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REVIEW

Mitochondrial Peroxiredoxins and Monoamine Oxidase-A: Dynamic Regulators of ROS Signaling in Cardioprotection

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Summary

An excessive increase in reactive oxygen species (ROS) levels is one of the main causes of mitochondrial dysfunction. However, when ROS levels are maintained in balance with antioxidant mechanisms, ROS fulfill the role of signaling molecules and modulate various physiological processes. Recent advances in mitochondrial bioenergetics research have revealed a significant interplay between mitochondrial peroxiredoxins (PRDXs) and monoamine oxidase-A (MAO-A) in regulating ROS levels. Both proteins are associated with hydrogen peroxide (H_2O_2), MAO-A as a producer and PRDXs as the primary antioxidant scavengers of H_2O_2. This review focuses on the currently available knowledge on the function of these proteins and their interaction, highlighting their importance in regulating oxidative damage, apoptosis, and metabolic adaptation in the heart. PRDXs not only scavenge excess H_2O_2, but also act as regulatory proteins, play an active role in redox signaling, and maintain mitochondrial membrane integrity. Overexpression of MAO-A is associated with increased oxidative damage, leading to mitochondrial dysfunction and subsequent progression of cardiovascular diseases (CVD), including ischemia/reperfusion injury and heart failure. Considering the central role of oxidative damage in the pathogenesis of many CVD, targeting PRDXs activation and MAO-A inhibition may offer new therapeutic strategies aimed at improving cardiac function under conditions of pathological load related to oxidative damage.

Key words

Mitochondria • Peroxiredoxin • Monoamine oxidase-A • Reactive oxygen species • Cardioprotective signaling

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Introduction

Mitochondrial dysfunction contributes to pathophysiological processes that lead to various neurodegenerative, metabolic, and cardiovascular diseases (CVD). One of the causes of mitochondrial derangement is the imbalance of reactive oxygen species (ROS) and reactive nitrogen species, including hydroperoxides, which causes oxidative damage [1]. Biological hydroperoxides produced by mitochondria such as hydrogen peroxide (H_2O_2), peroxynitrites, and various organic hydroperoxides are involved in regulating cellular signaling pathways when present at low, physiological levels [1,2]. ROS as signaling molecules modulate multiple processes, including cardiac contractility [3], hypertrophic responses [4], heart development [5], the pathogenesis of CVD [6], and adaptation to energy load [7,8]. However, when ROS production is excessive, it induces oxidative damage leading to mitochondrial dysfunction and cytotoxicity, as cellular macromolecules such as lipids, proteins, and DNA become damaged [9,10]. Increased oxidative damage is a major contributor to the progression of CVD, including heart failure and ischemic heart disease [11,12].

Among these, monoamine oxidases (MAO) have been described as a prominent source of ROS [13]. MAO are flavoenzymes at the outer mitochondrial membrane responsible for the oxidative deamination of catecholamines and dietary amines. They exist as two isoforms, A and B, differing in tissue distribution, substrate preference, and inhibitor specificity [14]. MAO-A is a predominant isoform in the myocardium generating H_2O_2 as a byproduct [15,16]. Under physiological conditions, antioxidant mechanisms are active, crucial for maintaining the balance of ROS levels and ensuring proper mitochondrial function. Several mitochondrial antioxidant enzymes have been identified, including manganese-dependent superoxide dismutase (MnSOD), which catalyzes the dismutation of the superoxide radical to H_2O_2. This H_2O_2 is subsequently reduced to water by mitochondrial peroxidases, such as glutathione peroxidase 1, glutathione peroxidase 4, peroxiredoxin-3 (PRDX3) and peroxiredoxin-5 (PRDX5) [17,18]. Among these, peroxiredoxins (PRDXs) are particularly effective antioxidant enzymes for regulating oxidative damage and H_2O_2-mediated intracellular signaling. Various experimental studies have highlighted the potential of PRDXs as therapeutic targets in CVD [19]. Notably, PRDX3, as a major antioxidant scavenger, can remove nearly 90 % of mitochondrial H_2O_2, thereby helping to maintain mitochondrial homeostasis [20,21].

The balance between oxidative damage and antioxidant defense plays a critical role in determining whether cardiac cells can adapt to or succumb to injury [22,23]. Therefore, understanding the interplay between MAO-A, which produces H_2O_2, and PRDXs, which act as antioxidant scavengers, is essential, particularly in the context of cardiac energetics [24,25]. This review aims to summarize current findings on the roles of PRDXs and MAO-A in cardiac health and disease, with particular focus on their mechanisms of action, functional connection, and potential as therapeutic targets for improving cardiac function under the conditions of increased energetic demand.

Mitochondrial peroxiredoxins in the heart

Function of peroxiredoxins

PRDXs are antioxidant proteins abundantly expressed in the heart, where they protect cellular components by reducing peroxides such as H_2O_2 [26,27]. They operate through a thiol-disulfide exchange mechanism. In PRDXs, a reactive cysteine (known as the "peroxidatic cysteine") is oxidized by peroxides (e.g. H_2O_2), forming a sulfenic acid. In some isoforms, this oxidized form reacts with another cysteine residue, creating a disulfide bond, which is subsequently reduced by thioredoxin or another reducing agent [28,29]. Beyond their peroxidase activity, PRDXs also function as molecular chaperones and participate in redox signaling, modulating signaling pathways that connect oxidative damage to cellular metabolism [30].

The PRDXs family includes six main isoforms – PRDX1 to PRDX6. Each of them has a specific localization and function in peroxide detoxification [31,32]. Some isoforms primarily target H_2O_2, while others also reduce organic peroxides and peroxynitrite [33]. This review focuses primarily on mitochondrial PRDXs, including PRDX3, which is exclusively localized in mitochondria, and PRDX5, which is found not only in mitochondria but also in the cytosol, in peroxisomes, and in the nucleus (Table 1).

The ability of PRDX3 to detoxify peroxides produced during the increased metabolic activity of cardiac function allows it to serve a protective role against oxidative damage, thereby preserving mitochondrial integrity [34,35].

Recent studies indicate that the overexpression of PRDX3 can stabilize mitochondrial membranes and enhance the efficiency of the electron transport chain, actively supporting mitochondrial respiration under conditions of high metabolic demands [36,37].

In addition to its protective function in various cell types, PRDX3 helps moderate inflammation, which is linked to the pathogenesis of CVD. Studies highlight the importance of PRDX3 in preventing mitochondrial oxidative damage and its involvement in regulating mitochondrial dynamics, such as fusion, fission, and mitophagy [34,38]. In PRDX3-deficient mice, the absence of this protein leads to significant mitochondrial dysfunction, characterized by cardiac hypertrophy, reduced mitophagy, and the accumulation of damaged mitochondria [39]. These findings suggest that PRDX3 not only protects against oxidative damage but also plays a role in regulating mitochondrial clearance by stabilizing phosphatase and tensin homolog-induced kinase 1 (PINK1), which is essential for mitophagy. While some studies have reported protective effects of other PRDX isoforms against atherosclerosis, the specific role of PRDX3 in atherosclerosis remains unclear. However, it may be related to its involvement in the mitophagy process mentioned earlier. Regarding to connection between

Table 1. Mitochondrial peroxiredoxins and monoamine oxidases – summary of their specific localization within the mitochondria and respective functions.

Protein	Localization	Function
PRDX3	Mitochondrial matrix	Can remove nearly 90 % of mitochondrial H_2O_2; major antioxidant scavenger [20]
PRDX5	Mitochondrial matrix, peroxisomes, cytosol, nucleus	Reduces alkyl hydroperoxides or peroxynitrite over H_2O_2; cytoprotective antioxidant enzyme [41]
MAO-A	Outer mitochondrial membrane	Catalyzes preferentially the oxidative deamination of norepinephrine and serotonin; is inhibited by clorgyline; predominant isoform in the rat heart; genetic deletion protects against I/R injury, pressure overload, and heart failure [14,16]
MAO-B	Outer mitochondrial membrane	Has major affinity for phenylethylamine and benzylamine; is inhibited by selegiline; predominant isoform in the mice heart; genetic deletion protects against oxidative damage, apoptosis, and ventricular dysfunction [14,16]

PRDX3 expression and cardioprotection, Matsushima *et al.* [40] demonstrated that overexpression of PRDX3 protected the heart from left ventricular remodeling and failure after myocardial infarction. This was confirmed by the observed reduction in key markers of myocardial infarction.

Another isoform among PRDXs that was the last-discovered in mammals is PRDX5. PRDX5 is also found in mitochondria and represents the only mammalian atypical 2-Cys PRDX. PRDX5 functions as a peroxidase, using either cytosolic thioredoxin 1 or mitochondrial thioredoxin 2 as reductants to reduce alkyl hydroperoxides or peroxynitrite with high-rate constants, whereas its reaction with H_2O_2 is more modest (Table 1). Studies have shown that PRDX5 overexpression protects cells against nitro-oxidative damage, while reduced expression makes cells more vulnerable. PRDX5 is primarily recognized as a cytoprotective antioxidant enzyme that defends against both endogenous and exogenous peroxides, whereas typical 2-Cys PRDXs primarily act as redox sensors [41].

Several studies have confirmed that PRDX5 is involved in the inhibition of inflammatory reactions [42]. PRDX5 deficiency significantly increases renal inflammation after ischemia/reperfusion (I/R) injury. Similarly, PRDX5 deficiency leads to susceptibility to high-fat-diet-induced obesity and related metabolic disorders [19]. However, the role of PRDX5 in cardioprotection still needs further clarification. In the study Andelova *et al.* [43], the stimulation of the heart's adaptation mechanisms to increased energy demand was monitored in an experimental diabetes mellitus (DM) model, with a focus on antioxidant mechanisms – specifically changes in the expression of PRDX3 and PRDX5 proteins. Dichloroacetate (DCA), a substance that serves as a metabolic modulator that simultaneously has effects on regulating ROS levels, has been used to modulate experimental DM. In mitochondrial samples isolated from the hearts of diabetic rats, an increase in PRDX3 expression was observed after DCA administration, but no changes were noted in PRDX5 expression (Fig. 1).

Interestingly, mitochondrial PRDX3 and PRDX5 function through a compensatory mechanism. This was demonstrated in a study by van der Eecken *et al.* using pig liver mitochondrial samples, where the loss of PRDX5 was associated with increased expression of PRDX3 and glutathione peroxidase 4 [17].

There are also studies on PRDX3 that have emphasized its role beyond antioxidant defense, particularly in relation to mitochondrial dysfunction. In the context of dilated cardiomyopathy (DCM), mitochondrial dysfunction is recognized as a critical factor in the disease's progression [44,45]. Proteomic analyses of cardiac tissues from DCM patients revealed significant alterations in proteins involved in energy metabolism and mitochondrial function [46,47]. One of the most notable findings was the overexpression of PRDX3 in mitochondria, which was strongly correlated

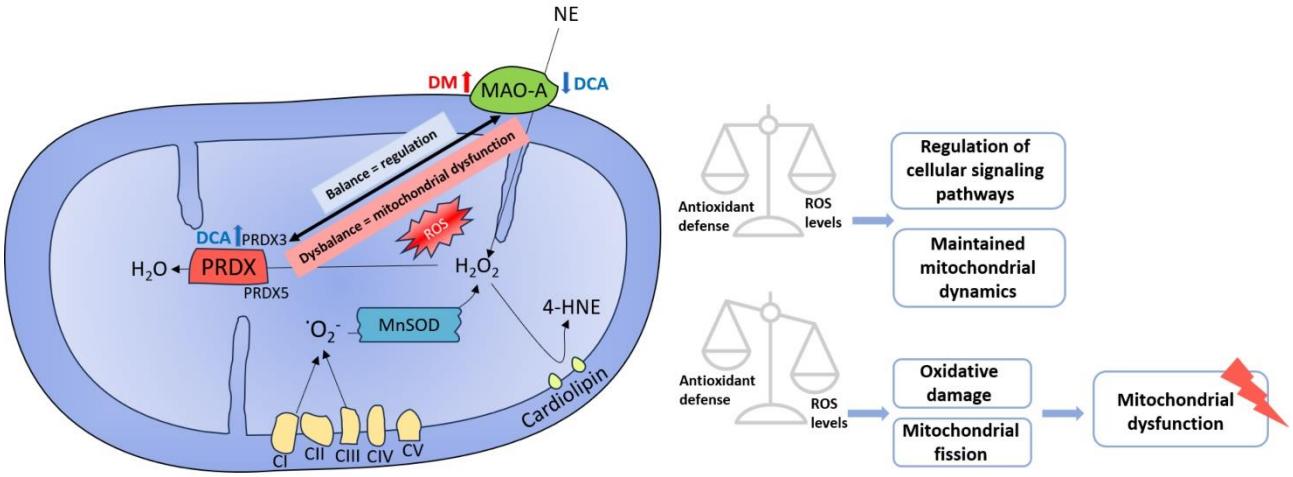

Fig. 1. The interplay between MAO-A, a producer of H_2O_2, and mitochondrial PRDXs, which act as antioxidant scavengers, is crucial in the regulation of ROS levels and in the overall maintenance of the heart's energetic balance. Increased activation of MAO-A and the generation of H_2O_2 lead to cardiolipin peroxidation and accumulation of 4-HNE inside the mitochondria. PRDXs scavenge mitochondrial H_2O_2 and help preserve mitochondrial homeostasis. When ROS levels are balanced with antioxidant mechanisms, ROS contribute to the regulation of cellular signaling pathways. However, a disbalance between antioxidant defenses and ROS levels results in oxidative damage and ultimately, mitochondrial dysfunction. Elevated MAO-A expression also promotes mitochondrial fission. In contrast, PRDX3 activation supports mitochondrial fusion, preserving both mitochondrial function and energy production. In the model of experimental DM, increased MAO-A expression can result in oxidative damage. DCA helps normalize ROS levels by reducing their excessive production due to MAO-A and enhancing PRDX3 activation under experimental DM conditions. For more details, see the text. CI-CV – respiratory chain complexes I-V; DCA – dichloroacetate; DM – diabetes mellitus; H_2O_2 – hydrogen peroxide; MAO-A – monoamine oxidase-A; MnSOD – manganese-dependent superoxide dismutase; NE – norepinephrine; PRDXs – peroxiredoxins; PRDX3 – peroxiredoxin-3; PRDX5 – peroxiredoxin-5; ROS – reactive oxygen species; 4-HNE – 4-Hydroxynonenal.

with impaired ventricular function. The overexpression of PRDX3 was associated with detrimental changes in left ventricular dimensions, including increased end-systolic and diastolic diameters, along with reduced fractional shortening and ejection fraction. This suggests that while PRDX3 plays a significant role in managing mitochondrial oxidative damage, its dysregulation in DCM may contribute to worsening cardiac function. These findings highlight the importance of PRDX3 in maintaining mitochondrial health and suggest that targeting PRDX3 could represent a potential therapeutic strategy, not only in DCM but also for other diseases characterized by mitochondrial dysfunction [48].

Given the role of PRDX3 in managing oxidative damage within the mitochondria, the potential for antioxidant-based therapies becomes particularly relevant. The application of exogenous antioxidants has been shown to reduce ROS levels in affected tissues, thereby suppressing or altering the progression of oxidative damage. However, current research is shifting towards the use of antioxidant enzymes, which are proving more effective than low-molecular-weight antioxidants. Among these enzymes, PRDXs are particularly noteworthy. For example, Sharapov *et al.* demonstrated that recombinant PRDX1 and PRDX2 are effective in preventing and treating renal I/R injury, suggesting their broader potential in mitigating oxidative damage-related in various tissues [49].

Peroxiredoxins signaling pathways

The effect of PRDXs, particularly PRDX3, has also been studied in relation to the phosphoinositide 3-kinase (PI3K)/Akt metabolic pathway, which plays a key role in regulating glucose homeostasis. In 2008, Chen *et al.* conducted a study aimed at better understanding the role of mitochondrial H_2O_2 in aging and the pathogenesis of age-related diseases. To achieve this, they generated transgenic mice that overexpress PRDX3. These mice exhibited elevated levels of PRDX3 across various tissues, with the protein being specifically localized in mitochondria [50]. In these transgenic mice, a reduction in mitochondrial H_2O_2 levels was observed, leading to increased activation of Akt, a key protein in the PI3K pathway [51]. Akt promotes glucose uptake and storage by phosphorylating glycogen synthase kinase 3 (GSK3), thereby inhibiting its activity [52]. This molecular cascade enhances insulin sensitivity and glucose metabolism [53], protecting the mice from glucose intolerance and hyperglycemia, especially under conditions such as a high-fat diet [54]. Thus, PRDX3 not

only alleviates mitochondrial oxidative damage but also has a broader impact on metabolic regulation. By reducing mitochondrial ROS levels, it indirectly activates the PI3K/Akt pathway, improving glucose metabolism and offering protection against metabolic diseases like DM [50]. These findings highlight PRDX3 as a promising therapeutic target for disorders related to oxidative damage and metabolic diseases [55].

Additionally, PRDX3 significantly influences nuclear factor erythroid 2-related factor 2 (Nrf2), a key regulator of the cellular antioxidant response [56,57]. During oxidative damage, Nrf2 is activated, leading to the upregulation of antioxidant enzymes, including PRDX3, glutathione peroxidase and superoxide dismutase [58]. The enhanced Nrf2 activity associated with elevated PRDX3 levels effectively protects cardiomyocytes from oxidative damage, presenting a potential therapeutic opportunity to harness the cardioprotective abilities of PRDXs [59].

Recent research has demonstrated that quercetin, a potent flavonoid, induces the expression of PRDX3 and PRDX5 through activation of the Nrf2/NRF1 transcriptional pathway. This mechanism was studied in trabecular meshwork cells, where quercetin upregulated PRDX3 and PRDX5, providing protection against oxidative damage. The involvement of NRF1 in this process was confirmed, as silencing NRF1 significantly reduced the expression of both PRDX3 and PRDX5. Additionally, NRF1 activation was shown to be dependent on Nrf2, indicating a coordinated antioxidant response. These findings highlight the importance of quercetin and the Nrf2/NRF1 pathway in regulating mitochondrial antioxidant defenses, expanding the therapeutic potential of PRDX3 in treating oxidative damage-related diseases, including ocular conditions such as glaucoma [60]. Overall, these insights reinforce the broader role of PRDX proteins in cellular protection and metabolic regulation.

Mitochondrial peroxiredoxins in cardioprotection

Cardioprotective strategies can preserve or improve heart function, protect the heart from damage, and reduce the risk of CVD. These approaches include e.g. adaptation to chronic hypoxia (CH) [61], various forms of acute conditioning [62], and regular exercise [63], all of which can effectively protect the heart against acute I/R injury.

Adaptation to CH is associated with increased ROS formation, which is important for the induction of a protective cardiac phenotype [64]. ROS-dependent signaling can increase the capacity of antioxidant defense systems in chronically hypoxic hearts, prevent excess oxidative damage and thus, reduce myocardial injury induced by ischemic insult [65]. PRDXs seem to be involved in CH-induced signaling as well. Zhu *et al.* demonstrated that chronic intermittent hypoxia increased PRDX5 levels in rat heart [66]. Kasparova *et al.* examined various regiments of CH, finding out that PRDX5 levels were significantly elevated in all of them [67]. According to Sabharwal *et al.*, PRDX5 operates in the mitochondrial intermembrane space, where its antioxidative capacity reduces ROS levels under the conditions of CH. By doing so, PRDX5 protects mitochondria from oxidative damage and moderates the activation of hypoxia-inducible factor 1-alpha (HIF-1α), preventing its overactivation [68].

The cardioprotective effect of PRDX3 has been investigated in hypercholesterolemic pigs exposed to chronic exercise [69]. Hypercholesterolemia reduces the expression of mitochondrial antioxidant enzymes, including PRDX3, increases mitochondrial oxidative damage, and enhances the mitochondrial permeability transition pore (mPTP) opening in the porcine myocardium. Chronic exercise training restored PRDX3 levels and reversed these detrimental alterations. In addition, Richters *et al.* showed that downregulation of MnSOD induced maladaptive cardiac hypertrophy. Regular exercise upregulation of the antioxidative defense system including PRDX3 in both wild-type and heterozygous MnSOD knockout mice [70].

Recent findings have linked PRDX3 functionality to the phenomenon of ischemic preconditioning, where a series of brief episodes of ischemia provide protection against subsequent severe ischemic event [71]. Increased expression of PRDX3 was shown to activate several intracellular signaling pathways crucial for protecting cardiomyocytes from ischemic injury [19].

PRDX3 also appears to participate in the beneficial effects of certain compounds on diabetic heart. Dekkers *et al.* showed that pretreatment with resveratrol, a compound found in red wine, reduced infarct size in diabetic hearts and increased the levels of PRDX3 and PRDX1 [72]. Similar findings were observed with a bioflavonoid quercetin in rat hearts. Quercetin treatment led to increased PRDX3 expression, not only in diabetic rats but also in control groups [35]. However, PRDX5 levels remained unchanged in both studies. These results are consistent with the findings of Chen *et al.*, which showed that mice overexpressing PRDX3 were resistant to hyperglycemia and glucose intolerance induced by a high-

fat diet [50]. PRDXs were also shown to take part in nitrate-induced cardioprotection against doxorubicin cardiotoxicity. In animals exposed to doxorubicin without a nitrate-rich diet, PRDX3 levels increased while PRDX5 remained unchanged. However, with a nitrate-rich diet, PRDX5 levels increased while the level of PRDX3 did not change compared to untreated controls [73].

Mitochondrial ROS production by monoamine oxidase-A in cardiac dysfunction

In addition to the respiratory chain, widely considered the primary source of mitochondrial ROS in the heart, the enzyme MAO-A is also a significant contributor to ROS production [74,75]. MAO-A plays a crucial role in terminating noradrenaline signaling in cardiac tissue. During noradrenaline degradation, MAO-A generates H_2O_2 as a byproduct, which contributes to oxidative damage [76]. This enzyme has been identified as a key mediator of oxidative damage and mitochondrial dysfunction in cardiac cells, linking it to various CVD, including heart failure and ischemic injury [15] (Table 1). The dual role of MAO-A in both neurotransmitter regulation and ROS production highlights its critical involvement in the pathophysiology of heart disease. This also underscores its potential as a therapeutic target for reducing ROS production directly at its mitochondrial source [77].

Increased ROS production due to elevated MAO-A expression is not only a natural consequence of aging but is also significantly exacerbated under pathological conditions such as hypertension, pressure overload, and DM [14,78]. Overexpression of MAO-A occurs at both transcriptional and post-transcriptional levels, leading to heightened oxidative damage and mitochondrial dysfunction in cardiac tissue [74].

In conditions like pressure overload, chronic MAO-A activation results in excessive ROS accumulation, contributing to maladaptive cardiac remodeling and the development of heart failure. Similarly, in diabetic cardiomyopathy, hyperglycemia-induced oxidative damage stimulates MAO-A activation, linking metabolic dysregulation to mitochondrial oxidative damage [14,78]. This overproduction of ROS overwhelms the heart's antioxidant defenses, leading to protein oxidation, lipid peroxidation, and mitochondrial DNA damage, ultimately accelerating the decline in cardiac function. Therapeutic interventions targeting MAO-A overexpression offer promising potential for reducing ROS levels and mitigating mitochondrial dysfunction, providing a novel approach to treating CVD [79].

Activation of monoamine oxidase-A and production of 4-hydroxynonenal

Excessive ROS production by MAO-A leads to the accumulation of 4-hydroxynonenal (4-HNE) within mitochondria, a highly reactive aldehyde generated as a byproduct of lipid peroxidation [80]. 4-HNE is especially harmful due to its longer half-life, allowing it to interact more extensively with cellular macromolecules [81]. By forming covalent adducts with proteins, 4-HNE modifies the structure and function of essential mitochondrial proteins, what can impair the electron transport chain, hinder ATP synthesis, and exacerbate mitochondrial function [82,83]. Furthermore, 4-HNE-induced protein adduct formation can trigger downstream effects, such as impaired calcium (Ca^{2+}) homeostasis [84], increased mitochondrial membrane permeability, and the release of pro-apoptotic factors like cytochrome c, leading to cardiomyocyte apoptosis and necrosis [85].

In mice with cardiac overexpression of MAO-A, a significant decrease in cardiolipin content, a unique phospholipid essential for the integrity and function of the inner mitochondrial membrane, was observed. This loss further contributes to mitochondrial dysfunction and the progression of cardiac pathology [15].

The study by Santin *et al.* was the first to demonstrate that MAO-A activation and the subsequent production of H_2O_2 directly led to cardiolipin peroxidation and mitochondrial accumulation of 4-HNE (Fig. 1) [84]. This peroxidation not only compromised the structural integrity of the mitochondrial membrane but also impaired the function of key mitochondrial complexes, particularly complex IV (cytochrome c oxidase), further worsening oxidative damage and mitochondrial dysfunction. Their research provided compelling evidence that 4-HNE plays a significant role in MAO-A-related ventricular dysfunction by disrupting mitochondrial bioenergetics, reducing ATP production, and increasing the heart's susceptibility to apoptosis [15].

Moreover, the accumulation of 4-HNE and cardiolipin peroxidation may also affect mitochondrial dynamics by disrupting the balance between fission and fusion processes [82]. This imbalance leads to mitochondrial fragmentation, exacerbating mitochondrial dysfunction and oxidative damage – both hallmarks of several CVD, including hypertrophy, heart failure, and ischemic injury [86]. Given the central role of MAO-A in

generating ROS and 4-HNE, targeting this enzyme or preventing cardiolipin peroxidation represents a promising therapeutic strategy for preventing and treating of mitochondrial dysfunction in CVD [87].

Proteomic and biochemical analyses have revealed that 4-HNE selectively binds to key mitochondrial proteins, including the voltage-dependent anion channel (VDAC) and the mitochondrial calcium uniporter (MCU). This interaction profoundly affects mitochondrial Ca^{2+} homeostasis, primarily by disrupting the regulation of Ca^{2+} influx into the mitochondria, particularly in response to increased MAO-A activity [84]. This dysregulation can impair mitochondrial function and contribute to cellular stress.

Increased ROS production and elevated mitochondrial Ca^{2+} levels exacerbate mitochondrial dysfunction, especially under conditions of oxidative damage. This has been well-documented in acute I/R injury, where excessive ROS and Ca^{2+} act synergistically to promote the mPTP opening. The simultaneous rise in ROS and Ca^{2+} levels not only induce mPTP opening but also impairs ATP production, causes mitochondrial swelling, and leads to the release of pro-apoptotic factors such as cytochrome c, resulting in cardiomyocyte death. This dual insult of ROS and Ca^{2+} overload is a major driver of cellular damage in CVD, further linking MAO-A activation and mitochondrial dysfunction to the progression of heart disease [88]. Targeting both ROS and Ca^{2+}, particularly by MAO-A inhibition or preventing the formation of 4-HNE adducts, presents a promising therapeutic strategy to mitigate mitochondrial dysfunction and protect the heart from I/R-induced damage [16].

Moclobemide: A promising inhibitor of monoamine oxidase-A in cardiac protection

Inhibition of MAO-A has emerged as a promising therapeutic strategy to alleviate mitochondrial dysfunction and reduce cardiac damage associated with excessive ROS production.

Moclobemide, a selective and reversible inhibitor of MAO-A, has been shown to effectively lower ROS levels and mitigate the downstream effects of mitochondrial dysfunction, particularly in the context of cardiovascular pathologies [89,90]. By inhibiting MAO-A activity, moclobemide reduces the formation of H_2O_2 and the subsequent production of 4-HNE, thereby alleviating oxidative damage and preventing the modification of mitochondrial proteins critical for Ca^{2+} homeostasis [15]. This reduction in mitochondrial Ca^{2+} overload is crucial for preventing the opening of the mPTP, preserving mitochondrial function, and preventing cardiomyocyte death.

In preclinical models, moclobemide has demonstrated protective effects against I/R injury by maintaining mitochondrial integrity, reducing oxidative damage, and improving cardiac function [14,16]. These findings suggest that MAO-A inhibition could be a valuable therapeutic strategy not only for acute cardiac events but also for chronic conditions such as heart failure, where persistent ROS production accelerates disease progression [75].

Moreover, targeting MAO-A with specific inhibitors like moclobemide opens the possibility of combination therapies that address both ROS reduction and Ca^{2+} homeostasis restoration, offering a multi-targeted approach to preserving mitochondrial function and improving outcomes in CVD [91]. Ongoing research is crucial to fully understand the long-term benefits and potential clinical applications of MAO-A inhibition in various cardiac and systemic pathologies.

Mitochondrial peroxiredoxins and monoamine oxidase-A: Roles in dynamics and signaling

Recent research has revealed a direct role of MAO-A in regulating mitochondrial dynamics. Mitochondrial dynamics – specifically, the processes of fission and fusion – are essential for maintaining mitochondrial integrity and enabling cardiomyocytes to adapt to changing conditions [92]. Increased expression of MAO-A not only causes oxidative damage but also promotes mitochondrial fission, which impairs mitochondrial function and contributes to cell apoptosis [93,94]. In contrast, upregulation of PRDX3 encourages mitochondrial fusion, preserving both mitochondrial function and energy production (Fig. 1). By facilitating fusion and mitigating oxidative damage, PRDX3 helps maintain energy efficiency and supports optimal cardiomyocyte function, even during ischemic injury [95]. This dynamic interplay between PRDXs and MAO-A highlights the importance of therapeutic strategies aimed at targeted interventions that modulate mitochondrial dynamics.

MAO-A is one of the most affected proteins in various models of heart failure in rats, as well as in pathological conditions such as DM and hypertension [16]. Proteomic analyses of cardiac mitochondria in a study by

Andelova *et al.* confirmed increased MAO-A expression in rats with experimental DM compared to healthy controls. In relation to the regulation of cardioprotective mechanisms and ROS signaling, the proteins PRDX3 and PRDX5 were also assessed in these proteomic analyses of isolated heart mitochondria. After the administration of DCA, MAO-A expression decreased in the experimental DM group, while PRDX3 expression increased, indicating a positive effect of DCA in reducing ROS production [43]. MAO-A activation has been linked to a loss of mitochondrial membrane potential [43,96]. In animals with experimental DM, increased ROS levels were associated with a decrease in membrane potential. The study by Andelova *et al.* demonstrated that DCA, combined with reduced oxygen utilization induced by experimental DM, simultaneously stimulated the antioxidant protein PRDX3 and suppressed MAO-A expression (Fig. 1). This dual effect lowered ROS production and increased mitochondrial membrane potential, bringing it closer to the levels seen in the healthy control group [43].

In terms of CH, there are various contradictory studies. It is necessary to note that these studies differ in the length of hypoxic protocols, or the animal species used. Sebastiani *et al.* showed that MAO activity and distribution appear to vary across tissues of Gulf toadfish, with mild normobaric hypoxia (up to 24 h) decreasing MAO level in the heart [97]. Maher *et al.* observed no changes in MAO activity in different regions of the goat heart exposed to hypobaric hypoxia for 10 days [98]. In contrast, exposure of spontaneously hypertensive rats (SHR) and in a conplastic SHR-mtBN strain, characterized by the selective replacement of the mitochondrial genome of SHR with that of the more ischemia-resistant Brown Norway strain, to chronic normobaric hypoxia (10 % O_2, 3 weeks) increased the expression and activity of MAO-A in both strains [99]. Dănilă *et al.* studied the effect of two MAO inhibitors, clorgyline and pargyline, on cardioprotection induced by preconditioning in isolated rat hearts. While the infarct size was comparable among control and pretreated rats, post-ischemic functional recovery was further enhanced in the presence of MAO inhibitors [100].

Conclusions

Implementing integrative therapeutic strategies that target both PRDXs activation and MAO inhibition could provide a comprehensive approach to managing oxidative damage-related CVD. Such combined therapies would enhance the heart's ability to adapt to and recover from oxidative damage. Focusing on these integrative strategies highlights the dynamic interplay between PRDXs and MAO, emphasizing their significance in developing multifaceted interventions that modulate both antioxidant defenses and mitochondrial function. Further research is needed to fully understand the mechanisms behind their interactions and how optimization of these pathways may benefit cardiac health.

The dual roles of PRDXs and MAO in regulating ROS levels and supporting energy metabolism underscore the importance of maintaining a balanced redox state for optimal cardiac function. The interaction between PRDX3 and MAO-A illustrates the potential for innovative therapeutic strategies aimed at optimizing heart health, particularly in patients at risk of cardiovascular diseases driven by oxidative damage and mitochondrial dysfunction.

Conflict of Interest

There is no conflict of interest.

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