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MULTI-AUTHOR REVIEW

Melatonin and mitochondrial function during ischemia/reperfusion injury

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Abstract Ischemia/reperfusion (IR) injury occurs in many organs and tissues, and contributes to morbidity and mortality worldwide. Melatonin, an endogenously produced indolamine, provides a strong defense against IR injury. Mitochondrion, an organelle for ATP production and a decider for cell fate, has been validated to be a crucial target for melatonin to exert its protection against IR injury. In this review, we first clarify the mechanisms underlying mitochondrial dysfunction during IR and melatonin's protection of mitochondria under this condition. Thereafter, special focus is placed on the protective actions of melatonin against IR injury in brain, heart, liver, and others. Finally, we explore several potential future directions of research in this area. Collectively, the information compiled here will serve as a comprehensive reference for the actions of melatonin in IR injury identified to date and will hopefully aid in the design of future research and increase the potential of melatonin as a therapeutic agent.

Keywords Melatonin · Mitochondria · Ischemia/reperfusion injury · Oxidative stress

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Introduction

Ischemia/reperfusion (IR) injury occurs when the blood supply to the tissue is blocked for minutes to hours (ischemia) and then restored (reperfusion) [1]. Ischemia elicits tissue anoxia which is the basis of ischemic injury and primes the tissue for subsequent reperfusion damage. IR injury affects many organs and tissues including brain [2, 3], heart [4, 5], liver [6, 7], lung [7, 8], kidney [9, 10], skeletal muscles [11, 12], testes tissue [13], and endothelial tissue [14] contributing to morbidity and mortality worldwide [15, 16]. Numerous efforts have attempted to search for proper agents for the treatment of IR injury every year. Notably, melatonin is the particularly promising one among various candidates.

Melatonin, an ancient molecular existing in various organism, is validated to be a potent antioxidant and exerts beneficial effects on many pathological conditions [17], including diabetes [18, 19], depression [20, 21], infection [22, 23], neurodegeneration [24, 25], and metabolic syndrome [26, 27]. The roles of melatonin on IR injury get much attention in recent years and multiple novel mechanisms have been revealed [28, 29]. Melatonin is highly concentrated in mitochondria and its roles on mitochondria have been widely explored in previous studies [30–32]. Mitochondrion, an organelle for ATP production and a decider for

cell fate, has been verified to play crucial roles in IR injury and the protection of mitochondrion can inhibit IR injury in multiple organs [33–35]. Similar to studies about other pathophysiological processes, melatonin's protective actions on IR injury are mainly achieved by inhibiting mitochondrial dysfunction [32, 36, 37]. Melatonin has been shown to ameliorate IR-induced disturbance in mitochondrial redox state, membrane structure, biogenesis, dynamics, and mitophagy and has attracted attention as an appealing therapeutic strategy [17, 30, 32].

The focus of this review is to summarize the latest research progress regarding the roles of melatonin in IR injury. First, we introduce the mechanisms underlying mitochondrial dysfunction in IR and melatonin's protection of mitochondria under this condition. Thereafter, the protective effects of melatonin against IR injury in various organs and tissues, including brain, heart, liver, and others are presented. Finally, we explore several potential future directions of research in this area. Collectively, the information compiled here will serve as a comprehensive reference for the actions of melatonin in IR injury identified to date and will hopefully aid in the design of future research and increase the potential of melatonin as therapeutic agent.

Mitochondrial dysfunction induced by IR

Mitochondrial dysfunction has been validated to be a crucial event in IR injury by numerous studies [38]. The period of ischemia primes the tissue for subsequent damage upon reperfusion which leads to a burst of free radical from mitochondria [39]. The excessive free radical directly causes oxidative damage to mitochondrial respiratory chain and metabolism enzymes further leading to more electron leakage and free radical production [40, 41]. Moreover, free radical is also validated to damage mitochondrial membrane structure [42] and increase mitochondrial permeability transition pore (MPTP) opening [43], resulting in loss of membrane potential and more free radical production [41]. The increased mitochondrial permeability also increases pro-apoptosis factors' release to cytoplasm [44] (Fig. 1). Moreover, IR-induced damages also impair mitochondrial

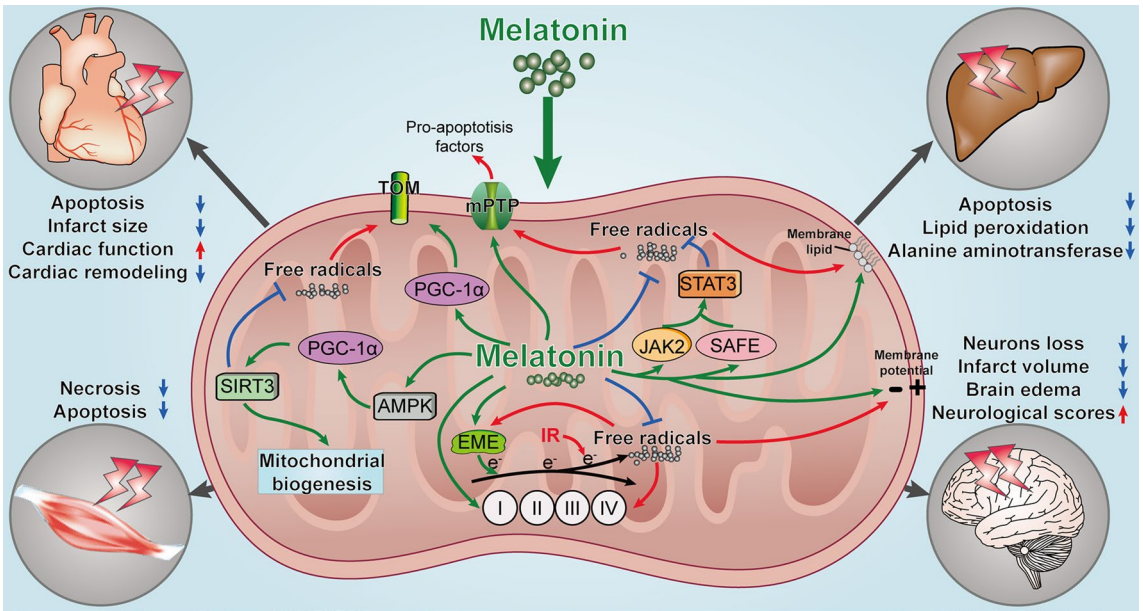

Fig. 1 The mechanisms underlying mitochondrial dysfunction in IR and melatonin's protection of mitochondria under this condition. IR leads to electron leakage and excessive free radical production in mitochondria. The excessive free radical directly causes oxidative damage to mitochondrial respiratory chain and EME further leading to a burst of electron leakage and free radical production. Moreover, free radical also damages mitochondrial membrane structure (TOM complex reduction and mitochondrial membrane lipid peroxidation) and increases MPTP opening, resulting in membrane potential loss and pro-apoptosis factor release. Apart from directly scavenging free radical, melatonin also activates STAT3, a transcription factor for antioxidant enzymes, by activating SAFE pathway and JAK2. Melatonin activates AMPK–PGC-1α–SIRT3 axis to reduce mitochondrial oxidative stress and enhances its biogenesis. By activating PGC-1α, melatonin also upregulates TOM complex, the entry gate for the majority of precursor proteins that are imported into the mitochondria. As a result, melatonin exerts protective effects on diverse organs enduring IR injury. *Red arrows* damaging processes. *Green arrows* promotion or amelioration. *Blue arrows* inhibitory effects (*AMPK* adenosine monophosphate-activated protein kinase, *EME* energy metabolism enzymes, *IR* ischemia/reperfusion, *JAK2* Janus kinase 2, *MPTP* mitochondrial permeability transition pore, *SAFE* survivor activating factor enhancement, *SIRT3* silent information regulator 3, *STAT3* signal transducer and activator of transcription 3, *PGC-1α* peroxisome proliferator-activated receptor-gamma coactivator-1α, *TOM* translocases in the outer membrane)

dynamics and mitophagy thereby affecting quality control of mitochondrial network [45, 46]. Eventually, mitochondrial dysfunction leads to increased apoptosis and exacerbates IR-induced injury in various organs and tissues.

Melatonin protects mitochondria from IR injury

From the above brief clarification, we note that it is of great importance to break the vicious circle between free radical and mitochondrial injury during IR process. Notably, melatonin is an ideal candidate. First of all, as a potent-free radical scavenger, melatonin is highly concentrated in mitochondria, indicating its capacity to resist mitochondrial oxidative injury [32, 47]. Apart from directly scavenging free radical, melatonin also exerts antioxidant activity by upregulating antioxidant enzymes and downregulating pro-oxidant enzymes [48–50]. Besides, melatonin has been documented to upregulate the activity of all four complexes in respiratory chain under IR conditions [51, 52] which may reduce the production of free radical. At decreased level of oxidative stress, lipid peroxidation is repressed and the mitochondrial membrane structure is well preserved by melatonin [36]. Moreover, melatonin is also documented to regulate mitochondrial membrane permeability by modulating the translocases in the outer membrane (TOM) complex [28] and MPTP activity [53]. As a result, melatonin well preserves mitochondrial membrane potential and inhibits release of pro-apoptosis proteins including cytochrome *c* [54] and high-temperature requirement protein A 2 (HtrA2) [55]. Apart from above actions, melatonin was also validated to maintain a healthy mitochondrial network by regulating mitochondrial biogenesis [51], dynamics, and mitophagy [56]. Eventually, melatonin restores mitochondrial and organ function under IR conditions. Mechanistically, nuclear melatonin receptor RORα [57] and multiple pathways are revealed to be involved in the protection of melatonin, including silent information regulator 1 (SIRT1) [2], Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) [58], survivor activating factor enhancement (SAFE) [29], and adenosine monophosphate-activated protein kinase (AMPK) [51], which will be clarified later (Fig. 1). The activation or block of these targets could promote or repress the protective effect of melatonin on mitochondria.

Protection of melatonin against IR injury in nervous system

The ischemic insult in the nervous system is accompanied by multiple physiopathological events, including reactive oxygen species (ROS) burst, Ca^{2+} dyshomeostasis, mitochondrial dysfunction, proinflammatory mediator release, excitotoxicity, and eventually programmed neuronal cell death [59, 60]. Melatonin was validated to be protective against ischemic injury in nervous system. In oxygen–glucose deprivation (OGD)-treated primary cerebrocortical neurons, melatonin inhibits loss of mitochondrial membrane potential, release of mitochondrial factors, and activation of caspase-1 and -3, thereby attenuating OGD-induced apoptosis [61]. After hypoxic exposure, the retinal ganglion cell showed mitochondrial dysfunction and increased oxidative stress. Melatonin treatment preserves mitochondrial function as indicated by a reduction in cytochrome *c* leakage into the cytosol [62]. The in vivo study revealed that melatonin decreases infarct size and improves neurological scores after permanent middle cerebral artery occlusion (MCAO) in mice, which is also associated with reduced cytochrome *c* release and caspase-3 activation in ischemic tissue [61].

Subsequent reperfusion exacerbates ischemia-induced injury in nervous system. The in vitro study revealed that melatonin application during reoxygenation inhibits the hypoxia/reoxygenation-induced loss of the mitochondrial membrane potential, release of mitochondrial cytochrome *c* and activation of caspase-3 [63]. Multiple in vivo studies also validated the protective role of melatonin after reperfusion. Fukaya and colleagues conducted a series of studies about the protective effect of melatonin on fetal brain IR injury. Their results showed that melatonin pre- or post-treatment effectively reverses IR-induced reductions in the respiratory control index (RCI) (a marker of mitochondrial respiratory activity) and in the ADP/oxygen ratio and also reduces the elevation in concentration of thiobarbituric acid-reactive substances in the mitochondria of fetal brain [37, 64, 65]. Melatonin also preserves mitochondrial function and ameliorates neuronal cell injury of newborn rats after hypoxia–ischemia/reperfusion [66, 67]. Similar protective effects were also observed in brain of adult animals. The mitochondrial complex I and IV activities were impaired with transient MCAO while melatonin administration restored them. Moreover, melatonin treatment after MCAO significantly inhibits inducible nitric oxide synthase (NOS) activity and attenuated expression of the inducible isoform, resulting in decreased total NOS activity and tissue nitrite levels [52]. Also in MCAO rats, melatonin regulates mitochondrial membrane permeability by inhibiting MPTP opening after IR, leading to decreased cytochrome *c* release and less caspase-3 activation in infarct area [53]. Our study on IR injury of adult mice brain revealed that melatonin confers a cerebral-protective effect through the activation of SIRT1 signaling which is associated with a well-preserved mitochondrial membrane potential, mitochondrial complex I activity, and mitochondrial cytochrome *c* level [2]. As a result, melatonin treatment diminishes the loss of neurons,

decreases the infarct volume, lowers brain edema, and increases neurological scores after cerebral IR.

Apart from melatonin, melatonin's precursor or metabolite also exerts neuroprotective effects under ischemia and IR conditions. *N*-Acetylserotonin, an immediate precursor of melatonin, inhibits cell death induced by OGD or H_2O_2 in primary cerebrocortical neurons, primary hippocampal neurons and organotypic hippocampal slice in vitro, meanwhile reduces hypoxia/ischemia injury in the MCAO mouse model of cerebral ischemia in vivo. Notably, the neuroprotective effects of *N*-acetylserotonin are also associated with its actions on MPTP opening, mitochondrial fragmentation, and subsequent pro-apoptosis factor release [68]. 6-Hydroxylmelatonin, a normal metabolite of melatonin in vivo, is shown to scavenge ROS, maintain mitochondrial transmembrane potential, and inhibit lactate dehydrogenase and cytochrome *c* release, and caspase-3 activity during IR [69]. However, unlike melatonin, melatonin's precursor or metabolite cannot provide neuroprotection through the activation of melatonin receptors. Moreover, unlike free melatonin, the nanocapsulated melatonin is more slowly degraded by light and cleared by the circulating blood, which exhibits higher potential to rescue neuronal cells and mitochondria during cerebral IR insult [70].

Protection of melatonin against myocardial IR injury

Myocardial ischemia leads to cardiomyocyte anoxia, which is detrimental to the survival and function of these cells. In isoproterenol (ISO)-induced myocardial ischemia rat model, melatonin treatment reduces ischemia-induced mitochondrial dysfunction and rescues cardiac tissue [71]. The further study revealed that ISO induces myocardial ischemia and increases mitochondrial oxidative stress, leading to decreased activity of key enzymes of the Kreb's cycle and the respiratory chain. Melatonin inhibits above changes and enhances the antioxidant enzymes activity, preserving mitochondrial redox potential [36]. The modulation of mitochondrial membrane permeability is also involved in melatonin's protective effects during ischemia. The TOM complex located in the outer membrane of mitochondria is the entry gate for the majority of precursor proteins that are imported into the mitochondria [72]. TOM70 is an important receptor in TOM machinery and ischemic/hypoxic insult reduced TOM70 expression in cardiomyocytes which partially accounts for increased mitochondrial fragmentation and ROS overload. Melatonin was demonstrated to promote TOM70 expression by activating peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) and ameliorate ischemic injury which is absent in TOM70-deficient mice [28]. Moreover, in the long run, the improved mitochondrial function by melatonin is able to mitigate adverse left ventricle remodeling after myocardial infarction [73].

Ischemic injury is usually accompanied by subsequent reperfusion injury. Reperfusion was reported to significantly alter multiple mitochondrial parameters, including mitochondrial oxygen consumption rates, complex I and complex III activity, H_2O_2 production as well as the degree of lipid peroxidation [74]. Melatonin has been demonstrated to possess protective effect against myocardial IR injury through mitochondria-dependent mechanism. The STAT3 is a transcription factor of the *manganese superoxide dismutase* (*MnSOD*) gene and interacts with MnSOD protein to increase its antioxidant activity, which plays crucial roles in mitochondrial antioxidant defense [75, 76]. In cultured neonatal rat cardiomyocytes and isolated rat hearts, melatonin pretreatment attenuates IR-induced mitochondrial oxidative damage via the activation of the JAK2/STAT3 signaling pathway [58]. Moreover, melatonin can also activate mitochondrial STAT3 through SAFE pathway to reduced myocardial IR injury [29]. The regulation of mitochondrial membrane permeability is also involved in the protective actions of melatonin. The MPTP opening in the first few minutes of reperfusion is known to be a critical determinant of myocardial IR injury, contributing up to 50% of the final myocardial infarct size [77]. Also in isolated perfused rat hearts, melatonin desensitizes mitochondria from reperfused hearts to MPTP opening as demonstrated by their higher resistance to Ca^{2+}, thereby improving the functional recovery and reducing myocardial injury after IR [4]. Moreover, when IR is combined with diabetes, melatonin preserves mitochondrial function by reducing mitochondrial oxidative stress and enhances its biogenesis, mainly by activating AMPK–PGC-1α–silent information regulator 3 (SIRT3) axis [51]. Apart from adult rat, melatonin was also documented to protect diabetic mother–offspring from myocardial IR injury. Diabetic mother–offspring exhibited augmented infarct size, cardiac dysfunction, and myocardial apoptosis in response to IR, in association with exaggerated activation of mitochondria- and endoplasmic reticulum (ER) stress-mediated apoptosis pathways and oxidative stress. The maternal melatonin application can improve the tolerance to myocardial IR injury in their offspring via restoring cardiac insulin receptor substrate 1/Akt signaling [78].

Melatonin receptors play important roles in the cardiac protection of melatonin. Melatonin receptors include membrane melatonin receptor 1, melatonin receptor 2, and nuclear RZR/ROR receptors. In a study of hypoxia/reoxygenation model of H9c2 cells, melatonin receptor agonist Neu-p11 offers protection for mitochondria, inhibits cell apoptosis, and improves the morphology and rhythm of myocardial cells [79]. Melatonin could

promote PGC-1α/TOM70 expression in ischemic myocardium but not when combined with melatonin receptor antagonist luzindole [28]. Moreover, RORα plays important roles in melatonin-exerted cardioprotection, in particular against myocardial IR injury. RORα deficiency promotes IR-induced mitochondrial impairments resulting in significantly increased myocardial infarct size, myocardial apoptosis and exacerbated contractile dysfunction [57].

Notably, cardiac mitochondria are considered as two distinct populations: subsarcolemmal mitochondria (SSM) located immediately underneath the plasma membrane and interfibrillar mitochondria (IFM) situated among the myofibrils [34]. SSM are more susceptible to calcium overload-mediated cytochrome *c* release and damage having a more rapid progression of ischemic injury than in IFM [34, 80]. However, this different response to ischemia and IR injury was neglected by above studies. Therefore, further studies can pay some attention to such issue for better clarification of melatonin's roles.

Protection of melatonin against hepatic IR injury

Liver is one of the most frequently affected organs by IR injury and the protection by melatonin administration is highly evaluated [81]. Melatonin application after hepatic IR was shown to increase the energy charge and decrease the levels of plasma nitrite, tumor necrosis factor-α, aspartate aminotransferase, alanine aminotransferase, lipid peroxidation products, and inducible nitric oxide synthase, resulting in elevated 7-day survival rates in the end [82]. The maintenance of mitochondrial function is involved in such protective effects of melatonin. Melatonin was shown to restore mitochondria respiratory function as indicated by the preserved RCI, ADP/O and State 3 respiration [6]. In addition, melatonin treatment is able to decrease ROS production [83], increase mitochondrial glutathione peroxidase activity, and attenuate mitochondrial lipid peroxidation after IR [6]. Moreover, melatonin attenuates the extent of the mitochondrial permeability transition after hepatic IR as indicated by the decreased rate of mitochondrial swelling and cytochrome *c* release [54, 84]. Dynamin-related protein 1 (Drp1) is involved in mitochondrial outer membranes fission, a process that helps to maintain mitochondrial morphology and to reduce the accumulation of functional and structural defects in mitochondria [85]. In hepatic IR injury mouse model, melatonin was documented to ameliorate mitochondrial morphology and attenuate IR injury via restoring Drp1.

Protection of melatonin against IR injury in other organs and tissues

IR injury of skeletal muscles is a common pathophysiology during peripheral vascular injury and surgeries [11], which usually induces significant necrosis and apoptosis in the skeletal muscle cells. Mitochondrial dysfunction, such as the depolarization of mitochondrial membrane potential and the release of the proapoptotic protein, is induced by IR in skeletal muscle and melatonin significantly inhibited above changes [86]. Testicular IR injury is usually induced by torsion/detorsion, which causes an enhanced ROS formation and contributes to the pathophysiology of tissue damage [87, 88]. The melatonin treatment improves testicular histological appearance after IR, attenuates cell apoptosis, promotes cell proliferation, and increases testosterone in testis tissue, partially via the inhibition of mitochondrial degeneration [89]. Moreover, melatonin was also shown to protect placenta from IR injury. Maternally administered melatonin inhibits IR-induced changes in placental RCI and fetal growth restriction [90].

Different from other tissues, nitrosative stress is more common in endothelial tissue during OGD [91, 92]. OGD in endothelial cells was shown to promote peroxynitrite formation which further initiates the release of mitochondrial HtrA2 [55]. The mitochondrial protease HtrA2 is an acknowledged mitochondrial proapoptotic protein which participates in caspase-dependent apoptosis when released into the cytoplasm [93]. As a potent antioxidant, melatonin application provides significant protection against OGD-induced peroxynitrite formation and mitochondrial HtrA2 release, thereby attenuating ischemic-like injury in endothelial cells [55].

Tissue regeneration is a promising approach for IR injury treatment and stem cells are of great interest to achieve it [94, 95]. Apart from direct beneficial effect, melatonin was demonstrated to improve stem cell therapy efficacy on IR injuries [8]. Melatonin promotes the survival of engrafted mesenchymal stem cells under hypoxia and serum deprivation condition partially through the preservation of mitochondrial membrane potential [96]. In the rat model of small bowel IR injury, combined melatonin–adipose-derived mesenchymal stem cell treatment was shown to increase mitochondrial cytochrome *c* content, an indicator of mitochondrial integrity, in intestinal mucosal cells, offering beneficial effect against small bowel IR injury [97].

Further perspectives

Among the many recent findings on melatonin, the interaction between melatonin and other important cellular

processes of IR injury and the regulatory roles of melatonin in kidney IR injury may hint at possible research opportunities.

We have discussed the free radical-induced mitochondrial damage and the melatonin's protective effect under IR conditions. Actually, in addition to redox state, mitochondrial dynamics and mitophagy also play important roles in IR injury [45, 46]. The dynamic processes of mitochondrial fusion and fission allow for damaged mitochondria to be segregated and facilitate the equilibration of mitochondrial components such as DNA, proteins, and metabolites [45]. Melatonin's roles on mitochondrial dynamics are drawing more attention in recent years and have been explored in multiple conditions, including cadmium-induced neurotoxicity [98], 1-methyl-4-phenylpyridinium-induced Parkinson's disease model [99], lipotoxicity-mediated hepatic stellate cell activation [100], and methamphetamine-induced neurotoxicity [101]. Moreover, the free radical-damaged mitochondria can be selectively removed from the integrated network via an autophagy-related process, termed mitophagy. Melatonin exerts its roles on mitophagy under conditions including liver fibrosis [102], liver cancer [103], and traumatic brain injury [104]. Mitochondrial dynamics and mitophagy are very important for mitochondrial quality control while the roles of melatonin in such processes have not been well clarified under IR conditions. A recent study by Zhou and colleagues demonstrated that IR injury activates Drp1-dependent mitochondrial fission, which subsequently induces voltage-dependent anion channel 1 (VDAC1) oligomerization, hexokinase 2 (HK2) liberation, MPTP opening, PINK1/Parkin upregulation, and ultimately mitophagy-mediated cardiac microcirculation endothelial cell death. Melatonin activates AMPKα and inhibits mitochondrial fission–VDAC1–HK2–MPTP–mitophagy axis, thereby protecting cardiac microvasculature against IR injury [56]. However, the regulatory roles of melatonin on mitochondrial dynamics and mitophagy in cardiomyocytes, or in brain, kidney, lung, and liver have not been fully explored, which deserves much attention in the future.

ER is an important intracellular membranous organelle which is responsible for protein folding and trafficking, lipid synthesis, and the maintenance of calcium homeostasis [105, 106]. ER stress, which is caused by a buildup of misfolded proteins, has been implicated in a series of pathophysiological processes [107]. Melatonin's roles on ER stress have been studied in multiple conditions [106, 108–112], especially in myocardial [57, 78, 113] and cerebral [60, 114] IR injuries. Moreover, a previous study revealed that ER stress is able to promote mitochondrial damage under the condition of bacterial infection [115]. However, it has been not validated if melatonin exerts its beneficial roles on IR injury via modulating ER stress–mitochondrial damage axis in multiple organs and tissues.

Kidney IR injury occurs in multiple clinical conditions, being a great problem complicating the course and outcome [116]. Similarly, mitochondrial oxidative damage is a significant contributor to the early phases of kidney IR injury and mitochondria-targeted antioxidants were validated to be potential protectors for renal dysfunction caused by IR injury [117]. Melatonin has been demonstrated to preserve renal ultrastructural integrity after IR injury in the male rat, as indicated by decreased serum creatinine level, urine protein-to-creatinine ratio, podocyte injury score, kidney injury score, indicators of glomerular damage, renal tubular-damage, and glomerular integrity [9]. However, the mitochondrial protective effect has not been well investigated in melatonin's protection of kidney IR injury, which deserves much attention.

Conclusion

Mitochondrial dysfunction is deeply involved in IR injury of various organs and tissues. Excessive free radical induced by ischemia and subsequent reperfusion directly damages multiple mitochondrial components including respiratory chain, metabolism enzymes, and mitochondrial membrane structure. Such damages result in mitochondrial malfunction, ATP shortage, and pro-apoptosis factor release. Moreover, the damaged mitochondria have impaired mitochondrial dynamics and mitophagy which are crucial for quality control of mitochondrial network [45, 46]. The above mitochondrial changes lead to increased apoptosis and exacerbate IR-induced injury in organs and tissues (Fig. 1).

Melatonin, an endogenous indolamine related to circadian rhythms, is a potent agent that could be for use in the treatment of IR injury. The application of melatonin ameliorates IR-induced disturbance in mitochondrial redox state, membrane structure, biogenesis, dynamics, and mitophagy and has attracted attention as an appealing therapeutic strategy. The impressive efficacy and safety of melatonin herald it as a promising agent for the treatment of IR injury. It also deserves our attention that the interaction between melatonin and other important cellular processes of IR injury and the regulatory roles of melatonin in kidney IR injury may hint at possible research opportunities in the future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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