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Insight into the effects of melatonin on endoplasmic reticulum, mitochondrial function, and their cross-talk in the stroke

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Ischemic stroke has remained a principal cause of mortality and neurological disabilities worldwide. Blood flow resumption, reperfusion, in the cerebral ischemia prompts a cascade in the brain characterized by various cellular mechanisms like mitochondrial dysfunction, oxidative stresses, endoplasmic reticulum (ER) stress, and excitotoxicity, finally resulting in programmed cell death. Any changes in the ER-mitochondria axis are probably responsible for both the onset and progression of central nervous system diseases. Melatonin, a neurohormone secreted by the pineal gland, has antioxidative, anti-inflammatory, and anti-apoptotic properties. Most studies have shown that it exerts neuroprotective effects against ischemic stroke. It was observed that melatonin therapy after the stroke not only leads to reduce mitochondrial dysfunction but also cause to alleviate ER stress and inflammation. This review discusses the impact of melatonin on mitochondrial, ER function, and on the crosstalk between two organelles as a therapeutic target for stroke. Given that the influences of melatonin on each organelle separately, its effects on mechanisms of crosstalk between ER and mitochondria are discussed.

Key Words: Endoplasmic reticulum stress, Stroke, Melatonin, Mitochondria dysfunction.

Introduction

Stroke is the rapid progress of neurologic deficit and is considered the second leading cause of death in the world, with a 5.5 million mortality every year (1). Overall, the risk of being affected by stroke in lifelong is 8–10%, as estimated 1 in 4 adults will experience a stroke in their lifetime (2). Estimation of the World Health Organization (WHO) showed that a stroke happens every 5 s (3). Strokes generally can be classified into 2 categories, ischemic (caused by the blood vessel occlusion) or hemorrhagic (caused by the blood vessel rupture). The prevalence of hemorrhagic strokes is low but more likely to be fatal (4).

It was observed the key role of endoplasmic reticulum (ER) and mitochondrial dysfunction in different neurological diseases such as stroke, so investigating the crosstalk between these two organelles could be a beneficial approach to discovering a new therapeutic target. Recently, there has been a great interest in understanding the crosstalk between the ER and mitochondria. Physical and functional interaction of the ER-mitochondria exerts a critical role in various cellular pathways and growing evidence emphasizes its alteration in numerous neurological diseases, like Alzheimer's Disease (AD), Parkinson's Disease (PD), and stroke. There are inter-organellar interactions between these two organelles, especially in Ca^{+2} homeostasis (5), mitochondrial fragmentation (6), and apoptosis (7). These organelles are often tightly connected to mitochondria-associated ER membrane (MAM) proteins,

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which enable the transfer of Ca^{2+} from the ER to mitochondria and contributing to mitochondrial metabolism (8). Detailed investigation of ER-mitochondria crosstalk and disrupted functions of these two organelles in ischemia can be a good target for pharmacological interventions.

Melatonin (N-acetyl-5-methoxy-tryptamine), an indole mainly produced in the pineal gland, has been demonstrated to be an important cellular antioxidant and is able to scavenge toxic free radicals and consequently associated reactants (9). There is evidence supporting melatonin anti-inflammatory mechanisms in numerous diseases, such as cardiovascular disease (10) and neurologic dysfunctions (11,12). There have been shown multiple beneficiary effects of melatonin in brain infarct through inhibiting ER stress and autophagy, alleviating mitochondrial dysfunction (13), decreasing neuron apoptosis (14), and reducing infarct volume (15). Given that stroke leads to mitochondrial and ER dysfunction, and regarding this fact that dysfunction of each organelle aggravates their effects, using appropriate drug intervention that improves the function of ER and mitochondria lonely or in crosstalk connection can be a useful treatment for stroke. The main aim of the current review was the evaluation of melatonin effects on ER-mitochondria crosstalk following the IR injuries.

Pathophysiology of Stroke

Following blood flow interruption, continuous oxygen and glucose supply which is crucial for maintaining neuronal transmembrane gradient are ceased, leading to neuronal signaling impairment. During inadequate blood supply, progressive neuronal depolarization that is called anoxic depolarization occurs and leads to neurotransmitter release from presynaptic terminals (16,17). Glutamate, which is one of the major released excitatory neurotransmitters in the brain, accumulates in extracellular space and activates 3 classes of ionophore-linked postsynaptic receptors: N-Methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA), and kainate (KA) (18). NMDA receptor stimulation induces alteration of intracellular Ca^{2+} and Na^{2+} concentration that results in several downstream lethal reactions such as protease, kinase, lipase, and endonuclease activation, thus triggering intrinsic apoptosis pathway (19). Increased Ca^{2+} concentration in neuronal cells leads to the neuronal nitric oxide synthase (nNOS) activation and subsequent free radicals formation which contribute to oxidative stress on ischemic tissue (20). NMDA receptor activation also induce nNOS and play a critical role in excitotoxic-mediated injury (21). Another source of oxygen-derived free radicals in ischemic stroke is mitochondria, which contribute to produce reactive oxygen species (ROS) during the electron transport process (22). Activated microglia and infiltrated leukocytes can also generate ROS via the NADPH oxidase system following ischemia-reperfusion (I/R) (23).

After the ischemic insult, both resident cells of the brain and infiltrated leukocytes can initiate inflammatory responses in the penumbral region of damage. However, activated microglia induce the production of proinflammatory cytokines, enzymes, and toxic metabolites (24). Astrocytes can secrete neuroprotective and neuroinflammatory factors like erythropoietin, TGF-β1, and metallothionein 2 (25). Activated transcription factors result in more endothelial cell adhesion molecule (CAM) production in post-infarct tissue which contributes to leukocyte infiltration and more inflammatory responses (26).

Mitochondrial Dysfunction in Stroke

Mitochondria are critical organelles involved in important intracellular functions such as oxidative phosphorylation, calcium homeostasis, as well as ROS regulation (27). Regarding its significance in numerous disease, recently has been focused on mitochondrial pathophysiology as an area of research (28). In the stroke, an early and initiating event that occurs in the neurons is mitochondrial dysfunction that will eventually lead to cell death (29). Ischemia caused to depolarization of mitochondrial membrane potential ($\Delta\Psi m$), start excessive ROS production, reduction of ATP production following oxidative phosphorylation, increasing the PINK1 (PTEN-induced putative kinase 1) accumulation, recruitment of Parkin, overloading the calcium of matrix, the opening of mitochondrial permeability transition pore (mPTP), as well as the release of cytochrome c followed by apoptosis, and finally neuronal death (30,31).

Mitochondrial selective autophagy (mitophagy) is a critical cellular process that happens following mitochondrial damage or stress (32). It is recently focused on the role of mitophagy on stroke and has been evidenced in cultured neurons and some *in vivo* models. In ischemic stroke, the signaling pathway involved in mitophagy is the PINK1/Parkin pathway. Several previous studies acknowledge mitophagy as a double-edged sword due to its controversial protective or destructive role after experimental stroke (33–37). It appears that depend on the severity of mitophagy, symptoms of neuronal survival (physiological or mild levels) or exacerbating the ischemic brain injury (intensive or excessive levels) becomes evident (30). Zhang X, et al. showed that after middle cerebral artery occlusion (MCAO) in the reperfusion phase, mitophagy was activated and play a part in the inhibition of post-stroke apoptosis (33). By contrast, some previous studies also have been reported the destructive role of mitophagy following cerebral ischemia (34,35), also excessive induction of mitophagy triggers cell death in neonatal stroke (35). Mitochondria as highly dynamic cellular organelles have been contributed to processes of fission (divided into two or more daughter organelles), fusion (integration of organelles), and also mitochondrial transport to strategic locations and required guanosine triphosphatases

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(GTPases) (38–40). While mitochondrial fusion helps to repair damaged mitochondria and also cell survival through exchanging of mitochondrial DNA (mtDNA), metabolites, and also membrane, mitochondrial fission allows the damaged mitochondria segregation that subsequently is eliminated by autophagy (41). In ischemic stroke, mitochondrial dynamics in cells play a fundamental role in cell fate (30). Ischemic neuronal death occurs following mitochondrial fission by mediating Dynamin-related protein 1 (Drp1), and also Mitofusin 1 and 2 (Mfn1/2) (42–44). In mice with MCAO, during 3 h post-reperfusion, the mitochondrial fission became to appear (42). In both of the *in vivo* and also *in vitro* models of ischemia, a decrease of fusion protein Mfn2 was reported which this reduction resulted in mitochondrial dysfunction and as well as Ca^{2+} homeostasis disruption (43,44). So, overexpression of Mfn2 has improving effects on mitochondrial morphology and attenuated mitochondrial dysfunction (43,44).

In recent researches it has been described that following cerebral ischemia, mitochondria are transferred from astrocytes to neurons through cell-to-cell communication as a "help-me signaling" messenger (45). Mitochondrial transfer is a potential phenomenon that has been reported in several experimental models of cardiovascular injury and also in stroke (45–47). Several previous studies considered mitochondrial transfer as a protective mechanism for the salvage of injured cells from mitochondrial dysfunction in response to stress (45,48,49). Indeed, the possible way to lessen neuronal death after stroke might be mitochondrial transfer (50).

Endoplasmic Reticulum Dysfunction in Stroke

The endoplasmic reticulum (ER) is one of the cellular organelles responsible for synthesis, folding, and also structural maturation of about a third of all proteins produced in the cell, (51,52) as well as arranging intracellular calcium homeostasis(49). Acute ischemia and subsequent neuronal loss have a complex pathology that appears that involve ER stress (53–56). So that previous studies reported that ischemic preconditioning has protective effects on I/R injury through the reduction of excessive ER stress (57,58). During ischemic stroke, a stressful condition consisting of glucose and oxygen deprivation, activation of NMDA receptors and depletion of ER Ca^{2+} stores, and exposure to free radicals could be seen in the damaged cells. This result is in the aggregation of unfolded proteins in the ER lumen which disturbs ER function, a condition described as ER stress (51,59). Ischemia causes the unfolded protein response (UPR) because of the disturbing physiological function in the ER which followed by activation of several complex signaling pathways. It has been shown that in response to the UPR several signaling pathways become active including; protein kinase-like ER kinase (PERK), activating transcription factor 6 (ATF6), and also inositol-requiring enzyme 1(IRE1) (60). In ER dysfunction, glucose-regulated protein (GRP78) uncouples from PERK, ATF6, and IRE1 and finally commence pro-apoptotic signaling by activating CHOP (61,62). Activated CHOP can play a critical role in ER stress-related apoptosis by down-regulation of anti-apoptotic factor B cell lymphoma-2 (Bcl-2) and also ROS upregulation (63). Pharmacologic agents inhibiting ER stress-induced apoptosis may have a curative role in the treatment process of stroke in the near decades. Furthermore, a recent study in both the MCAO stroke model and in the primary neuronal cultures following hypoxia/reoxygenation, approved that taurine (as an inhibitory neurotransmitter) has a protective effect against ER stress by inhibiting the ATF6 activation. This fact indicating the harmful role of ATF6 in stroke (64). Besides, Hayashi T, et al. indicated that transient forebrain ischemia in normal rats to induction of neuronal cell death in the hippocampal CA1 subfield leads to significant phosphorylation in the eukaryotic translation initiation factor 2α (eIF2α) and PERK which are the signs of ischemia-induced ER stress (65).

ER and Mitochondria Interactions

The ER as an organelle with numerous membranes can connect to other membranous structures and act synergistically with them. Various intracellular organelles including the Golgi apparatus, peroxisomes, endosomes, lysosomes, and mitochondria have interacted with the ER, but the most studied and well-characterized connection is related to ER interaction with mitochondria (66). It has been estimated that the distance between ER and mitochondria was originally 100 nm (67), but later, researchers suggested that it can be smaller, also approximately 10–25 nm (68). In both yeast and mammals, ER-mitochondrial crosstalks represent an important link to triggering multiple cellular pathways, like proliferation, death, mitochondria dynamics, lipid metabolism, autophagy, Ca^{2+}signaling, inflammation, mtDNA distribution, bioenergetics, and unfolded protein response (UPR) (8,69).

In both ER and mitochondria, calcium and lipid metabolism are critical for function and the regulation of these organelles, however, there is a physical contact among their membranes for close integrative signaling. Mitochondrial and ER membranes join together at punctate sites like synapses formation in the nervous system referred to as the MAM so that recently identified more than 1000 distinct "MAM proteins" (66). It has been corroborated that MAMs structure plays an important role in cellular lipid synthesis and trafficking (70,71). Also, aggregation of calcium transporters and ion channels at these sites allows calcium flux between the two organelles and subsequent functionality links in a bidirectional manner (72,73). Thus, calcium-mediated ER signals to fulfill the need for protein synthesis could activate the tricarboxylic acid (TCA)

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cycle, stimulate the electron transport chain in mitochondria, and finally ATP production. In turn, ER responds to this cellular energy and mitochondrial activity by the preservation of intracellular calcium homeostasis via sarcoendoplasmic reticulum (SR) calcium transport ATPase (SERCA) pumping. It is critical the controlling contact between the two organelles because Ca^{2+} overloading by mitochondria could result in cell death (72,74). However, regulatory and chaperone proteins that are present at MAMs are involved in mitochondrial fission and fusion, demonstrating the indirect role of ER on mitochondrial morphology modulation in stress conditions (75). ER-mitochondria contact sites play a role in the assembling process and maturation of autophagosomes (66). Hamasaki M, et al. reported that the ER-mitochondria interface probably is involved in the formation of autophagosome in this location (76). So, following induction of autophagy, autophagy related genes (ATG) ATG14, ATG5 (as a pre-autophagosome marker), and DFCP1 (an omegasome marker) during the phagophore biogenesis, change their localization and shift significantly to the MAMs (76). Interestingly, data from previous studies support the important role of MAMs in inflammasome formation. The release of mitochondrial DNA is a triggering factor for inflammasome activation (77) and this proves the strategy of NOD-like receptor protein 3 (NLRP3) inflammasomes localization in the ER-mitochondria interface, providing immediate signal sensing and subsequent inflammatory responses (66).

Thus, MAMs in addition to the detection of extracellular inputs, provide a structural environment that accommodates different regulators or effector proteins (66). Considering The functional significances of the ER-mitochondria interface in numerous molecular pathways and the involvement of MAMs alterations in different pathological conditions, so that, the modulation of this axis could be a good candidate for a therapeutic approach, aimed at preventing the onset and progression of devastating diseases.

ER–Mitochondrial Crosstalk Dysfunctions in Stroke

For a long time, communication among the ER and mitochondria has focused on the neurology field. One of the common hallmarks in different neurological disorders is significant changes in their functional and physical tethers, due to their modulatory effects on a multitude of physiological processes (78). It was observed that mitochondrial dysfunctions and also ER stress are pathological events that mainly happened following cerebral ischemia (28,79). Following the excessive release of Ca^{2+} from ER, an overload of Ca^{2+} happen in mitochondria and lead to apoptosis (66). This Ca^{2+} overload caused changes in mitochondrial permeability, and release of the cytochrome c, followed by caspases-9 and -3 activation, and finally, trigger the initiation of cellular death (78). The close proximity of these two organelles through MAMs provides a direct pathway to the entrance of Ca^{2+} to mitochondria from the ER and consequently leads to remarkable elevation of Ca^{2+} concentration in mitochondria (80,81). Following cerebral ischemia and prolonged ER stress conditions, an elevation in mitochondrial matrix free Ca^{2+} can occur and subsequently reach a critical threshold to induce the mPTP opening which followed by apoptotic cascade initiation. Some previous studies demonstrated that ER stress-induced apoptosis has a mandatory mitochondrial component, moreover highlighting the close connection between ER and mitochondria (79).

The ER chaperones proteins by exerting Ca2+ regulation and ensuring proper protein folding, protect regional cells from ischemic damage. Furthermore, it was observed that MAMs coexist with numerous molecular chaperones (73). Hence, it is important to focus on to close relationship between ER–mitochondrial Ca^{2+} transfer and different molecular chaperones following cerebral ischemia. In the brain, excitotoxicity following the ER calcium release is a neuronal death mechanism that is critical in various neurodegenerative diseases (Fig. 1).

It was observed that some important chaperones are existed prominently in MAM and have a critical role in Ca^{2+} signaling between these two organelles. Mitochondrial chaperone GRP75 is one of these chaperones which has a key role in the regulation of inositol trisphosphate receptor (IP3R)-mediated mitochondrial Ca^{2+} signaling (82). It was found that following *in vivo* and *in vitro* cerebral ischemia, GRP75 overexpression could improve mitochondrial function (83,84).

In summary, finding demonstrated the coordinating function of ER and mitochondrial chaperones in the regulation of Ca^{2+} signaling between these organelles and control bioenergetics, cell survival mechanisms, and cell death decision. Also, it was found that the release of ER calcium directly induces excitotoxicity which is an important neuronal death mechanism in acute and chronic neurodegenerative diseases (79). Identifying the complete role of chaperons, as well as Ca^{2+} handling *in vivo* should provide new therapeutic strategies, also maybe about melatonin, to protect brain cells during ischemia.

Effects of Melatonin on Brain Ischemia–Reperfusion Injury

Melatonin activity is mediated by the two specific receptors in the cellular membrane, belonging to the seven-transmembrane G protein-coupled receptor (GPCR) superfamily, MT1, and MT2 (85). MT1 receptor is also located on the mitochondrial membrane. Moreover, melatonin transport into mitochondrial and ER is facilitated by the oligopeptide transporters, PEPT1/2 (86,87). Evidence suggests the role of melatonin in regulation of numerous physiological functions like the regulation of sleep, behavior and mood, anti-inflammatory activities, radical

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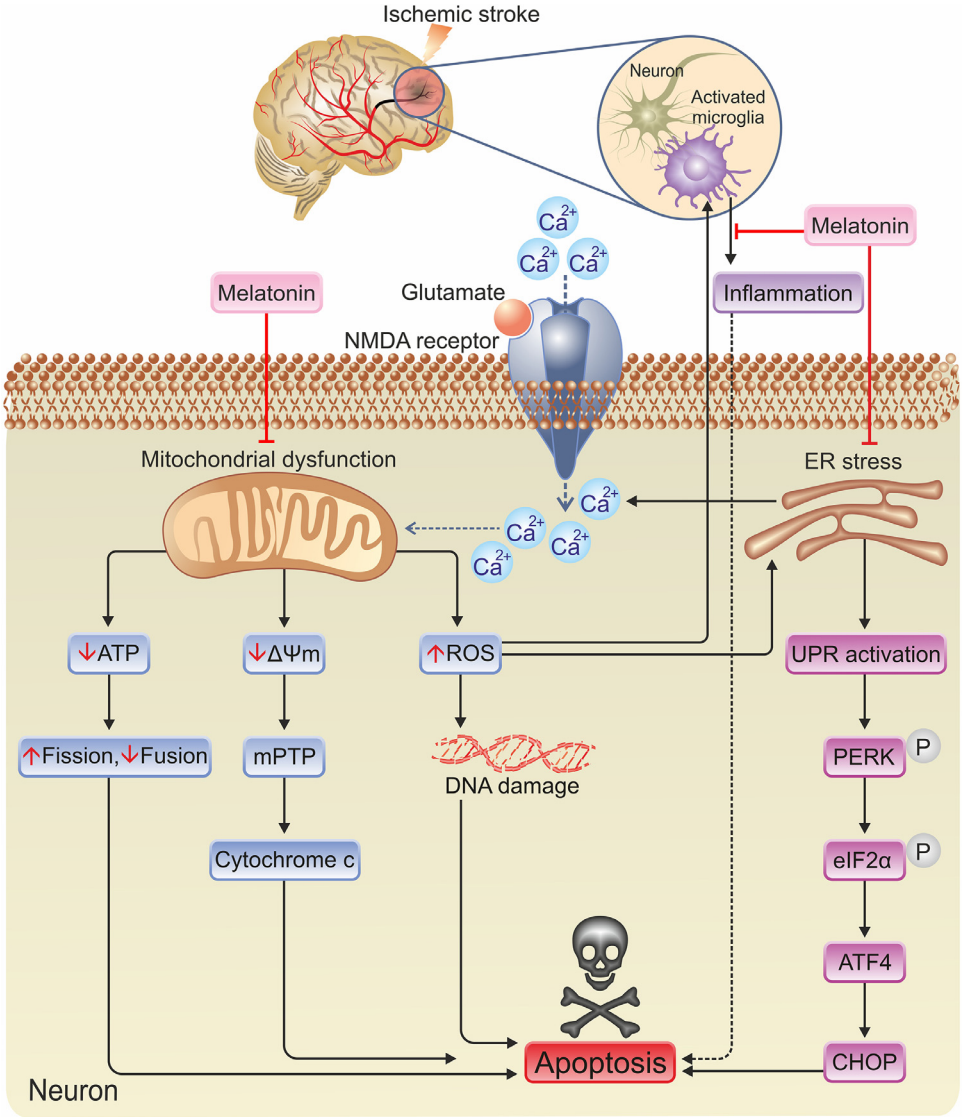

Figure 1. Schematic of the ischemic stroke-induced endoplasmic reticulum-mitochondrial Crosstalk and role of melatonin in this cascade. Stroke causes glutamate excitotoxicity and excessive Ca2+ influx followed by mitochondrial dysfunction and ROS generation consequently several pathological processes including an imbalance of mitochondrial fission and fusion, DNA damage, ATP attenuation, depolarization of mitochondrial membrane potential ($\Delta\Psi m$). ER stress activation after stroke leads to the release of Ca2+ which triggers mitochondrial dysfunction. Finally, ER stress cellular pathway accompanied with mitochondrial cascade led to apoptotic cell death. Melatonin can ameliorate ischemic injury via reduction of inflammation, ER stress, and mitochondrial dysfunctions. UPR: unfolded protein response, ER: endoplasmic reticulum, PERK: protein kinase RNA-like endoplasmic reticulum kinase, eIF2α: Eukaryotic Initiation Factor 2, ATF4: alpha Activating Transcription Factor 4, ROS: reactive oxygen species, CHOP: CCAAT-enhancer-binding protein homologous protein.

scavenging, immunomodulatory and antiangiogenic activity, and anti-carcinogenic characteristics (88). It has been shown that melatonin is a scavenger of a number of reactive oxygen and reactive nitrogen species both *in vitro* and *in vivo* (89). It stimulates antioxidant enzymes, enhances mitochondrial oxidative phosphorylation efficiency, and reduces electron leakage from ETC (90,91).

There is evidence supporting melatonin anti-inflammatory mechanisms in cardiovascular disease. Melatonin could decrease the apoptosis level of cardiomyocytes (92). Melatonin neuroprotective effects are also remarkable. Kang JC, et al. showed useful impacts of melatonin exogenous supplementation during the inflammatory-demyelinating process for the nerve fibers myelin status improvement (11). Chen J, et al. in 2014 showed that melatonin supplementation in a rat model of subarachnoid hemorrhage attenuates early brain injury after bleeding, highlighting the beneficial effects of melatonin in the modulation of pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α (12).

There is a great inter-relation between melatonin and cellular organelles. There has been found a high amount

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of melatonin in mitochondria, which renders mitochondria a potential target for melatonin (93,94). Melatonin may apply its neuroprotective mechanisms by inhibiting the mitochondrial cell death pathway (95,96).

ER stress and cytokine-dependent microenvironments have been demonstrated as main factors implicated in the pathology and progression of cerebral I/R injury (97). P21-activated kinase 2 (Pak2), a novel ER function regulator, inhibits hypoxia-reoxygenation injury which contributes to ER stress activation, oxidative stress, and calcium overload (98). It has been reported that melatonin pretreatment alleviated ER stress in N2a neuroblastoma cell HR injury by activating the AMPK-Pak2 pathway and attenuating caspase-12-mediated apoptosis whereas inhibition of AMPK with Compound C abolished the protective effects of melatonin (99).

ER stress triggers autophagy via both the PERK and IRE1 pathways during I/R injury, while melatonin preischemia treatment (10 mg/kg/d, intraperitoneally, 7 d) suppressed ER stress and autophagy as well as alleviated mitochondrial dysfunction in a MCAO mouse model (13). Lin YW, et al. demonstrated that 5 mg/kg of melatonin decreased ischemic infarct size and ER stress in MCAO rats. Also, they found that pretreatment with melatonin (10–100 mmol) reduced the levels of p-PERK and p-eIF2α and decreased neuron apoptosis in cultured neurons after oxygen-glucose deprivation (OGD) injury (14). Accumulating evidence has shown that microglia cells, multifunctional immune cells in the central nervous system, act as mediators of neuroinflammation (100,101). They have dual roles at different stages after stroke and can change their phenotypes and functions, pro-inflammation toward anti-inflammation and vice versa in response to microenvironmental changes (102).

Liu and coworkers revealed that melatonin injection at o and 24 h after ischemia diminished brain infarct and improved markedly neurological functions by regulating microglia/macrophage polarization toward anti-inflammatory phenotype in a STAT3-dependent in mouse distal MCAO model (99). In addition, *in vitro*, they found that melatonin decreased the neurotoxic effect of pro-inflammation microglia on post- OGD neurons (103). A study has reported that melatonin reduced brain damage in focal ischemia through the mechanism of elimination free radical, regulation of circadian rhythm, inhibition of inflammatory responses (104). Administration of melatonin can enhance BBB integrity, reduce brain edema and improve behavioral outcomes in animal models of cerebral ischemia (105,106).

Experimental findings discovered that neuroprotection by melatonin against stroke related to the activation of the SIRT3 signaling pathway and reduction apoptosis in the following rodent transient MCAO model (107,108). Recently, a study has described that OPA1-related mitochondrial fusion is repressed by cerebral IR injury due to inactive Yap-Hippo signaling. Restoring OPA1-related mitochondrial fusion via melatonin treatment attenuates mitochondrial damage and reduces the infarct area and death of neurons (109).

Parada E, et al. investigated the effect of melatonin against brain ischemia both *in vitro* and *in vivo* and found that injection of 15 mg/kg melatonin post-ischemia could reduce infarct volume and improve motor skills (15). In addition, melatonin can reduce OGD-induced ROS production to basal levels. The neuroprotective effect of melatonin is related to modulation of a7 nAChRs and activation of the transcription factor Nrf2 followed by overexpression of heme oxygenase (HO-1), an anti-inflammatory and antioxidant enzyme (15). It has been shown that the neuroprotective effect of melatonin administrated 1 h after MCAO in rats is mediated by a reduction in iNOS activity and nitrite levels (110). Also, melatonin administrated 2 h after ischemic-stroke in mice promotes neurogenesis (111).

Melatonin also can reduce subarachnoid hemorrhagic (SAH) injury in the brain under various mechanisms. It has been reported that melatonin effectively attenuated early brain injury after SAH via the JAK-STAT signaling pathway (112). In this JAK/ STAT pathway, melatonin increased p-STAT and expression of JAK1, leading to improved neurological score, reduced brain edema and neuronal apoptosis, and also decreased caspase-3 expression (109). Several studies have demonstrated that administration of melatonin after SAH induction diminished brain edema, reduced mortality, and improved neurological function (12,113).

Intracerebral hemorrhage (ICH) is one of the most serious forms of stroke (114). Necroptosis, programmed necrosis, plays a crucial role in the pathogenesis of stroke (115). A20, TNFAIP3, is a deubiquitinating enzyme and potent anti-inflammatory protein which controls microglial activation to regulate neuroinflammation. A20 limits RIP3-dependent necroptosis. It has been shown that pre-treatment with melatonin inhibits microglial necroptosis via the A20/RIP3 pathway, thereby reducing cell death, inflammation, and mitochondrial damage (112).

Melatonin exerts its effect against brain injury following SAH by increasing the expression of Nuclear Factor Erythroid-2 Related Factor 2 (Nrf2), decreasing ER stress, and mediating mitophagy (116). Moreover, a study showed that melatonin ameliorated intracerebral hemorrhage-induced brain injury via suppressing apoptosis, inflammation, oxidative stress, DNA Damage, and mitochondria injury (117). Recent evidence has demonstrated crosstalk between mitochondrial fission and Mst1-Hippo signaling. Due to inactive Mst1-Hippo signaling following cerebral IR injury, MFN2-associated mitochondrial fusion represses while melatonin can restore MFN2-related mitochondrial fusion via suppressing the Mst1-Hippo pathway and decrease mitochondrial damage and increase neuron survival (118).

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Table 1. Summary of effects of melatonin on stroke

Species	Dose	Time of treatment	Findings	References
N2a cells	1–20 mmol	2 h before HR injury	Modulation of the AMPK-Pak2 attenuated ER stress and caspase-12	(99)
Rat	150 mg/kg	2 h after SAH	Reduced the expression of caspase-3, release of cytochrome c, autophagy	(12)
Mouse	10 mg/kg consecutive 7 d	Pre -ischemia	Reduced cerebral infarction, brain edema, neuronal apoptosis, and ER stress	(3)
Rat	5 mg/kg	Reperfusion onset, for 90 min	Reduced infarction volumes and ER stress, and increased numbers of surviving neurons	(14)
Mouse	20 mg/kg	0 and 24 hours after ischemia	Improved neurological functions and reduced inflammation	(108)
Rat	10 mg/kg	15 min prior to onset of ischemia and at 6 h and12 h reperfusion	Modulation of DNA damage and apoptosis, reduced infarct areas	(107)
Mouse	20 mg/kg	before reperfusion	Upregulated SIRT3 expression and alleviated the neurological dysfunction and apoptosis	(103)
Mouse	10 and 20 mg/kg	24 h before IR injury	Reduced infarct area and suppressed neuron death and inflammatory response, activated the Yap-Hippo pathway, and enhanced OPA1-related mitochondrial fusion	(109)
Rat	10 mg/kg	2 h after SAH	Improved neurological function, reduced neuronal apoptosis, decreased cleaved caspase-3 level, and upregulated expresstion of JAK1	(108)
Mouse	20 mg/kg	30 min before ICH	Inhibited microglial necroptosis via the A20/RIP3 pathway, reduced cell death, inflammation, and mitochondrial damage	(112)
Mouse	150 mg/kg	2 and 12 h after SAH	Increased the neurological score, inhibited the apoptosis, mediated mitophagy and upregulated Nrf2	(116)
Rat	5 mg/kg	1, 24, and 48 h after ICH induction	Lessend severe brain edema and behavior disorders, and reduced DNA damage, inflammation, oxidative stress, apoptosis, and mitochondria damage	(117)
Mouse	20 mg/kg	24 h before ischemia	Activated MFN2-related mitochondrial fusion through suppressing Mst1-Hippo pathway reduced mitochondrial oxidative stress,	(118)

Matrix metalloproteinase-9 (MMP-9) involved in the pathogenesis of cerebral I/R injury. Following the onset of ischemia, the MMP-9 enzyme markedly activates which induces endothelial damage as well as cleaves protein components of the extracellular matrix (ECM) such as collagen, proteoglycan, and basal laminin, resulting in the transmigration of inflammatory cells and toxic molecules into the brain parenchyma (119). Delayed vascular reperfusion leads to disturbance of the blood–brain barrier (BBB) by up-regulated MMPs, finally lethal brain edema and hemorrhage (119) Hence, inhibition of MMPs can be beneficial to reduce I/R brain (120). A study found that melatonin inhibited MMP-9 activation through dual modulation of plasminogen/plasmin system and endogenous MMP inhibitor in mice exposed to transient focal cerebral ischemia (121) (Figure 1). Hence, according to findings of studies mentioned above, it can suggest that melatonin therapy improves mitochondrial and ER damages via different signaling pathway and lead to decline I/R brain injury. The effects of melatonin during stroke injury reported in studies have been summarized in Table 1.

Conclusions and Future Remarks

In the current review, we discussed the ER-mitochondria interface in stroke and the therapeutic effects of melatonin in this crosstalk. It has been demonstrated that ER-mitochondrial interactions play critical roles in various physiological and pathophysiological processes. In the ischemic brain, ER-mitochondria crosstalk is involved in multiple cellular functions such as mitochondrial Ca2+ homeostasis, the start of autophagosome formation, cellular apoptosis, lipid transportation, and also mitochondrial fission site determination. Based on the findings of previous studies, melatonin has an improving effect on each organelle function. Melatonin therapy showed that not only reduced mitochondrial dysfunction but also alleviated ER stress and inflammation. Hence, it seems that melatonin may exert a protective role on the crosstalk between the mitochondria and ER stress mechanisms following stroke.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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Ethical Approval

Not required.

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