy, and Ferroptosis

PRDX3 is a critical node at the intersection of multiple regulated cell death pathways, particularly ferroptosis. During ferroptosis, lipid peroxides trigger PRDX3 hyperoxidation, which not only inactivates its peroxidase function but also prompts its translocation to the plasma membrane where it inhibits cystine uptake, thereby exacerbating glutathione depletion and ferroptotic death [34]. This establishes hyperoxidized PRDX3 as a specific biomarker for ferroptosis [35]. Furthermore, PRDX3 interacts with key regulators of other death pathways; it can be degraded via selective autophagy, and its loss modulates susceptibility to apoptosis by influencing mitochondrial ROS and the release of pro-apoptotic factors [36]. Thus, PRDX3 functions as a dynamic switch influencing cellular fate decisions under stress.

Tissue-Specific Protective Functions of PRDX3 in the Nervous System and Cardiac Tissue

In the nervous system, PRDX3 is essential for neuronal survival, particularly in redox-vulnerable regions like the substantia nigra. Loss-of-function mutations in PRDX3 cause severe cerebellar ataxia in humans, linked to mitochondrial dysfunction, increased oxidative stress, and neuronal apoptosis [37]. Therapeutic overexpression of PRDX3 has been shown to protect dopaminergic neurons and ameliorate motor deficits in a Parkinson's disease model [38]. In the heart, PRDX3 is crucial for cardioprotection against ischemia/reperfusion injury. Its activity, regulated by the SIRT3/PRDX3 axis, alleviates mitochondrial oxidative stress and dysfunction in cardiomyocytes, thereby reducing infarct size and improving cardiac function [39]. These findings highlight PRDX3 as a vital, tissue-specific protector in organs with high metabolic demand.

The Integrated Mechanism of the PRDX3-Ferroptosis Axis in Cardiac Ganglion Plexus Functional Homeostasis and Bradyarrhythmias

Evidence of Oxidative Stress and Ferroptosis in Cardiac Ganglion Plexus Injury

Oxidative stress is a critical pathological process implicated in cardiovascular diseases and can trigger ferroptosis, a regulated cell death driven by iron-dependent lipid peroxidation [40]. While direct evidence in cardiac ganglia is limited, studies in other neural tissues provide a conceptual framework. For instance, neurovascular oxidative stress induced in transgenic mouse models leads to mitochondrial dysfunction in neurons within nodose ganglia that innervate the heart, resulting in sensory ataxia and cardiac hypertrophy [41]. This model demonstrates that targeted oxidative stress within neural components of the cardiac regulatory system can cause significant functional and structural cardiac pathology. Furthermore, oxidative stress conditions, such as those induced by hydrogen peroxide, can heighten cellular susceptibility to ferroptosis inducers, establishing a clear link between the two processes [42]. The dysfunction of intracardiac ganglia (ICG), which form the final common pathway for parasympathetic innervation, is a hallmark of cardiac autonomic imbalance seen in conditions like heart failure and diabetic cardiomyopathy [43,44]. Given that oxidative stress and ferroptosis are interconnected mechanisms contributing to neuronal damage in various neurological disorders, it is plausible that similar pathways could mediate injury to the autonomic neurons within the cardiac ganglion plexus, potentially disrupting normal cardiac rhythm regulation.

The Promoting Effect of PRDX3 Deficiency or Dysfunction on Ganglion Plexus Cell Ferroptosis

Peroxiredoxin 3 (PRDX3), a mitochondrial antioxidant protein, plays a crucial role in defending against oxidative stress and regulating ferroptosis. Its deficiency or dysfunction can significantly promote ferroptotic cell death. In models of osteoarthritis cartilage injury, the downregulation of PRDX3 expression promoted injury via the induction of oxidative stress and mitochondria-dependent ferroptosis [45]. Similarly, in ovarian cancer stem-like cells, the degeneration of PRDX3 was associated with increased reactive oxygen species (ROS) generation and reduced cell viability, linking PRDX3 dysfunction to ferroptosis susceptibility [36]. A pivotal study identified hyperoxidized PRDX3 as a specific marker for ferroptosis, noting that during this process, PRDX3 undergoes hyperoxidation, translocates to the plasma membrane, and inhibits cystine uptake, thereby exacerbating ferroptosis [31]. This mechanism was also observed in boron-induced nephrotoxicity, where hyperoxidized PRDX3 (SO2/3-PRDX3) translocated to the cell membrane, impairing cystine uptake and glutathione synthesis, which critically exacerbated ferroptosis [34]. These findings establish that loss of functional PRDX3, either through reduced expression or post-translational hyperoxidation, creates a permissive environment for ferroptosis by disrupting key antioxidant and metabolic pathways, a mechanism that could directly translate to the vulnerability of neurons within the cardiac ganglion plexus.

Molecular Details of PRDX3 Influencing Ferroptosis by Regulating Mitochondrial Function and Lipid Metabolism

PRDX3 exerts its anti-ferroptotic effects primarily through its role in maintaining mitochondrial homeostasis and influencing lipid peroxidation, the core driver of ferroptosis. As a mitochondrial peroxidase, PRDX3 is central to scavenging mitochondrial ROS, thereby protecting against the oxidative damage that initiates lipid peroxidation [36]. Its function is regulated by post-translational modifications; for example, deacetylation of PRDX3 at lysine 92 by SIRT4 was shown to inhibit ferroptosis in liver ischemia-reperfusion injury, highlighting a precise regulatory mechanism linking mitochondrial protein modification to cell death resistance [30]. Conversely, hyperoxidation of PRDX3, triggered by mitochondrial lipid peroxides, converts it from a protective enzyme into a pro-ferroptotic signal. This hyperoxidized form translocates to the plasma membrane where it directly inhibits the cystine/glutamate antiporter (system xc-), leading to glutathione depletion and loss of lipid peroxide repair capacity [31,34]. Furthermore, PRDX3 interacts with other key players in the mitochondrial antioxidant network, such as thioredoxin 2 (TRX2), to regulate cellular redox status and lipid peroxidation levels, as seen in chemoresistant small cell lung cancer [46]. Therefore, PRDX3 sits at a critical nexus, where its functional status directly determines mitochondrial redox balance and the integrity of lipid membranes, thereby governing the susceptibility of cells, including cardiac ganglion neurons, to ferroptotic demise.

Hypothetical Model of Neural Regulation Imbalance and Bradyarrhythmias Caused by PRDX3-Ferroptosis Axis Disorder

A hypothetical model can be constructed where disruption of the PRDX3-ferroptosis axis within the cardiac ganglion plexus leads to neural dysregulation and bradyarrhythmias. The intracardiac ganglia (ICG) are essential for parasympathetic control of heart rate, and their dysfunction is linked to autonomic imbalance and arrhythmogenesis [44]. In this model, pathological insults such as chronic ischemia, metabolic stress (e.g., in diabetes), or oxidative inflammation could lead to PRDX3 deficiency or hyperoxidation within ICG neurons and/or surrounding glial cells. This would impair mitochondrial antioxidant defense, leading to the accumulation of lipid peroxides and the initiation of ferroptosis. The loss of these key parasympathetic postganglionic neurons through ferroptotic death would result in a withdrawal of cardiac parasympathetic tone, a known contributor to arrhythmia susceptibility. However, an initial inflammatory or ischemic insult might also cause transient hyperexcitability and dysfunction of surviving neurons before cell death, potentially leading to erratic autonomic signaling. This could manifest as inappropriate vagal activation or failure, disrupting the normal sinus node automaticity and

atrioventricular conduction, ultimately precipitating bradyarrhythmias such as sinus bradycardia, sinus arrest, or various degrees of heart block. Supporting this, remodeling of the ICG and diminished parasympathetic tone are documented in type 2 diabetes, a condition associated with oxidative stress [44].

Thus, PRDX3-ferroptosis axis disruption represents a plausible cellular mechanism linking upstream stressors to the neuronal loss and functional impairment within the cardiac autonomic network that underlies bradyarrhythmic events.

Potential Therapeutic Prospects for Targeting PRDX3 or Ferroptosis to Intervene in Bradyarrhythmias

Targeting the PRDX3-ferroptosis axis presents a novel therapeutic strategy for preventing or treating bradyarrhythmias stemming from cardiac ganglion plexus injury. The approach could be two-pronged: enhancing PRDX3 function or directly inhibiting ferroptosis. Pharmacological agents that upregulate or stabilize PRDX3, or that inhibit its hyperoxidation, could bolster mitochondrial antioxidant defenses in autonomic neurons. For instance, the bioactive compound atractylodin was shown to inhibit ferroptosis in gastrointestinal injury by activating SIRT3 and suppressing acetylated-PRDX3, suggesting that modulating the SIRT3/PRDX3 pathway is therapeutically viable [47]. Furthermore, direct ferroptosis inhibitors such as liproxstatin-1 or ferrostatin-1 have demonstrated efficacy in protecting against ferroptosis-driven damage in various disease models, including liver and kidney injury [30,48]. These inhibitors could be deployed to shield cardiac ganglion neurons from ferroptotic death during periods of acute stress, such as myocardial infarction or cardiac surgery, which are known to trigger autonomic remodeling. Additionally, since oxidative stress is a key inducer of ferroptosis, antioxidants or Nrf2 activators that enhance cellular redox capacity may provide indirect protection by maintaining PRDX3 in its reduced, active state [42].

The development of targeted delivery systems, such as lipid nanoparticles, to deliver PRDX3-stabilizing agents or ferroptosis inhibitors specifically to the cardiac ganglionated plexi could maximize efficacy while minimizing systemic side effects, offering a precise neuromodulatory intervention to preserve autonomic homeostasis and prevent bradyarrhythmias.

Conclusion

In conclusion, the pathogenesis of bradyarrhythmias is increasingly recognized as a complex, multifactorial process extending far beyond intrinsic pacemaker cell dysfunction. This review synthesizes emerging evidence to propose a novel and compelling mechanistic axis: ferroptosis of neurons and/or glial cells within the cardiac ganglionated plexi (GP), integral hubs of cardiac autonomic regulation, as a significant contributor to autonomic imbalance and subsequent bradyarrhythmia. Central to this proposed pathway is PRDX3, a crucial mitochondrial antioxidant guardian. By scavenging peroxides, maintaining intracellular iron homeostasis, and suppressing lipid peroxidation, PRDX3 acts as a key defender against ferroptosis within the GP. Its downregulation or functional impairment may thus sensitize these critical neural clusters to ferroptotic death, disrupting autonomic tone and precipitating rhythm disturbances. From an expert perspective, this hypothesis represents a paradigm shift, bridging the fields of cardiac electrophysiology, neuroscience, and redox biology. It necessitates a balanced consideration of both the "hardware" (structural integrity of sinoatrial/atrioventricular nodes) and the "software" (neural control) of cardiac rhythm generation.

While traditional models focus on the former, the PRDX3-ferroptosis-GP axis compellingly argues for the critical importance of the latter's viability. Future research must rigorously validate this axis in vivo, utilizing specific genetic and pharmacological models to establish causality and delineate the upstream triggers (e.g., chronic inflammation, metabolic stress) and downstream effectors linking GP ferroptosis to conduction system depression. Ultimately, targeting this pathway—via ferroptosis inhibitors or PRDX3 activators—holds significant therapeutic promise. It offers a novel strategic avenue for the precision medicine of neurogenic bradyarrhythmias, potentially complementing or providing alternatives to electronic pacemaker therapy. However, a balanced approach is essential; interventions must be carefully evaluated for specificity to avoid unintended systemic consequences of modulating a fundamental cell death pathway. The journey from mechanistic insight to clinical application will require robust translational studies, but the exploration of the PRDX3-ferroptosis nexus undeniably opens a new frontier in understanding and treating rhythm disorders of neural origin.

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