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Review

Targeting Mitochondrial Oxidative Stress: Potential Neuroprotective Therapy for Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) is a serious central nervous system (CNS) injury disease related to hypoxia-ischemia and inflammation. It is characterized by excessive reactive oxygen species (ROS) production, oxidative damage to nerve cells, and mitochondrial dysfunction. Mitochondria serve as the primary cellular origin of ROS, wherein the electron transfer chain complexes within oxidative phosphorylation frequently encounter electron leakage. These leaked electrons react with molecular oxygen, engendering the production of ROS, which culminates in the occurrence of oxidative stress. Oxidative stress is one of the common forms of secondary injury after SCI. Mitochondrial oxidative stress can lead to impaired mitochondrial function and disrupt cellular signal transduction pathways. Hence, restoring mitochondrial electron transport chain (ETC), reducing ROS production and enhancing mitochondrial function may be potential strategies for the treatment of SCI. This article focuses on the pathophysiological role of mitochondrial oxidative stress in SCI and evaluates in detail the neuroprotective effects of various mitochondrial-targeted antioxidant therapies in SCI, including both drug and non-drug therapy. The objective is to provide valuable insights and serve as a valuable reference for future research in the field of SCI.

Keywords: spinal cord injury; mitochondria oxidative stress; antioxidant therapy; mitochondrial electron transport chain; reactive oxygen stress

1. Introduction

Spinal cord injury (SCI) is a central nervous system traumatic disorder characterized by a high disability rate, resulting in impairments [1,2]. SCI resulting from vehicular crashes, gunshot wounds, high-altitude falling injuries and heavy falling injuries is the most pr from diverse etiologies and manifests varying degrees of sensory and motor functional evalent form in clinical practice [3]. According to clinical statistics, the global annual prevalence of SCI ranges from 10.4 to 83 cases per million population [4]. Furthermore, the cost of treatment and rehabilitation care is as high as $3 million per person [5]. SCI can be categorized into primary injury and secondary injury based on its mechanism [6]. The former is attributed to extrinsic influences and various factors leading to vascular rupture and soft tissue injury surrounding the spinal cord. The latter encompasses a cascade of malign processes following the initial injury, comprising inflammatory response, oxidative stress, neuronal and glial cell apoptosis, as well as diverse intracellular organelle damage [7,8]. Currently, the management options for SCI remain considerably restricted. Clinical intervention primarily revolves around surgical procedures aimed at alleviating compression and diminishing secondary pathological compression. Additionally, methylprednisolone, along with other pharmaceutical agents like riluzole and minocycline, is administered to mitigate inflammation and edema [9–19]. The employment of high-dose methylprednisolone as a therapeutic approach remains controversial due to the prevalence of numerous potential complications, including sepsis, infection, gastrointestinal hemorrhage, pneumonia, pulmonary embolism, and corticosteroid-related adverse effects [20]. Therefore, looking for new treatment strategies and an in-depth study of their mechanism is the main focus of our efforts.

Mitochondria are organelles that are enveloped by two membranes and participate in a wide range of regulatory functions. Their primary role is to generate cellular energy in the form of adenosine triphosphate (ATP) via the respiratory chain (ETC) reaction, which provides the requisite energy for cellular activities [21]. SCI can induce mitochondrial dysfunction [22]. One of the primary culprits responsible for secondary injury is oxidative stress. Mitochondrial oxidative stress can result in impaired mitochondrial function and impact cellular signal transduction. Excessive production of mitochondrial reactive oxygen species (mtROS) has been shown to directly impact biological macromolecules such as mitochondrial DNA (mtDNA), proteins, and lipids, thereby compromising the integrity of mitochondrial structure and function [23]. ETC represents the primary source of mtROS. Thus, remedying respiratory chain abnormalities and mitigating excessive mtROS production can ameliorate mitochondrial oxidative stress. Researchers have proposed several drug and non-drug treatments that target mitochondria, which have been demonstrated to counteract mitochondrial

oxidative stress and enhance motor function in SCI models. This article provides an in-depth analysis of the pathophysiological role of mitochondrial oxidative stress in SCI and the research advancements pertaining to treatments of SCI-related mitochondrial dysfunction.

2. Mechanism of Action of Mitochondrial Oxidative Stress and SCI

In normal mitochondria, the oxidation and antioxidant systems exist in a state of dynamic equilibrium. When there is an overactivity of the mitochondrial oxidation system or a deficiency in the antioxidant system, oxidative stress can occur. ROS are the most significant components of the mitochondrial oxidation system and are primarily present as the superoxide anion (O^{2-}), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH) [24]. Under normal circumstances, ROS in the body is kept at a minimal level to ensure normal mitochondrial function.

ETC localized in the mitochondria's inner membrane is the primary site of ROS generation. It comprises four membrane-bound complexes and two mobile electron carriers, namely, coenzyme Q (CoQ) and cytochrome C. Two distinct pathways of electron transfer exist within the ETC: the reduced form of nicotinamide adenine dinucleotide (NADH)-dependent complexes I/III/IV and the succinate-dependent complexes II/III/IV [25]. The electron transfer in mitochondria can lead to electron leakages that result in the formation of O^{2-} or H_2O_2 when some electrons cannot be transferred normally and react with oxygen. Complexes I and III in the ETC are known to contribute to this process [26]. Complex I is a site of prominent O^{2-} production, which occurs at two distinct locations. Firstly, the flavin mononucleotide (FMN) cofactor situated within the complex acts as an electron acceptor, receiving electrons from NADH. Secondly, the CoQ binding site at the end of Fe-S transfers two electrons to CoQ, culminating in the formation of O^{2-} [27]. During the forward electron transfer process, the electrons donated by NADH undergo a complete reduction of the FMN center within complex I, leading to the formation of O^{2-} through reaction with oxygen. The extent of O^{2-} generation at the FMN center is governed by the NADH/nicotinamide adenine dinucleotide-oxidized form (NAD+) ratio and remains relatively low under normal physiological conditions. Complex III, particularly at the $CoQH_2$ oxidation site, contributes to the production of O^{2-} in the ETC. Upon binding to complex III, $CoQH_2$ donates its two electrons to the Fe-S center and cytochrome C. This electron transfer sequence results in the formation of an unsteady Q species on CoQ, which reacts with oxygen to produce O^{2-} and generate ROS. Nevertheless, the pace of ROS generation at this locus stays modest during physiological circumstances [28].

At the 24-hour time point following contusion, a notable decline in respiratory control ratio (RCR) function is evident. Mitochondria are isolated from both the sham and injured animal groups at 6 to 24 hours post-injury, revealing an elevation in levels of 3-nitrotyrosine (3-NT), 4-hydroxynonenal (HNE), and protein carbonyls within the mitochondria subsequent to injury. SCI is accompanied by a detrimental cycle of heightened mtROS, culminating in amplified oxidative damage, ultimately leading to an escalation of mtROS to a pathological threshold [29]. Research findings indicate that within the rat SCI model, there is a notable 48% elevation in mitochondrial ROS levels after 4 hours of SCI compared to the control group. Furthermore, 24 hours post-injury, there is a substantial increase in catalase (CAT) activity and glutathione (GSH) concentration. These observations signify anomalous mitochondrial functionality and ROS levels subsequent to SCI [30]. Moreover, the ETC within the mitochondria is the first component to be adversely affected after SCI [31,32]. Impairment of the ETC adversely affects the function of complex I, resulting in NADH accumulation, elevation of the NADH/NAD+ ratio, and increased O^{2-} production. Complex I can generate a substantial quantity of O^{2-} through the reverse electron transport (RET) mechanism. RET is activated under conditions of low CoQ pool height and high proton motive force, thereby forcing electrons to revert from $CoQH_2$ to complex I and reducing NAD to NADH at the FMN site [33]. Moreover, complex III inhibition augments ROS generation. While complex II is not usually considered a significant contributor to ROS, some studies suggest that O^{2-} can also be generated following complex II impairment, but the underlying mechanism requires further investigation [25].

Apart from the aforementioned sources, ROS can also be formed by enzymatic action, including glycerol aldehyde-3-phosphate dehydrogenase (GAPDH), monoamine oxidase (MAO), cytochrome b5 reductase (Cb5R), and cytochrome P450 (p450). Meanwhile, it can also be composed of matrix enzymes and complexes, including aconitase, α-ketoglutarate dehydrogenase (αKGDH), and pyruvate dehydrogenase (PDH) [34–37]. In addition to the oxidation system, there is also an antioxidant system that maintains mitochondrial homeostasis. Notably, antioxidative proteins like glutathione peroxidase (GPX) and peroxiredoxin (Prxs) synergize to exert a pivotal function in the antioxidant system [38]. When SCI occurs, there is excessive production of ROS, leading to the disruption of the cell membrane structure. The maintenance of a stable state in the mitochondrial structure becomes challenging, resulting in impaired function. This directly impacts the cellular energy supply and ultimately leads to cell death. Therefore, it is imperative to preserve the stability of ETC function and regulate ROS levels within a safe concentration to suppress mitochondrial oxidative stress.

3. Role of Mitochondrial Oxidative Stress in Spinal Cord Injury

The preceding discussion provides a comprehensive account of how mitochondrial oxidative stress is generated in the context of spinal cord injury, including abnormalities in the ETC and the release of mtROS. Mitochondria primarily serve the vital physiological function of generating a substantial amount of ATP through oxidative phosphorylation (OXPHOS) to meet the body's energy demands. Furthermore, mitochondria are involved in regulating various cellular metabolic processes through intricate mechanisms, such as maintaining intracellular calcium homeostasis, governing programmed cell death, and modulating immune responses. However, in the presence of oxidative stress within mitochondria, detrimental effects are present, such as the opening of the mitochondrial permeability transition pore (mPTP), aberrant mitophagy, inflammation, and mitochondrial DNA (mtDNA) damage. These mechanisms contribute to the worsening of SCI. The subsequent section will delve into a detailed exploration of the role played by mitochondrial oxidative stress in SCI (Fig. 1).

3.1 Disruption of Mitochondrial Permeability Transition Pore Opening by Mitochondrial Oxidative Stress

The mPTP is a non-selective channel consisting of the voltage-dependent anion channel (VDAC) located in the outer mitochondrial membrane, the adenine nucleotide translocator (ANT), and cyclophilin D (Cyp-D) complex situated in the inner mitochondrial membrane [39]. An overabundance of mtROS can induce the opening of the mPTP. CypD functions as a modulator of mPTP and is capable of concealing the inhibitory binding site for phosphate on mPTP, thus heightening mPTP's sensitivity to ROS and Ca^{2+} [40]. Nevertheless, the administration of TRO-19622, an inhibitor of VDAC, or Mito-TEMPO, a scavenger specifically targeting mROS, can effectively alleviate the aforementioned consequences [41]. Multiple studies have provided evidence that the generation of mtROS in response to oxidative stress can be modulated via mitochondrial protective pathways, such as SIRT3. These pathways exert direct or indirect inhibitory effects on the mPTP, thereby attenuating the frequency of mPTP opening events [42].

In cases where the range of adjustment cannot be controlled, a feedback loop of negative consequences may ensue, leading to a 'vicious cycle'. Under pathophysiological circumstances, the reversible operation of ATP synthase occurs, wherein the hydrolysis of ATP takes place, creating an electrochemical gradient that traverses the mitochondrial inner membrane. These physiological phenomena may culminate in escalated ROS levels, consequently instigating the activation of mPTP [43]. Excessive accumulation of Ca^{2+} ions and heightened levels of ROS subsequent to SCI facilitate persistent activation of mPTP. The sustained activation of mPTP results in unimpeded diffusion of molecules with a mass greater than 1.5 kilodaltons (kDa) within the mitochondria, leading to a reduction in mitochondrial membrane potential [37]. The recurrent and persistent activation of mPTP obstructs electron transport and exacerbates the impairment of the mitochondrial electron transport chain. This leads to mtROS and Ca^{2+} overload, consequently intensifying the opening of mPTP [44]. Concomitantly, subsequent to mPTP activation, the persistent elevation of mtROS can precipitate the upregulation of pro-apoptotic pathways and elicit the translocation of pro-apoptotic factors (such as caspase3) to the mitochondria, thereby potentiating mPTP aperture [45]. Pyruvate carboxylase (PYC) exerts a stabilizing effect on mPTP by suppressing oxidative stress, which in turn ameliorates motor deficits following SCI and curtails neuronal apoptosis [46]. The aforementioned investigations have demonstrated an inextricable link between mPTP activation and mitochondrial oxidative stress. The initiation of mPTP will perpetuate oxidative stress, engendering a deleterious cycle that culminates in heightened cellular impairment.

3.2 Impact of Mitochondrial Oxidative Stress on Mitophagy

Autophagy is the process of combining damaged organelles or denatured proteins with lysosomes for self-degradation [47]. Mitophagy refers to a selective form of autophagy that functions to maintain mitochondrial homeostasis by selectively eliminating damaged or surplus mitochondria [48]. During this series of events, PTEN-induced putative kinase 1 (PINK1) perceives the depolarization of the mitochondrial membrane, leading to its accumulation on the outer membrane and the subsequent activation of Parkin. Upon activation, Parkin triggers the autophagic degradation process to achieve mitophagy. Additionally, activated Parkin can ubiquitinate other receptors located on the outer mitochondrial membrane, including NIP3-like protein X (NIX), FUNDC1, among others. These receptors can directly interact with microtubule-associated protein 1 light chain 3 (LC3), a molecule capable of sensitively detecting intracellular and extracellular signal changes and inducing the aggregation of autophagosomes [21].

The overproduction of mtROS causes a reduction in mitochondrial membrane potential (MMP). This, in turn, activates PINK1 located on the damaged outer mitochondrial membrane (OMM), engendering the initiation of ubiquitination and phosphorylation of OMM proteins, consequently promoting mitophagy [49]. Furthermore, heightened levels of ROS can trigger the initiation of mitophagy in vascular endothelial cells [50]. Mitophagy has the potential to reduce levels of ROS and may be involved in the amelioration of SCI [51]. Nonetheless, excessive mitochondrial oxidative stress can lead to an uncontrolled burst of ROS, ultimately disrupting the proper regulation of mitophagy, resulting in either an excess or deficiency of this process. This dysregulation of mitophagy is intricately as-

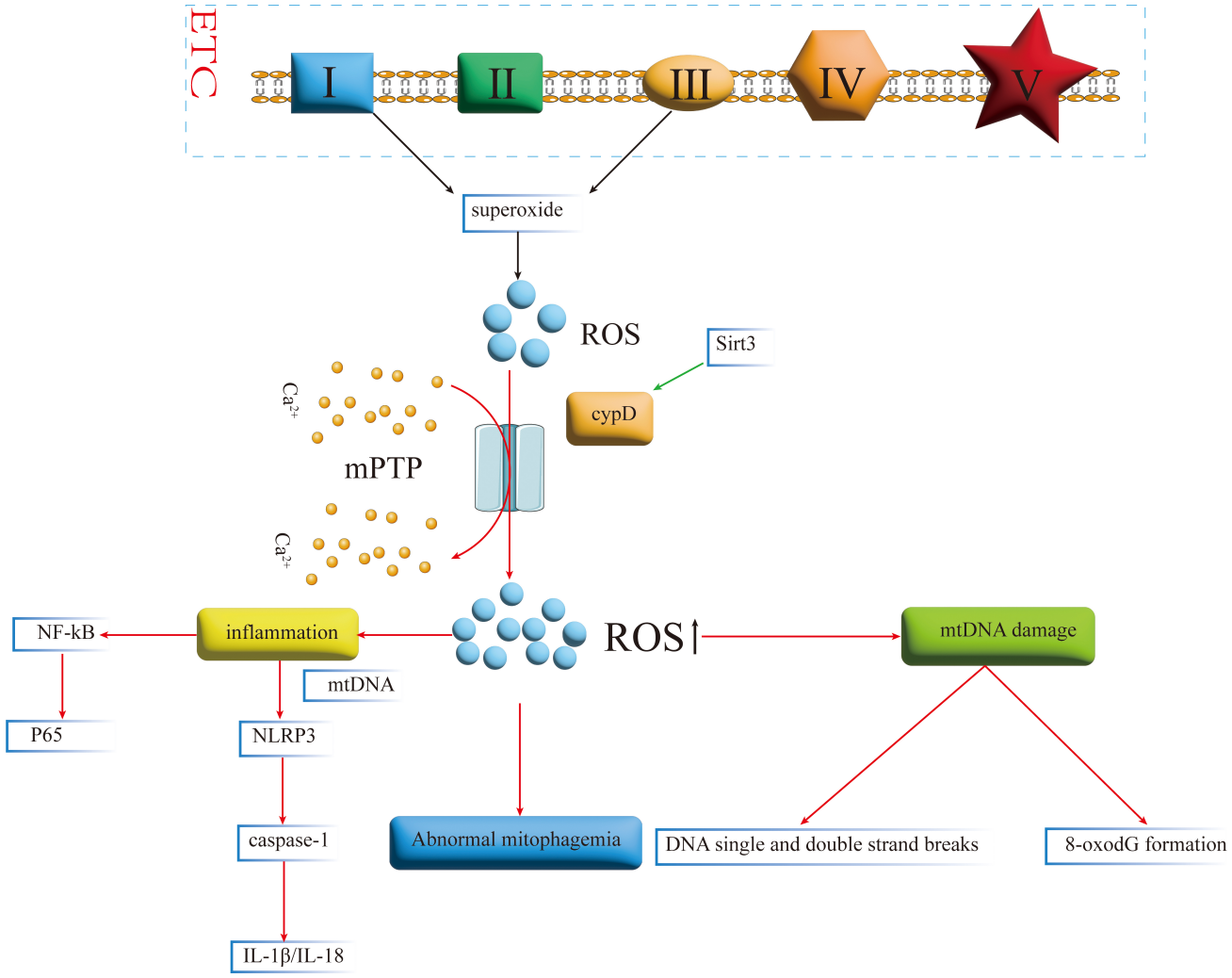

Fig. 1. Role of mitochondrial oxidative stress in spinal cord injury. Following spinal cord injury, electron transfer within the mitochondria gives rise to a fraction of electrons engaging in electron leakage with oxygen, leading to the formation of superoxide anion (O^{2-}) or hydrogen peroxide (H_2O_2). This phenomenon predominantly occurs in complexes I and III of the electron transport chain (ETC), resulting in elevated levels of reactive oxygen species (ROS) and subsequent initiation of the mitochondrial permeability transition pore (mPTP). Calcium ion (Ca^{2+}) overload and increased ROS concentrations following spinal cord injury further promote the persistent opening of the mPTP. Simultaneously, the opening of the mPTP can be directly or indirectly inhibited through mitochondrial protective pathways such as SIRT3, which curtails the frequency of mPTP opening. The surplus mitochondrial ROS (mtROS) provokes inflammation, disrupts mitochondrial function, and causes damage to mitochondrial DNA (mtDNA). Moreover, mtROS can modulate the production of the pro-inflammatory cytokines IL-1β and IL-18 by activating the p65 subunit of the NF-κB signaling pathway and stimulating caspase-1 through the activation of NLRP3 inflammasomes. ROS-induced mtDNA damage manifests in two principal consequences: (i) structural impairments involving single and double strand breaks of DNA arising from direct ROS assault and (ii) the generation of 8-hydroxyguanine (8-OH-G).

sociated with the onset and progression of certain pathologies. Following SCI, NIX can trigger an excessive level of mitophagy in neurons, subsequently promoting mitochondrial degeneration and neuronal cell death [52]. Research has demonstrated that betulinic acid (BA) can enhance autophagy in the context of SCI by activating the AMPK-mTOR-TFEB signaling pathway, thus promoting the induction of mitophagy and mitigating the accumulation of ROS [53]. Salidroside (Sal) has been shown to ameliorate mitochondrial dysfunction and structural abnormalities by mitigating the production of ROS. Moreover, Sal exerts its beneficial effects by augmenting the PTEN-induced PINK1-Parkin signaling pathway, which facilitates the initiation of mitophagy and enhances the clearance of impaired mitochondria [51]. These results indicate that mitochondrial oxidative stress may lead to abnormal mitophagy after SCI.

3.3 Induction of Inflammation by Mitochondrial Oxidative Stress

The generation of mtROS is intricately linked to the activation of pro-inflammatory cytokines [54]. The generation of ROS originating from the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system, as well as the production of O^{2-} from the ETC within mitochondria, collectively promote the amplification of proinflammatory cytokine production [55]. mtROS exert a significant regulatory influence on the activation of the NF-κB signaling pathway and the modulation of inflammatory vesicular signaling, consequently impacting the inflammatory response. Notably, mitochondria have been reported to play a role in the activation of NLRP3 inflammasomes through mtROS, mtDNA, and cardiolipin, although the precise contribution of mitochondria in this process remains controversial. Simultaneously, NLRP3 inflammasomes induce caspase-1-dependent damage to mitochondria, resulting in escalated mtROS production, dissipation of mitochondrial membrane potential, and compromised integrity of both the inner and outer mitochondrial membranes [56]. These findings unveil the significant involvement of mitochondrial oxidative stress in the initiation of inflammation. Activation of NLRP3 inflammasomes prompts caspase-1 activation, orchestrating the production of pro-inflammatory cytokines IL-1β and IL-18. These cytokines, upon binding to specific intracellular receptors, potentiate the inflammatory response, ultimately culminating in organ dysfunction [57,58]. The restitution of mitochondrial structural integrity and functional capacity impedes ROS generation, consequently mitigating the inflammatory response. Concurrently, mtROS triggers the activation of NLRP3 inflammasomes, and there is also a potential involvement of mtDNA oxidative damage in promoting a pro-inflammatory milieu [59]. Several studies have established a correlation between ETC activity and the activation of NLRP3 inflammasomes mediated by ROS. During cerebral ischemic injury, the elevated levels of succinic acid increased during ischemia, undergo oxidation. This oxidation, facilitated by reverse electron transport, stimulates ROS production within complex I, resulting in an initial surge of O^{2-} that contributes to ischemia-reperfusion injury. Consequently, the NLRP3-dependent secretion of IL-1β is heightened, exacerbating the inflammatory response [58]. Simultaneously, it has been observed that lipopolysaccharide (LPS)-activated microglia exhibit an overproduction of chemokines, cytokines, and ROS. Within this pro-inflammatory state, the suppression of mtROS induced by LPS assumes a regulatory role in governing the synthesis of pro-inflammatory mediators by impeding the activation of MAPK and NF-κB signaling pathways [60].

While no direct evidence of the impact of mitochondrial oxidative stress on SCI inflammation exists, research has demonstrated that the knockout of mitochondrial membrane protein phosphoglycerate mutase 5 (PGAM5) can furnish neuroprotection by engaging in the oxidative stress and inflammation cascade in microglia. Moreover, PGAM5 knockout can proficiently govern mtROS and GSH levels and enhance mitochondrial dysfunction [61]. The transmission of miR-155 through exosomes is implicated in the initiation of EndoMT and the production of mtROS in bEnd.1 cells stimulated by M3-BMDMs. MtROS activates the NF-κB signaling cascade via targeting the downstream inhibitors of cytokine signaling 6 (SOCS6), thereby restraining SOCS6-mediated p65 ubiquitination and degradation [62]. Melatonin has the capability to restrain NLRP3 inflammation activation by inducing the Nrf3/ARE pathway. This lessens the ROS and malondialdehyde (MDA) expression and boosts the superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX) activity, subsequently suppressing neuroinflammation, ameliorating mitochondrial dysfunction, and enhancing motor function recovery post-SCI [63]. This indirectly indicates that the correlation between mitochondrial oxidative damage and inflammation and requires further investigation.

3.4 MtDNA Damage Caused by Mitochondrial Oxidative Stress

mtDNA is a circular double-stranded molecule with a length of approximately 16.569, representing approximately 0.1%–1% of the total cellular DNA. The mtDNA coding region encompasses 37 genes, which consist of 22 transfer RNA (tRNA) genes, 2 ribosomal RNA (rRNA) genes, and 13 polypeptides [64]. The mtDNA is positioned in close proximity to the ETC. Due to its lack of nucleosomal protection and histone modification, mtDNA is vulnerable to damage, limited in its repair pathway, and prone to a high frequency of mutations, particularly under oxidative stress conditions. Thirteen peptides encoded by mtDNA play a crucial role in intracellular respiratory chain transmission and OXPHOS [65]. The mitochondrial transcription factor TFAM governs the modulation of mtDNA-encoded subunits in the ETC. Dysfunctional NRF1/2 signaling impedes the transcription of nuclear-encoded subunits of the respiratory chain complex and TFAM. The absence of TFAM packaging in the mtDNA prompts instability of the D-loop and impedes the transcription and replication of mtDNA. Consequently, diminished mtDNA transcription and replication accentuate the impairment of the respiratory chain [66]. One of the principal mechanisms by which ROS induces mtDNA damage is through oxidative modification of purine and pyrimidine bases, resulting in point mutations. ROS-mediated damage can lead to two main outcomes: (1) Structural damage, including single and double strand breaks of DNA, which are caused by direct ROS attack. The occurrence of DNA breakage following SCI was confirmed by comet assay. (2) Formation of 8-hydroxyguanine (8-OH-G). The primary products of mtDNA base damage include thymidinediol in pyrimidine

nucleosides and 8-hydroxy-2′deoxyguanosine (8-oxoG) in purines. The most extensively studied oxidative base damage is 8-oxodG, which is generated by ROS attack at the C8 position of guanine. 8-oxodG serves as a reliable marker for DNA oxidative damage [67]. Prior investigations have demonstrated that the levels of 8-oxodG increase following SCI, with significant increases in 8-oxodG observed at all time points from 3 hours post-injury (hpi) to 21 days post-injury (dpi) [68]. Nonetheless, 8-oxodG may exist in various forms of nucleic acids, including cytoplasmic RNA, nuclear DNA, and mitochondrial DNA. Further investigations are warranted to elucidate the precise source of 8-oxodG. During SCI, ROS can impact ETC function and OXPHOS via mtDNA-encoded peptides, which may lead to mtDNA damage [65]. These findings indicate that mtDNA is highly vulnerable to oxidative damage induced by ROS. In a rodent model of spinal cervical spondylosis, administration of riluzole mitigated oxidative DNA damage in the spinal cord post-decompression surgery and decreased the presence of 8-oxoG DNA. Moreover, *in vitro* investigations demonstrated that riluzole conserved mitochondrial functionality and decreased oxidative neuronal harm [69]. Currently, limited research has explored the mechanisms underlying mtDNA repair in SCI, with existing studies primarily focusing on evaluating alterations in gene expression subsequent to SCI. Further investigations are warranted to elucidate the association between mtDNA, mitochondrial oxidative stress, and their therapeutic interventions. As our scientific inquiry progresses, numerous gaps pertaining to the understanding of mtDNA damage and repair necessitate comprehensive investigation.

4. Treatment Strategies to Inhibit Mitochondrial Oxidative Stress

Mitochondrial oxidative stress triggers abnormalities in the ETC, leading to uncontrolled generation of mtROS, which subsequently triggers a cascade of pathophysiological changes such as opening of the mPTP, abnormal mitophagy, inflammation, and mtDNA damage. Therapeutic interventions targeting mitochondrial oxidative stress may represent a promising therapeutic approach. Despite its essential role in ATP production, the ETC also generates a considerable amount of ROS upon dysfunction. Following SCI, mitochondrial oxidative stress rapidly intensifies, creating a "vicious cycle". Within the scope of this manuscript, we provide a detailed overview of recent advances in antioxidant therapy for mitochondria after SCI. Our focus is on two approaches: correcting ETC abnormalities under pathological conditions, and removing excessive mtROS, to facilitate a more comprehensive and in-depth understanding of SCI treatment Table 1 (Ref. [70–85]).

4.1 Correct Mitochondrial Oxidative Respiratory Chain Abnormalities

4.1.1 Drug Treatment

The administration of SOD/CAT (NPs) nanoparticles was observed to significantly ameliorate the excessive production of mtROS resulting from impaired ETC transmission components after SCI, leading to an increase in MMP, a reduction in Ca^{2+} content, and enhanced ATP synthesis [70]. LY344864 is a 5-hydroxytryptamine 1F (5-HT_{1F}) receptor agonist, which has been demonstrated to attenuate the reduction in mtDNA content following SCI, reverse the downregulation of Nrf2, ATP Synβ, TFAM, and NDUFB8 protein expression after SCI, and improve the motor function of the lower limbs in mice. Thus, LY344864 holds promise as a potent 5-HT_{1F} receptor agonist for developing SCI therapeutic interventions [71]. Furthermore, research has indicated that the decrease in the OGDHC level following SCI restricts the tricarboxylic acid (TCA) cycle, leading to reduced production of NADH for oxidation in the ETC. This ultimately impairs crucial mitochondrial functions, including oxidative phosphorylation. Interventions with thiamine, a pleiotropic modulator, may activate neuroprotective mechanisms, enhance motor function recovery following SCI, and potentially mitigate the downregulation of OGDHC expression post-SCI [72]. It is noteworthy that research has demonstrated the potential utilization of certain bioenergetic compounds, such as intermediates of the TCA cycle, the administration of essential amino acids (EAAs), branched-chain amino acids (BCAA) and coenzymes thiamine and pyridoxine, collectively termed as α5. Oral administration of α5 has been found to ameliorate the TCA cycle and OXPHOS in spinal cord tissue, augment mitochondrial biogenesis and respiration, and mitigate oxidative stress at the site of injury [73]. The ketogenic diet has been reported to enhance the function of mitochondrial respiratory complexes I, II, III, and IV post-SCI while mitigating acute SCI-induced mitochondrial oxidative damage and dysfunction [74]. In the model of spinal cord ischemia-reperfusion injury (SCI/R), administration of NS309, a pharmacological activator of small conductance calcium-activated K+ (SK/K_{Ca}) channels, has been found to preserve the activity of mitochondrial respiratory complexes, thus preventing SCI/R by exhibiting antioxidant activity and inhibiting mitochondrial dysfunction [75]. In the rat model of cerebral ischemic injury, leptin has been shown to modulate the ETC through the STAT3 pathway, resulting in decreased mitochondrial damage and protection of brain tissue against mitochondrial oxidative stress during cerebral ischemia [76]. Whether this approach can be employed for the treatment of SCI requires further investigation. By modulating the ETC, the drugs exert regulatory control over cellular OXPHOS and disrupt the process of oxidative stress, thereby effectively counteracting oxidative stress and preserving compromised spinal cord tissue. The respiratory chain complex, integral to biological oxidation and OXP-

Table 1. Treatment strategies to inhibit mitochondrial oxidative stress.

Name	Mechanism	Dosage	Animal strains	Reference
NAC, NACA	GSH↑, mtROS↓	NAC 100 mg/kg was injected intraperitoneally once a day for 28 days. NACA (150 or 300 mg/kg/day) was continuously administered 24 hours or 7 days after SCI.	C57BL/6 mice; Female Sprague-Dawley rats	(Guo *et al*, [79] 2015; Patel *et al*., [80] 2014)
SOD/CAT (NPs)	Restore ETC function mtROS↓ Mitochondrial Membrane Potential↑ ATP synthesis↑	At 6 hours after spinal cord injury, 30 mg/kg was injected into a caudal vein.	Sprague-Dawley rats	(Andrabi *et al*., [70] 2020)
5-HT_{1F} receptor stimulant (LY344864)	ATP Synβ, TFAM and NDUFB8↑ Reduce mtDNA damage and improve mitochondrial dysfunction	One hour after spinal cord injury, 2.0 mg/kg was injected intraperitoneally once a day for 21 days.	Female C57BL/6J mice, male and female 5-HT_{1F} receptor gene knockout (KO) mice	(Simmons *et al*., [71] 2020)
Thiamine	OGDHC↑ Repair TCA cycle Improve ETC and OXPHOS	Within 15–20 hours after spinal cord injury, 200 mg/mL was injected intraperitoneally.	Female Sprague-Dawley rats	(Boyko *et al*., [72] 2021)
α5 (Including TCA cycle intermediates, EAAs, BCAA and cofactors thiamine and pyridoxine)	Repair TCA cycle Improve ETC and OXPHOS Mitochondrial mass and respiration↑ oxidative stress↓	Oral administration was given 3 days after spinal cord injury and continued until the end of the experimental procedure.	C57BL/6J mice	(Dolci *et al*., [73] 2022)
Ketogenic diet	Activity of complexes I, II, III and IV↑ mitochondrial oxidative damage↓	Ketogenic diet for 7 days after spinal cord injury	Male Sprague-Dawley rats	(Seira *et al*., [74] 2021)
NS309 (SK/K_{Ca} channel activator)	mitochondrial respiratory chain complex activity↑ antioxidation Correct mitochondrial dysfunction	After spinal cord ischemia-reperfusion injury, 2 mg/kg was injected intraperitoneally.	Adult New Zealand white rabbits	(Zhu *et al*., [75] 2019)
Leptin	Correct mitochondrial ETC abnormalities mitochondrial oxidative stress↓	Subcutaneous injection of 1 mg/kg was performed 3 hours before MCAO.	Male Sprague-Dawley rats	(Hu *et al*., [76] 2019)

Table 1. Continued.

Name	Mechanism	Dosage	Animal strains	Reference
NMES-RT	Mitochondrial electron transport chain complex I↑	Twice a week for 12 weeks, 45–60 minutes per session	Thirty-three individuals aged between 20 and 61 years with chronic (≥1 year post injury) SCI	(Gorgey *et al*., [77] 2021)
PBM	p-AMPK, PGC-1α, Nrf1, Sirt1 and TFAM↑ Restore mitochondrial respiratory chain complex activity	After spinal cord injury, the T10 spinal cord was exposed to PBM for 1 hour per day.	Sprague-Dawley rats	(Zhu *et al*., [78] 2022)
MitoQ	Mitochondrial specific antioxidants mtROS↓	MitoQ 5 mg/kg was intraperitoneally injected on day 0, 1 and 2 after spinal cord injury.	C57BL/6J mice	(Huang *et al*., [81] 2022)
Polydatin	Regulate mPTP, effectively remove mtROS, and reduce mitochondrial dysfunction.	Spinal cord ischemia-reperfusion injury was induced by gastric injection of 30 mg/kg 2 days before the operation for 7 days.	C57BL/6J mice	(Zhan *et al*., [82] 2021)
XJB-5-131	mitochondrial-targeted ROS scavenger, inhibition of CL, reduces neuronal apoptosis	15 mg/kg was injected intraperitoneally 30 minutes after spinal cord injury.	Female Sprague-Dawley rats	(Liu *et al*., [83] 2022)
Zn	mtROS↓	After spinal cord injury, ZnG (different concentrations) was injected intraperitoneally.	C57BL/6J mice	(Xu C *et al*., [84] 2023)
EPO	Reduce mitochondrial damage and improve mitochondrial membrane potential in ferroptosis.	After spinal cord injury, 1000 IU/kg and 5000 IU/kg were injected intraperitoneally once a week for 2 weeks.	Female Sprague-Dawley rats	(Kang *et al*., [85] 2023)

NAC, *N*-acetylcysteine; NACA, *N*-acetylcysteine amide; GSH, glutathione; mtROS, mitochondrial reactive oxygen species; SCI, Spinal cord injury; SOD, superoxide dismutase; CAT, catalase; ETC, electron transport chain; ATP, adenosine triphosphate; mtDNA, mitochondrial DNA; TCA, tricarboxylic acid; MCAO, middle cerebral artery occlusion; NMES-RT, neuromuscular electrical stimulation resistance training; PBM, photobiomodulation; mPTP, mitochondrial permeability transition pore; EPO, Erythropoietin; OXPHOS, oxidative phosphorylation; EAAs, essential amino acids; BCAA, branched-chain amino acids; CL, cardiolipin; ZnG, zinc gluconate. ↑ represents up regulation, and ↓ represents down regulation.

HOS, exhibits abundant sites for inhibition and activation. Consequently, distinct drugs or specific drug components exert varying effects on the mitochondrial respiratory chain complex, providing avenues for drug development in the context of spinal cord injury. These strategies include targeted drug delivery to specific sites within the ETC and its complex, as well as augmenting the proportion of specific drug components, thereby enhancing the drug's efficacy in disease treatment.

4.1.2 Non-Drug Therapy

Neuromuscular electrical stimulation resistance training (NMES-RT) has been shown to enhance peak oxygen uptake (V∂o2peak) of skeletal muscle in individuals with chronic SCI, possibly attributed to alterations in complex I of the ETC [77]. In rat models of SCI, photobiomodulation (PBM) has been found to stimulate the AMPK signaling pathway, leading to the upregulation of p-AMPK, TFAM, Nrf1, Sirt1 and PGC-1α. This activation of PBM can re-establish the functional activity of mitochondrial respiratory chain complexes, which subsequently augment the production of ATP [78].

4.2 Clear Excess mtROS

4.2.1 Drug Treatment

Glutathione reductase (GR) plays a vital role in the reduction of oxidized glutathione (GSSG) to reduce GSH, facilitating the scavenging of ROS and safeguarding mitochondrial membrane integrity. *N*-acetylcysteine (NAC), a GSH precursor, exhibits inhibitory effects on oxidative stress injuries induced by mitochondrial dysfunction and demonstrates a certain capacity for improving mitochondrial dysfunction following SCI [79]. However, NAC's biofilm permeability is limited. Studies have demonstrated that *N*-acetylcysteine amide (NACA) significantly elevates GSH levels within the body and reduces the production of mtROS, thereby mitigating mitochondrial oxidative stress subsequent to SCI [80]. In recent years, many mitochondrial antioxidants have been known. MitoQ can effectively remove mtROS, demonstrating a certain therapeutic effect of mitochondrial oxidative stress. Studies have reported that MitoQ enhances spinal cord angiogenesis by restoring impaired mitochondrial function and facilitating the recovery of mitochondrial structure and function following SCI [81]. Thus, MitoQ is considered a promising therapeutic intervention for mitigating mitochondrial oxidative stress subsequent to SCI. In the spinal cord ischemia-reperfusion model, Polydatin (PD) has been found to regulate MMP and mPTP opening by activating the Nrf2/ARE pathway, thereby effectively scavenging mtROS, restoring ATP synthesis and mitigating neuronal damage due to mitochondrial dysfunction [82]. The therapeutic potential of PD in SCI warrants further investigation. A novel mitochondrial-targeted ROS scavenger, XJB-5-131, has been developed, and studies have demonstrated its efficacy in inhibiting cardiolipin (CL) alterations in rats after SCI, reducing tissue damage, neuronal apoptosis, and improving motor function recovery following SCI [83]. Zinc (Zn) has been shown to promote autophagy via SIRT3, thus alleviating inflammation and mtROS production in damaged spinal cord and neurons [84]. Subsequent experiments demonstrated that Zn could also inhibit mtROS production via the PI3K/Akt signaling pathway [86]. Furthermore, dynasore has emerged as a promising combined ROS blocker for *in vivo* research and treatment of abnormal accumulation of mitochondrial ROS [87]. In recent years, researchers have been actively enhancing pharmaceutical agents through modulating administration modalities, augmenting the utilization of biologics, and continually refining delivery methodologies to establish a robust groundwork for clinical intervention. While the management of mtROS is not novel, it remains clear that the inhibition of ROS generation persists as a prominent contributor to mitochondrial oxidative stress.

4.2.2 Non-Drug Therapy

Research has indicated that the inhibition of the NF-κB pathway via down-regulation of exosome miR-155 in polarized M1 macrophages can enhance the proliferation of vascular endothelial cells and reduce the production of mtROS following traumatic SCI [62]. Currently, the research landscape concerning miRNA therapy targeting mitochondrial oxidative stress is relatively sparse, yet it remains a compelling and pertinent subject warranting our focused consideration.

4.3 Others

In addition to the aforementioned treatments, various drugs have been found to alleviate mitochondrial oxidative stress and have neuroprotective effects on SCI. These drugs include maltol, metformin, receptor-interacting protein (RIP) inhibitors, ligustrazine, ebselen, among others [88–93]. Erythropoietin (EPO) has been found to contribute to the recovery of reduced mitochondrial membrane potential in ferroptosis and reduce mitochondrial damage after SCI [85]. Ferrostatin-1 has been shown to inhibit mitochondrial lipid peroxidation, reduce ROS and MDA levels, and promote the expression of GSH and GPX4 in the RSL-93-induced ferroptosis model of oligodendrocytes [94]. Most antioxidants have difficulty passing through the blood-brain barrier, and the selective permeability of the mitochondrial membrane limits the targeting efficiency of many drugs on mitochondria, leading to diminished clinical effects. Thus, the efficient delivery of drugs to neuronal mitochondria while avoiding toxicity remains a challenge in SCI treatment. Moreover, apart from the aforementioned therapeutic approaches, the modulation of molecules implicated in mitochondrial oxidative stress, such as uncoupling proteins, deacetylases, and others, either individually or in combina-

tion, holds promise for reinstating neuronal mitochondrial functionality in SCI, thus affording protection to the spinal cord tissue.

5. Conclusions

Through extensive research, it has been elucidated that mitochondrial oxidative stress exerts disruptive effects on mPTP opening, mtDNA damage, mitophagy impairment, inflammatory induction, and other detrimental processes. This implies the pivotal role of mitochondrial oxidative stress in the cascade of secondary injury subsequent to SCI. Hence, the inhibition of mitochondrial oxidative stress remains a compelling avenue for exploration in the treatment of SCI. Multiple studies have substantiated this proposition, highlighting strategies such as targeted mitigation of excess mtROS through interventions at the ETC and its complexes, utilization of biological materials, and augmentation of drug efficacy by optimizing dosages. Furthermore, non-pharmaceutical approaches that target ETC and mtROS demonstrate promising potential for future spinal cord injury recovery. Intriguingly, the intricate distribution of molecular proteins within mitochondria, closely intertwined with mitochondrial function, holds considerable significance in maintaining mitochondrial homeostasis and functionality. Nonetheless, research on gene therapy and combination therapy for mitigating mitochondrial oxidative stress in the context of treatment remains limited. Given the multifaceted nature of spinal cord injury, focusing solely on the treatment of a specific secondary loss is unlikely to yield comprehensive efficacy. Hence, the exploration of combination therapy and the quest for single-drug interventions capable of addressing multiple secondary injuries represent imperative and worthwhile research directions.

Author Contributions

ZH was resposible for conceptualizing, writing and revising this article; CZ drew the illustrations; JXL developed the search strategy and literature search; FFZ is responsible for combing references; XYQ and FG designed and critically revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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