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Review Article

Role of melatonin on renal ischemia-reperfusion injury

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ABSTRACT

Acute kidney injury secondary to ischemia-reperfusion injury can occur after an infarction, sepsis or a renal transplantation. If not treated promptly, it can be fatal due to widespread oxidative tissue injury and inflammation. Melatonin, previously known for its circadian regulatory properties, has been of recent interest in preventing and treating renal ischemic reperfusion injury because of its antioxidant and anti-inflammatory properties. In this review we summarize the pharmacokinetic properties of melatonin, the pathophysiology of renal ischemic reperfusion injury and how we can use melatonin to prevent renal ischemic reperfusion injury. Furthermore, we discuss the recent clinical trials evaluating the impact of melatonin on the renal ischemic reperfusion injury. This review summarizes the current evidence on the beneficial effects of melatonin and prospects using melatonin to improve patient care and prevent fatalities from acute kidney injury. The initial data on the effects of melatonin in preventing and treating renal ischemic reperfusion injury looks promising. However, more randomized control trials on humans need to be conducted to evaluate the complete impact of melatonin on the renal ischemic reperfusion injury, the correct formulations, dosage and the possible adverse effects. Only then can melatonin be used as an agent to prevent renal ischemic reperfusion injury.

Keywords

Renal ischemia-reperfusion injury, melatonin, kidney, acute kidney injury.

Abbreviations

Reactive Oxygen Species (ROS); Melatonin Binding Receptor 1 (ML1); Melatonin Binding Receptor 2 (ML2), Guanosine-5'-triphosphate (GTP); Rapid Eye Movement (REM); gamma-Aminobutyric acid (GABA); Survivor Activating Factor Enhancement (SAFE); Low Density Lipoprotein (LDL); ST-Elevation Myocardial Infarction (STEMI); Percutaneous Coronary Intervention (PCI); Proliferating Cell Nuclear Antigen (PCNA); Hypoxia Inducible Factor-1α (HIF-1α); Nuclear Factor-κB (NF-κB); Reverse Transcription–Polymerase Chain Reaction (RT-PCR); Adenosine Triphosphate (ATP); Mitochondrial Permeability Transition Pore (mPTP); Membrane Attack Complex (MAC); Interleukins (IL); Leukocyte Adhesion Molecules (LAD); Intercellular Adhesion Molecule-1 (ICAM-1); Vascular Cell Adhesion Molecule-1 (VCAM-1); Nitric Oxide System (NOS); Heat-Shock Protein (HSP); Inducible Nitric Oxide Synthase (iNOS); Cyclo-Oxygenase 2 (COX - 2); Reactive Nitrogen Species (RNS); N^1-acetyl-N^2-formyl-5-metho (AMFK); N^1-acetyl-5-methoxykynuramine (AMK); Glutathione synthase (GPx), Superoxide Dismutase (SOD); Nitric Oxide (NO); Streptozotocin (STZ); Cytochrome C (Cyt C); Dynamin-related protein 1 (Drp1); Mitochondrial fusion protein (Mfn1); Janus Kinase (JAK); Signal Transducer and Activator of Transcription 3 (*STAT3*);

Phosphoinositide-3-Kinase (PI3K); Mammalian Target of Rapamycin (mTOR); cAMP Response Element (CRE); Glycogen Synthase Kinase-3 beta (GSK-3β); Voltage-Dependent Anion Channel (VDAC); Tumour Necrosis Factor alpha (TNF–α); Monocyte Chemoattractant Protein-1 (MCP-1) and C-X-C motif chemokine Receptor 3 (CXCR3); Myeloperoxidase (MPO); Nuclear factor erythroid 2-related factor 2 (Nrf2); Hemeoxygenase (HO-1); Silent Information Regulator 2 associated protein 1 (SIRT1); Fibroblast Growth Factor beta (FGF-β); Hepatic Growth Factor (HGF); SRY box transcription factor-9 (SOX9); Malondialdehyde (MDA); Blood Urea Nitrogen /serum Creatinine (BUN/Cr); Neutrophil Gelatinase-associated Lipocalin (NGAL); inducible Nitric Oxide Synthase (iNOS).

SUMMARY

1. Introduction

Melatonin, an endogenous methoxyindole hormone synthesized by the pineal gland, was initially known for its regulatory effect on circadian rhythm because of its chronobiotic and synchronizing properties that reinforce oscillations or adjusts the timing of the central biological clock[1]. Apart from its sleep regulatory effects, melatonin is a verified antioxidant and an anti-inflammatory molecule with numerous health benefits[2]. Melatonin has the ability to scavenge up to 10 reactive oxygen species (ROS) compared to a classic antioxidant that scavenges one or less ROS. Therefore, it exerts such immense antioxidant effects by directly preventing oxidative tissue damage and blocking transcription factors of pro-inflammatory cytokines[3].

According to its pharmacokinetics, it displays a short half-life, a fast turnover and undergoes high first pass metabolism[4]. Melatonin can cross the membranes of the cell, organelles, and the nuclear membrane, directly interacting with intracellular molecules in the non–receptor-mediated actions, via which it exhibits anti-inflammatory, anti-apoptotic and anti-oxidative properties[5]. Moreover, melatonin can interact with both the membrane and nuclear receptors, which lead to its receptor-mediated actions[6]. Melatonin manifests high lipophilic properties and wide distribution of receptors; therefore, it easily crosses through the cell membrane and has effects in most organs[7].

Sudden temporary impairment of blood flow to a particular organ causes ischemia-reperfusion injury, which is followed by the restoration of blood flow and re-oxygenation. In kidneys, the hypoxia and reperfusion cause robust inflammatory and oxidative stress responses, resulting in acute kidney injury[8]. Acute kidney injury is a world-wide public health problem affecting millions of people, and it has become increasingly prevalent in recent years[9]. Ischemia-reperfusion injury induced acute kidney injury may take place after infarction, sepsis and renal transplantation. These events aggravate tissue damage by facilitating the initiation of an inflammatory cascade, which includes ROS, chemokines, cytokines and activation of leukocytes[10, 11]. Some experimental studies stipulate that melatonin exerts beneficial effects on kidneys, primarily through its free radical scavenging ability, maintaining organ antioxidant defences, preventing lipid peroxidation and its potential ability to induce autophagy[12, 13].

Given that oxidative stress along with inflammation are the primary causes of tissue damage in ischemia-reperfusion injury and knowing that autophagy provides an adaptive response for cells to sustain physiological function in the presence of stressful condition, this review aims to provide a perception into the mechanism and potential therapeutic benefits of melatonin in renal ischemia-reperfusion injury.

2. Role of melatonin and its synthesis in the human body

Melatonin or N-acetyl-5-methoxytryptamine, the biological clock of the human body, is primarily synthesized from the pineal gland. It helps in orchestrating and maintaining the circadian rhythm of the body, which is essential for healthy living.

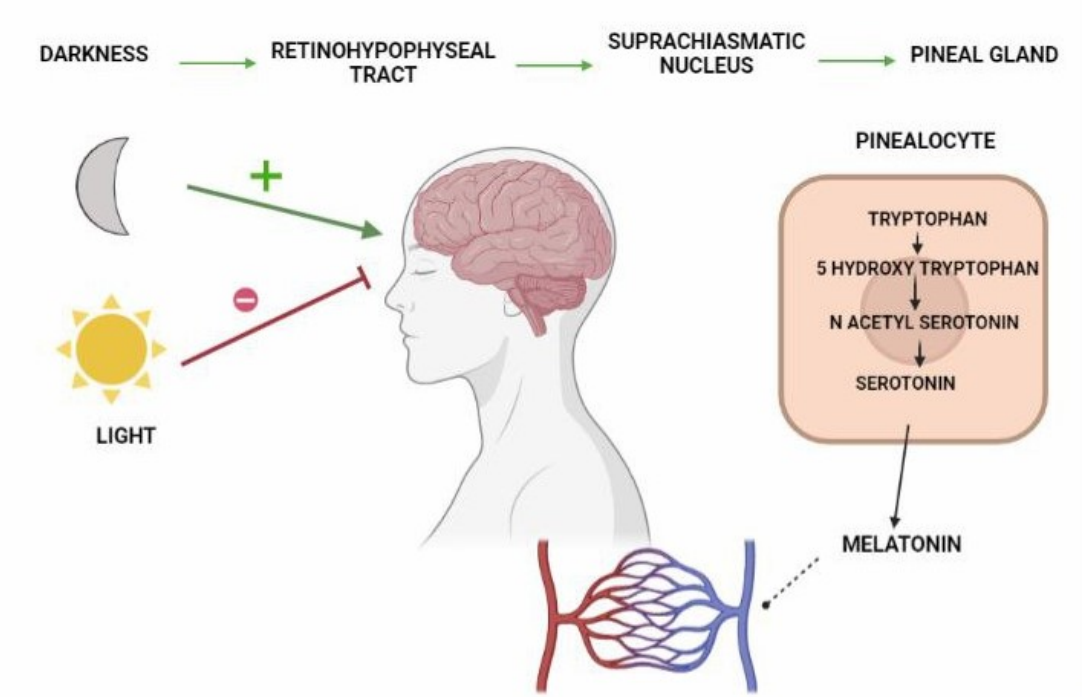

Figure 1. Melatonin Synthesis

This pleiotropic hormone, melatonin, is considered an example of a "zeitgeber". The term "zeitgeber" (meaning, time giver or time cue) refers to environmental or external cues that are capable of helping circadian time function properly[14]. Two receptors have been identified that bind melatonin - melatonin binding receptor 1 [ML1], which has high affinity and melatonin binding receptor 2 [ML2], to which melatonin binds with a lower affinity. ML1 receptors are found in the suprachiasmatic nucleus of the hypothalamus and help in the sleep-wake cycle. They are guanosine-5'-triphosphate (GTP) proteins, and act via the alpha and beta receptor pathways to inhibit adenylyl cyclase. Although widespread, the function and significance of ML2, has not yet been established and is still under study[6, 14-16].

In the human body, melatonin is endogenously formed in the pineal gland and a small part of its production is contributed by the retina. The formation of this hormone is regulated by the change in diurnal and seasonal variations where there is an increase in hormone secretion during the night, peaking from 2 am to 4 am and then there is a gradual decline[14]. The postganglionic retinal nerve fibers relay signals for the synthesis and secretion of the 'sleep-wake hormone' by passing via the retinohypothalamic tract, the suprachiasmatic nucleus, the superior cervical ganglion, and culminating the pathway at the final destination, the pineal gland. Tryptophan, an essential amino acid, is a key substance involved in the synthesis of melatonin in the cells of the pineal gland. The sympathetic nervous system, the alpha 1 and beta 1 receptors through cAMP signaling and the suprachiasmatic nucleus control the formation and release of the hormone[14, 17]. The pathway of melatonin synthesis is illustrated in Figure 1.

The word most commonly associated with melatonin is sleep. One of the most important functions of this hormone is regulating the sleep-wake cycle. Exogenous melatonin has been proven to be effective in disorders of sleep and arousal, such as jet lag, chronic insomnia, and others. Melatonin, when ingested, improves sleep propensity, improves wakefulness in the morning, and also increases the duration of rapid eye movement (REM) phase of sleep cycle[14]. Although unclear, the mechanism of melatonin in increasing REM sleep and improvement in sleep could be owed to a change in the regulation of gamma-aminobutyric acid (GABA) inhibition. Long-term consumption of melatonin, around 3 weeks, has shown an increase in the duration of sleep, in geriatric patients with insomnia[14].

Melatonin secreted by the ovary and placenta has an important part to play in pregnancy. It is suggested that melatonin helps maintain and

establish pregnancy by regulating the function of the corpus luteum. It was found to increase progesterone levels and maintain balance between luteotrophic and lytic factors. A synergistic effect with oxytocin has been established to facilitate delivery[18].

3. Role of melatonin in different diseases

A strong link between the absence of melatonin and an increased propensity for developing diabetes mellitus has been established. Melatonin serves to improve insulin sensitivity and reduce resistance. Some studies even explore the possibility of preventing diabetes mellitus by melatonin supplementation[19]. The strong antioxidant and free radical scavenging effect of melatonin, is also found in the beta cells of the pancreas, thus reducing its damage and helping in the prevention of type 2 diabetes mellitus[14].

Melatonin also serves as a cardioprotective agent, by upregulating the enzyme nitric oxide synthase, activating the survivor activating factor enhancement (SAFE), sirtuin-1/peroxisome proliferator-activated receptor gamma-coactivator alpha and endoplasmic reticulum-related signaling. It serves its purpose of cardioprotection by decreasing inflammatory reactions and cardiac muscle cell apoptosis. Additionally, it acts as an anti-atherosclerotic agent by reducing atherosclerotic plaque progression and cushioning the harmful effect of oxidative low-density lipoprotein (LDL) damage[19]. Dominguez-Rodriguez et al. illustrated a strong inverse relationship between endogenous melatonin levels and cardiovascular disease in a way that nocturnal melatonin synthesis and circulating levels are reduced in patients with coronary heart disease[20]. Clinical trials demonstrate that melatonin significantly reduces the area of myocardial infarction when used in the treatment of STEMI (ST-elevation myocardial infarction) patients after percutaneous coronary intervention (PCI)[21]. Obayashi et al. suggested that melatonin may have a role in the circadian rhythm of blood pressure (BP)[22]. This study supports the hypothesis that a low nocturnal melatonin level is associated with a non-dipping BP pattern. Also, solid evidence supports that night-time melatonin administration reduces blood pressure in hypertensive patients (Scheer et al., 2004; Grossman et al., 2006)[23]. Jin et al. has illustrated that hypoxia induced pulmonary hypertension is improved by melatonin as it subdues the hypoxia induced high expression of proliferating cell nuclear antigen (PCNA), hypoxia inducible factor-1α (HIF-1α), and nuclear factor-κB (NF-κB)[24]. Melatonin secretion decreases with age and decreased melatonin levels are found to be associated with various diseases, such as dementia, mainly neuro-degenerative disorders, especially Alzheimer's and other types of senile dementia[25, 26]. In affected individuals, the melatonin rhythm is also abolished. It has been clinically proven that adequate sleep and a well-functioning circadian clock offer protection against neurodegeneration. Melatonin therapy has been involved in multiple clinical trials to prevent early-onset Alzheimer's and to assist in healthy mental aging[18, 27].

Dysfunction of melatonin signaling leads to a plethora of consequences that goes far beyond sleep difficulties, i.e. leading to hypertension, anxiety, and free radical related injury to various organs[28].

4. Melatonin receptors in kidneys

Melatonin (N-acetyl-5-methoxytryptamine) reaches all tissues of the body shortly after circulating levels are attained from its secretion by the pineal gland, as well as from its exogenous administration. The major physiological function of melatonin is to maintain circadian rhythm by acting on Melatonin-1a (Mel1a=MT1) and Melatonin-1b (Mel1b=MT2) receptors in the suprachiasmatic nucleus of the hypothalamus[29,30]. Drew et al, 1998 have demonstrated gene expression for these receptors in the human fetal kidneys by detecting 2-(^{125}I) iodomelatonin binding sites at the outer periphery of the developing renal cortex. The genes for both the receptors were identified by reverse transcription–polymerase chain reaction (RT-PCR) of the human fetal kidney mRNA. Mel1a and Mel1b receptors are composed of 350 and 362 amino acids respectively and are G-protein coupled membrane receptors that act by inhibiting the formation of cAMP as well as cGMP. They have four intracellular and four extracellular domains, 7 transmembrane helices. The Mel1a receptor has higher affinity than the Mel1b and is responsible for most of the physiological actions. Protein kinase-Cα activation is mainly responsible for the production of the melatonin effect[18]. Retinoid-related orphan nuclear hormone receptor (RZR/RORα) is a nuclear receptor which belongs to the retinoic acid receptor superfamily and is responsible for the immunomodulation in

peripheral tissues, cellular growth, and differentiation of bone by melatonin[31].

5. Pathophysiology of renal ischemia-reperfusion injury

Renal ischemia reperfusion injury, a component of intrinsic acute kidney injury, is associated with high morbidity and mortality[32,33]. This is associated with adverse clinical outcomes in patients undergoing organ transplantation, major surgery, or sepsis[34]. The depletion of adenosine triphosphate (ATP) and guanosine triphosphate (GTP) due to tissue hypoxia during ischemia reperfusion injury activates numerous intracellular pathways and systems that directly or indirectly destroy cytoskeleton resulting in cell death via necrosis or apoptosis[35]. Neutrophilic infiltration following vascular endothelial insult results in a cascade of inflammatory changes, including the release of cytokines, reactive oxygen species, and myeloperoxidase, resulting in subsequent tissue damage[36].

The reduction in the production of ATP during hypoxia diminishes the activity of the Na/K ATPase pump, leading to the intracellular accumulation of sodium. To rid the cell of the excess sodium, hyperactivity of the Na/H and Na/Ca exchanger is observed. This, however, increases intracellular calcium and decreases intracellular pH[37]. High levels of free calcium within the cell activate numerous enzymes which damage the cell membrane, cytoskeleton and degrade DNA. The increase of free calcium induces the opening of the mitochondrial permeability transition pore (mPTP), which in turn activates inflammatory and pro-thrombogenic cascades causing cytokine release and apoptosis[38].

The release of cytokines, interleukins (IL), and enzymes like proteases, myeloperoxidase, and endonuclease during ischemia-reperfusion injury are responsible for local tissue injury. Cytokines like midkine (MK) are produced locally and cause tubulointerstitial damage[39]. A group of proteases called caspases activate cellular apoptosis and cause the release of pro-inflammatory cytokines including IL-1 and IL-18 [40]. Ischemia-reperfusion injury also activates the complement system through the alternative pathway by endogenous ligands (DAMPs) which form a membrane attack complex (MAC). MACs cause direct injury to renal epithelial tubular cells by inducing their apoptosis. The release of C3a and C5a during this process promotes pro-inflammatory cytokine release, ROS formation, and inflammatory cell recruitment furthering tissue necrosis and cellular apoptosis[41]. Besides this humoral response, a cell-mediated response to ischemia-reperfusion injury is also observed. The increased expression of leukocyte adhesion molecules (LAD), such as selectins, mucins, integrins, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), result in the infiltration and activation of leukocytes, which contribute to the inflammatory cascade by producing cytokines and ROS[42]. To counteract these inflammatory destructive mechanisms, the renal tubular and interstitial cells have developed reno-protective mechanisms against ischemia, like the nitric oxide system (NOS), heat-shock protein (HSP) activation, and adenosine 2a, 3 activations[37].

6. Melatonin's role in oxidative stress/free radical injury and inflammation following ischemia-reperfusion injury

Free radicals such as superoxide, hydroxyl free radical, and peroxynitrite anion are important mediators of inflammatory tissue damage following ischemia/reperfusion. They also lead to activation and secretion of inflammatory cytokines, such as tumor necrosis factor-α, interleukin-1, and interleukin-6, and facilitate the induction and expression of inducible nitric oxide synthase (iNOS) and cyclo-oxygenase (COX)-2[43]. Melatonin has been well known for its potent antioxidant effects, which is due to electron donation, and scavenges of free radicals[44].

Melatonin has been extensively studied as a reno-protective agent in ischemia-reperfusion injury. Melatonin administration before the induction of ischemia-reperfusion injury resulted in significant preservation of renal function by decreasing oxidative stress, pro-inflammatory cytokines, and infiltration of neutrophils and macrophages[45]. Melatonin directly scavenges free radicals, such as the ROS and reactive nitrogen species (RNS), which is mediated by its main metabolites 6-hydroxymelatonin, N^1-acetyl-N^2-formyl-5-metho (AMFK), N^1-acetyl-5-methoxykynuramine (AMK) and cyclic 3-hydroxy melatonin[13, 17, 46-48]. The indirect antioxidant effect if mediated by upregulating the synthesis of enzymes, such as the

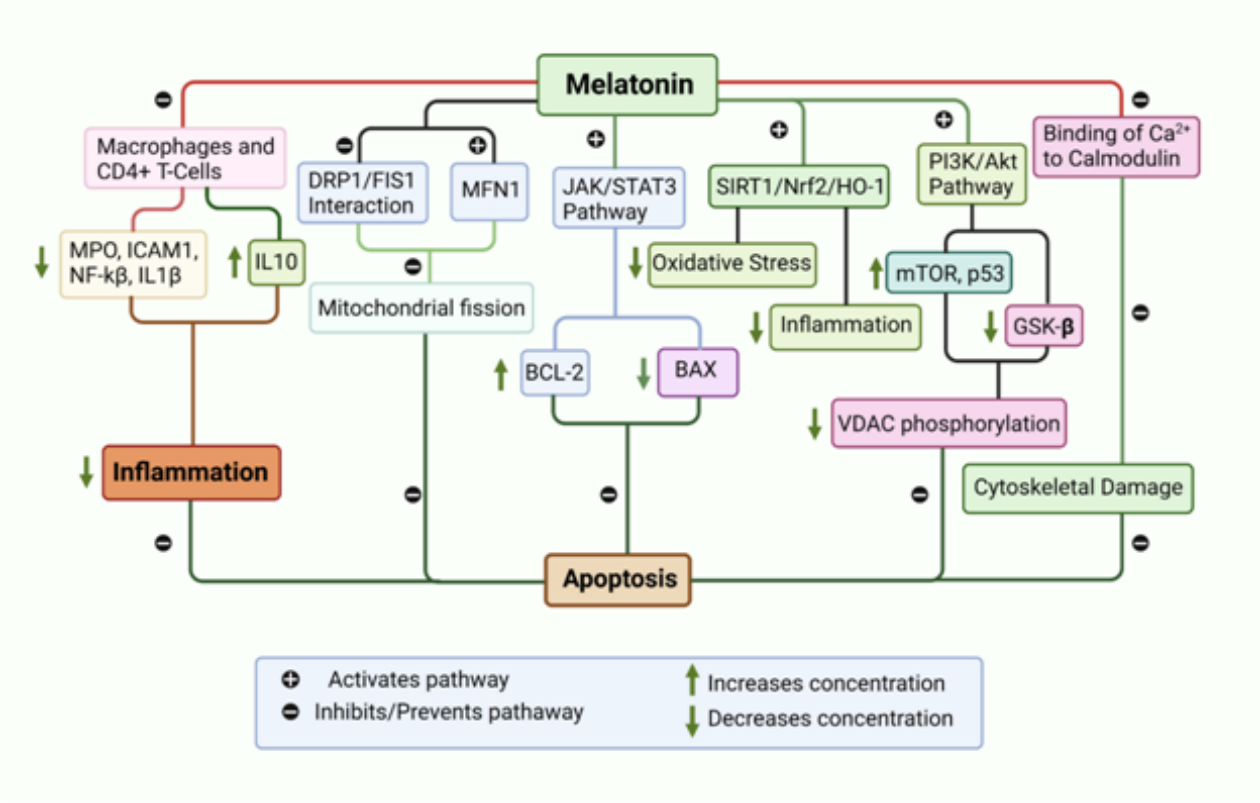

Figure 2. Summary of melatonin's role in prevention of ischemia-reperfusion injury on kidney

glutathione synthase (GPx), superoxide dismutase (SOD) and catalase, which catalyse the conversion of very harmful free radicals to neutral or non-harmful substances; and downregulating pro-oxidant enzymes like lipases, lipoxygenases, cyclo-oxygenase, proteases, and endonucleases[49-51]. Studies have shown that chronic melatonin treatment reduces renal damage by restricting lipid oxidation and nitric oxide (NO) production in streptozotocin-induced diabetic rats exposed to renal ischemia-reperfusion injury[52]. It has also been shown to down-regulate the expression of nuclear factor kappa beta (NF-kβ), p65, iNOS, and caspase-3, thus exerting anti-apoptotic action[51,53]. The role of melatonin in renal ischemia-reperfusion injury through different mechanisms is summarized in Figure 2.

As discussed earlier, reperfusion following a period of ischemia produces cellular and organellar injury. Mitochondrial free radical overproduction exceeding the renal antioxidant reserve puts the structural and functional integrity of renal cells at risk. Mitochondrial membrane damage leads to electron leakage and loss of electrochemical gradient. Thus, there is a decrease in the ATP generation. It also leads to the release of cytochrome C (Cyt C) which activates apoptosis of the affected cells as well as the generation of free radicals. Melatonin acts at the level of the electron transport chain by stimulating NADH-coenzyme Q reductase (Complex I) and cytochrome c oxidase (Complex IV) enzyme activity leading to a reduction in electron leakage and free radical generation, a process known as radical avoidance[17]. Melatonin helps prevent or reduce the abnormal release of Cyt C and Bax, mitochondrial translocation of dynamin-related protein 1 (Drp1) and Drp1/mitochondrial fission protein (Fis1) interaction. Upregulation of mitochondrial fusion protein (Mfn1) and Bcl-2 modulation via the Janus kinase (JAK)/STAT3 pathway is also mediated by melatonin[54]. Studies have shown that signal transducer and activator of transcription 3 (*STAT3*) activation exerts protective effects on renal proximal tubular epithelial cells after ischemia-reperfusion injury[55] which is further supported by an experiment in which increased serum creatinine is determined in mice harboring a genetic deletion of *STAT3* present only in the endothelium, compared with control mice after ischemia-reperfusion injury[56].

PI3K/Akt/mTOR intracellular signaling pathway plays a central role in the regulation of cell cycle, cell proliferation, survival, and growth in response to extracellular stimulation. It is downregulated following acute cellular insult like ischemia-reperfusion injury. Melatonin has been found to activate this pathway and exerts renoprotection following ischemia-reperfusion injury[57]. In 1998, Yano et al. found that Akt serine/threonine kinase can be activated by phosphoinositide-3-kinase (PI3K)-dependent or independent pathways. This in turn leads to upregulation of mammalian target of Rapamycin (mTOR) and increased expression of p53 molecule[57]. This pathway has also been found to upregulate various transcription factors that have an anti-apoptotic effect like cAMP response element (CRE) binding protein (CREB) and NF-kβ[58, 59]. HadjAyedTka et al. in 2015 mentioned that activated Akt downregulates glycogen synthase kinase-3 beta (GSK-3β) by phosphorylation which in turn decreases the level of phosphorylated voltage-dependent anion channel (VDAC), thus preventing activation of the apoptotic cascade[60]. VDAC is located in the outer mitochondrial membrane and plays a role in membrane permeability and apoptosis[60,61]. Melatonin exerts suppressive effects on macrophage and CD4+ T-cells accumulation in the renal cells. Consistently elevated mRNA levels of pro-inflammatory cytokines secreted from macrophages and T cells, including tumour necrosis factor alpha (TNF–α) and interleukin-6 (IL-6), and chemokines that play a critical role in attracting macrophages and T cells into the tissues, including monocyte chemoattractant protein-1 (MCP-1) and C-X-C motif chemokine receptor 3 (CXCR3), were also significantly decreased by melatonin[62]. Findings of decreased myeloperoxidase (MPO) level and intercellular molecule-1 (ICAM1), IL1β, NF-κβ mRNA levels and increased IL10 mRNA level in the kidney of rats with renal ischemia-reperfusion injury is also consistent with the anti-inflammatory property of melatonin[63].

A study performed in 2019 by Si Shi et al. found a significant reduction in diabetic renal inchemia-reperfusion injury in melatonin treated rats, which was mediated by melatonin dependent activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) /Hemeoxygenase (HO-1) signaling pathway by up-regulating the expression of Silent Information Regulator 2 associated protein 1 (SIRT1). SIRT1 plays a vital role in reducing oxidative stress, inflammatory stimuli, cell senescence, and apoptosis. Nrf2 is a major transcriptional regulator of antioxidant proteins and kept in the cytoplasm by a cluster of proteins under normal conditions. Following stressful events like ischemia-reperfusion injury, it migrates to the nucleus which is further enhanced by SIRT1. SIRT1 plays a role in melatonin dependent manner in the activation of Nrf2 leading to increased intranuclear accumulation, DNA binding capacity, and transcriptional activity. This in turn upregulates the activity of a potent antioxidant enzyme Heme Oxygenase-1 (HO-1)[52]. Melatonin also exerts cytoskeletal protection of renal cells as it has a high affinity for Ca^{2+} -binding proteins like calmodulin and calretinin. Calcium starts to accumulate in the ER following ischemia which is further aggravated by reperfusion of the tissue. Melatonin acts by strongly inhibiting the binding of Ca^{2+} to those binding proteins, thus preventing cytoskeletal damage[52]. All these mechanisms lead to an increase in tissue repair and regeneration which is evidenced by decreased kidney injury histopathological score and mediated by the expression of regeneration-related proteins fibroblast growth factor beta (FGF-β), hepatic growth factor (HGF), and SRY box transcription factor-9 (SOX9)[63].

Melatonin was also found to regulate the enhancement of autophagy through the TLR4/MyD88/MEK/ERK/mTORC1 signaling pathway in ischemia-reperfusion injury when given prophylactically[45]. Another mechanism by which melatonin decreased the oxidative stress in renal ischemia-reperfusion injury was by the reduction in renal malondialdehyde (MDA), myeloperoxidase (MPO), and protein oxidation[64]. A few studies also observed an increase in glutathione production and a decrease in lipid peroxidation when melatonin was administered in renal ischemia-reperfusion injury[64,65].

7. Melatonin's role on ischemia-reperfusion injury of other organs

Melatonin has shown similar benefits in ischemia-reperfusion injury in many other organs, including the liver, lungs, brain, and heart[66-70]. By increasing glutathione production and decreasing the generation of free radicals and neutrophil-mediated damage, melatonin was found to be cytoprotective in ischemia-reperfusion injury in hepatic, ileal, and

lung tissue[66]. Along with this, the increase in NO production and decrease in endothelin observed in melatonin pre-treatment in ischemia-reperfusion injury was found to preserve hepatic function and structure[67]. Melatonin pre-treatment in lung ischemia-reperfusion injury resulted in reduced neutrophil infiltration, intra-alveolar hemorrhage, and pulmonary edema[68,69]. The beneficial effect of melatonin was also observed in cardiac muscle cells by decreasing the oxidative damage seen in myocardial ischemia-reperfusion injury, thereby conserving myocardial tissue microstructure[69].

8. Recent studies on the renoprotective role of melatonin on ischemia-reperfusion injury

As discussed, melatonin is a receptor-independent intracellular free-radical scavanger with potent antioxidant capacity and anti-inflammatory properties widely used to tackle ischemic reperfusion injury. This allows the neutralization of free radicals and stabilizes the membranes[70]. Thus, a lot of studies have focused on identifying the role of melatonin to limit ischemia-reperfusion injury in various organs including liver, heart and kidneys. Reynoso *et al*. in his study explained the effect of melatonin on increasing glutathione levels and reducing lipid peroxidation[65]. These helped in reversing the ischemic reperfusion injury caused by renal transplant. Melatonin also preserved renal function and prevented the rise in nitrite oxide (NO) levels, which is postulated to be the main cause of renal injury[65]. As we have discussed before, hypoxia and acidosis are the main contributing factors in causing renal injury. Beckman et al.[71] in his study postulated that the production of nitric oxide can also aggravate the ischemic insult on the vital organs of the body. This theory is still being scrutinized as the effects of NO differ according to its sites of production, action and concentration according to Goldstein et al.[72]. NO at high concentrations interacts with superoxide to produce peroxynitrite (ONOO). Peroxynitrite also oxidizes sulfhydryl groups and produces hydroxyl radicals (OH) which are able to induce membrane lipid peroxidation[65]. As mentioned in the previous sections, melatonin and its effects on these free radicals have been studied widely and is said to be the scavenger of these free radicals[73,74]. Hence, giving melatonin can prevent the formation of these radicals and this along with the increased production of glutathione can prevent renal ischemic reperfusion injury[65]. Panah *et al*. designed the first randomized clinical trial studying the effects of melatonin on renal ischemic reperfusion injury in humans[75]. Forty transplant patients were randomly assigned to receive either 3 mg of melatonin or a placebo. Two blood samples were collected and later were studied to see the effect of melatonin on renal ischemic reperfusion injury. Melatonin, blood urea nitrogen / serum creatinine (BUN/creatinine) and neutrophil gelatinase-associated lipocalin (NGAL) levels in both groups were measured that these levels were higher in the group receiving melatonin as compared to the placebo group. Melatonin not only was associated with significant improvement in renal function as shown by the decreased BUN and creatinine, it also reduced the inflammatory and oxidative stress markers. This study, conducte that the use of melatonin can reduce the complications of ischemia-reperfusion injury due to its renoprotective effects in human kidney transplantation model. Although much has to be studied about the correct dosage of melatonin for its renoprotective effect in humans, a dose of 3mg oral melatonin showed significant effect in the study conducted by Panah *et al*.[75]. One of the studies conducted by Ahmadiasl et al. compared the anti-inflammatory effects of melatonin with erythropoietin and concluded that melatonin pretreatment was more beneficial than erythropoietin in protecting the kidney against inflammation and oxidative damage caused in renal ischemic reperfusion injury[76]. Another study by Yilmaz et al. also reported promising results on protective effects of zinc and melatonin on preventing the oxidative damage in renal ischemic reperfusion injury in rats. Furthermore, melatonin has been found to be beneficial in kidney transplant patients as it protects the graft from ischemia reperfusion injury[77]. This was further supported by a study done by Li et al. who explained how melatonin protected the kidney donor grafts through its anti-oxidative, anti-apoptotic and NF-kB inhibitory capacity[78]. While the initial trial in humans by Pana et al. looks promising, much is needed to be investigated before using melatonin to prevent renal reperfusion injury. It is yet to be determined whether melatonin works best alone or in combination with other agents. The correct dose to prevent renal ischemic injury without having any significant adverse effects is also to be determined. A summary of studies revealing renoprotective

effect of melatonin on ischemia-reperfusion injury is presented in Table 1.

9. Conclusion

Renal ischemia-reperfusion injury can be highly fatal due to excessive inflammation and overproduction of free radicals. Melatonin, due to its antioxidant, anti-inflammatory and free radical scavenging effects, looks promising in preventing renal ischemic reperfusion injury. While the initial studies have paved a way to widely test the reno-protective effect of melatonin in humans, much is yet to be determined before hailing it as a wonder drug. New frontiers that need to be explored include the safety profile, doses and duration of melatonin therapy. These investigations will not only help us understand the true significance of melatonin in

Table 1. Summary of studies revealing renoprotective effect of melatonin on ischemia-reperfusion injury

No.	Author/Study Country	Study Design	Subjects	Sample Size	Intervention (dosage and administration)	Outcome
1	Panah F et al./Iran[75]	Randomized Controlled Trial (RCT)	Patients undergoing renal transplant	40	3 mg/day oral Melatonin, first dose given 24 hours before RT until discharge from hospital (n=20)	Serum of oxidative stress markers such as malondialdehyde (MDA), CP, TNF-α were significantly reduced in melatonin group compared to placebo group
2	Deniz et al./Turkey[79]	Animal Intervention Study (AIS)	Male Wistar Rats	28	Intraperitoneal (IP) injection of melatonin (10mg/kg) in the last 5 days of a 15-day trial period. I/R was induced at the end of 15 days.	Melatonin group had significantly reduced BP, oxidative stress, improved renal function and limited microscopic structural changes in kidney
3	Kurcer Z et al./Turkey[48]	AIS	Male Sprague-Dawley rats	48	IP melatonin 4mg/kg/day for 15 days	Melatonin group had reduced levels of MDA, protein carbonyl (PC) and Nitric Oxide (NO). Histological damage was reduced by melatonin
4	Erson N et al./Turkey[53]	AIS	Male Sprague-Dawley rats	32	IP injection of melatonin (10mg/kg), 6 hours prior to ischemia and at the beginning of reperfusion	Melatonin group had reduced level of oxidative stress products and decreased alteration from ischemic injury
5	Rodriguez-Reynoso S et al./Mexico[65]	AIS	Male Sprague-Dawley rats	120	Melatonin 10 mg/kg dissolved in 1 ml of 1% ethanol was administered by IP route	Melatonin group had reduction of the increase in creatinine and inducible nitric oxide synthase (iNOS) expression along with decreased oxidative products
6	Li Z et al./Germany[78]	AIS	Lewis rats	20	Melatonin (5 mg/kg body weight) dissolved in 5 ml milk via gavage 2 hours before left donor nephrectomy	Melatonin group had down-regulation in the expression of NF-kb 65, iNOS and caspases-3. It showed improved survival and decrease in blood urea nitrogen (BUN), creatinine, transaminases and LDH
7	Sener G et al./Turkey[64]	AIS	Wistar albino rats	48	Melatonin 20 mg/kg was administered subcutaneously 15 minutes prior to ischemia	BUN and creatinine levels after the injury were reversed by melatonin treatment

Table 1. Continued.

No.	Author/Study Country	Study Design	Subjects	Sample Size	Intervention (dosage and administration)	Outcome
8	Shi S et al./China[52]	AIS	Male Sprague-Dawley rats	36	Melatonin was injected 10 mg/kg dissolved in 1% ethanol before renal I/R injury model	Melatonin prevents cell apoptosis, and oxidative stress in kidney, and decreased expressions of SIRT1, Nrf2, and HO-1
9	HadjAyedTka K et al./Tunisia[60]	AIS	Wistar rats	18	Melatonin (10 mg/kg) was administered intraperitoneally 30 minutes before renal clamping	Melatonin decreased the cytolysis and lipid peroxidation and also improved renal function compared to control group
10	Oguz E et al./Turkey[80]	AIS	Male Wistar albino rats	46	Melatonin 10 mg/kg dissolved in 1% ethanol was administered by IP route	Melatonin group had reduction in the increase of serum TNF-α levels and decrease histopathological injury in renal tissue
11	Cetin N et al./Turkey[81]	AIS	Albino New Zealand male rabbit	30	Melatonin (2.5 mg/kg delivered intraperitoneally) administered one hour prior to ischemia	In the melatonin group BUN and creatinine level was found decreased along with suppression of oxidative stress compared to control group
12	De Souza AV et al./Brazil[82]	AIS	Male Wistar rats	44	IP injection of melatonin 50 mg/kg 40 minutes before left renal ischemia	Melatonin was able to decrease but not prevent acute tubular necrosis
12	Atilgan D et al./Turkey[83]	AIS	Adult male rats	24	Melatonin 50 mg/kg was injected by IP route 30 min ureteral obstruction	Melatonin reduced the oxidative stress and preventive the partial unilateral ureteral obstruction effect induced oxidative damage
13	Kurcer Z et al./Turkey[48]	AIS	Male Wistar albino rats	14	Melatonin (10mg/kg IP) was administered 10 minutes before ischemia	Melatonin group demonstrated decrease in biochemical indices without any change in the cytokine levels and decrease the histopathologic changes caused by IR

Animal Intervention Study (AIS); Randomized Controlled Trial (RCT); IP - intraperitoneal; malondialdehyde (MDA); I/R – ischemia-reperfusion;

preventing ischemia-reperfusion injury, but they will also help us develop the correct strategies for its use in preventing and treating renal ischemic-reperfusion injury.

Conflict of Interest

The authors declare no conflict of interest.

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MRA collected the data, performed the background literature review for the manuscript. MRA, AJ, SK, AM, KT, YMN, SS, HS, GK, FNA contributed equally in drafting the initial manuscript. MRA and FNA revised the manuscript. MRA supervised the project. All authors significantly contributed to the design and/or writing and approved the final version of the manuscript.

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