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PII: S1043-6618(17)31474-3
DOI: https://doi.org/10.1016/j.phrs.2018.01.022
Reference: YPHRS 3808

To appear in: *Pharmacological Research*

Received date: 16-11-2017
Revised date: 17-12-2017
Accepted date: 29-1-2018

Please cite this article as: Roohbakhsh Ali, Shamsizadeh Ali, Hayes AWallace, Reiter Russel J, Karimi Gholamreza.Melatonin as an endogenous regulator of diseases: The role of autophagy.*Pharmacological Research* https://doi.org/10.1016/j.phrs.2018.01.022

Melatonin as an endogenous regulator of diseases: The role of autophagy

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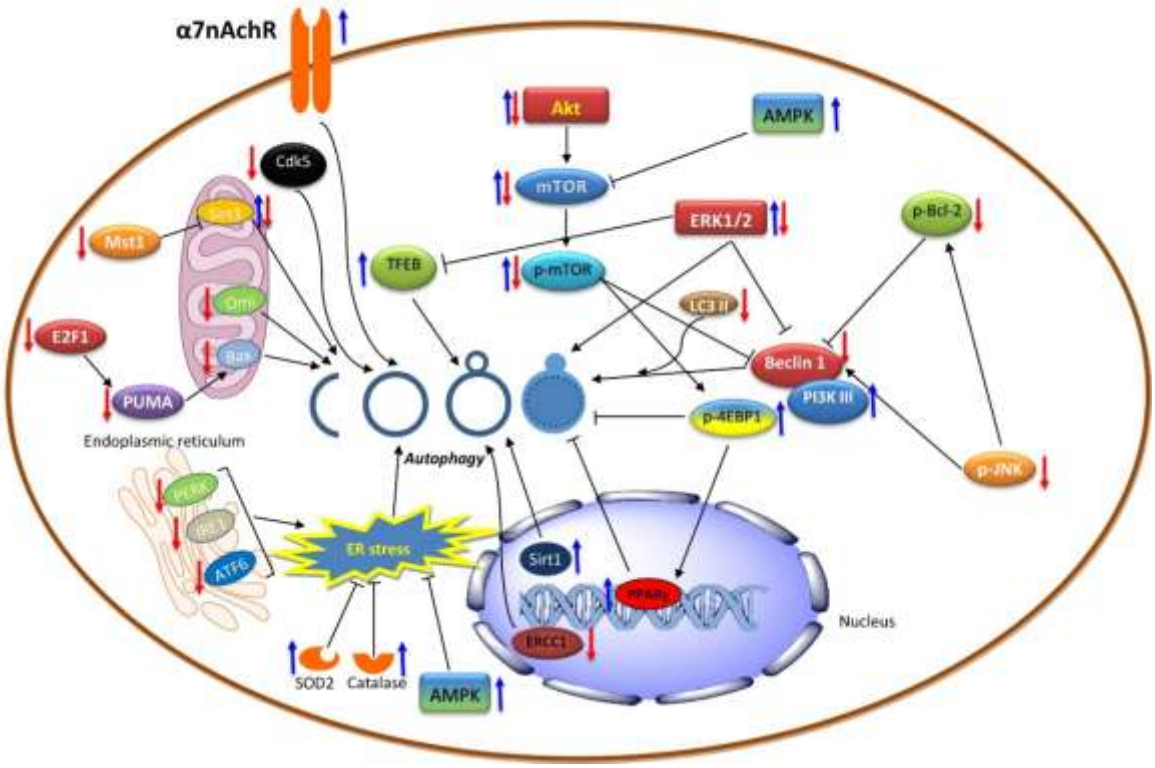
Graphical abstract



Abstract:

Melatonin has long been known for its apparent effects on sleep and circadian rhythm. It may participate as a possible therapeutic agent in neurodegenerative, cardiovascular, and endocrine disorders as well. Autophagy is a lysosomal degradation process that occurs in response to starvation and other stresses. Recent studies have reported that melatonin may modulate the autophagy process. We reviewed the current literature that has reported on how different diseases and/or experimental models change autophagy parameters. We also discussed the effect of melatonin on autophagy parameters in the central nervous,

cardiovascular, gastrointestinal and endocrine systems as reported in nonclinical studies. Moreover, the molecular targets for melatonin are discussed in details. In summary, melatonin has been reported to enhance significant protective effects in different *in vitro* and *in vivo* studies either through enhancement or inhibition of the autophagy process. Melatonin holds promise in the treatment of several major diseases. Regulation of autophagy by melatonin is a determinant parameter that should be considered in the future studies.

Keywords: Melatonin, Autophagy, Cardiovascular, Nervous system, Endocrine

Introduction:

Autophagy is a lysosomal degradation process in eukaryote cells that removes misfolded proteins and damaged organelles in order to maintain cellular homeostasis in response to starvation and other stresses [1]. During autophagy, damaged components are engulfed in double-membrane vesicles, or autophagosomes. Then, autophagosomes fuse with lysosomes and create autophagolysosomes. The contents of autophagolysosomes are degraded by lysosomal hydrolytic enzymes [2]. There are particular forms of autophagy in which specific proteins or components are delivered to the autophagolysosomes for degradation. These selective types of autophagy include degradation of endoplasmic reticulum (ER-phagy), peroxisomes (pexophagy), and mitochondria (mitophagy) [3].

Activation of a molecular complex containing the serine/threonine kinase ULK1 is the first step in the initiation of autophagy which is inhibited following activation of the mammalian target of rapamycin (mTOR) [4]. Nucleation of the autophagosomal membrane is controlled by the Bcl-2-interacting protein (beclin)-1 which increases phosphatidylinositol 3-phosphate production. Two distinct ubiquitin-like conjugation systems participate in the elongation step of autophagy. The ubiquitin-like autophagy-related (Atg)7 activation promotes Atg12 conjugation to Atg5 forming a complex with Atg16L1. In the second conjugation system, the microtubule-associated protein 1 light chain (LC)3-I is converted to a membrane-bound LC3-II form. Then, LC3 binds to the adaptator protein p62 sequestrosome 1 (p62/SQSTM1) which facilitates the degradation of damaged components in the lysosomes [2]. Thus, the LC3-II/LC3-I ratio is considered an index of autophagy.

The basal level of autophagy has several functions including quality control of protein conformation and for maintenance of cell homeostasis and survival [5]. However, depending on the stress and cell types, autophagy has been reported to play a dual role either as pro-survival or as pro-death [6]. It is important to mention that induction of autophagy participates in many cellular and physiological responses including antigen presentation [7], development [8], embryogenesis [9], metabolism, and infection removal [10]. Moreover, recent studies have demonstrated that autophagy has a role in various neurological [2], cardiovascular [11], gastrointestinal [12], immunological [10], and skin [13] disorders.

Melatonin (N-acetyl-5-methoxy tryptamine), a hormone, is synthesized by the pineal gland and various other tissues including brain, skin, gut, retina, lens and bone marrow [14]. This indoleamine molecule participates in many physiological functions such as sleep promotion, circadian rhythms modulation, immunomodulation [15], and thermoregulation [16] It also has been reported to have anti-microbial [17], anti-cancer [18] and anti-inflammatory [19] properties with potential beneficial effects on neurodegenerative [20], periodontal [21] and cerebrovascular [22] diseases. Melatonin has both direct and indirect antioxidant properties which are superior to other antioxidants, such as vitamin C, β-carotene [23] and garlic oil [24]. Very recent studies have suggested that melatonin, induces its effects through modulation of autophagy. The aim of this review was to evaluate the recent literature mostly after 2012, regarding the role of autophagy in the beneficial effects of melatonin and to discuss the underlying molecular mechanisms as currently understood.

Melatonin and the central nervous system

In neurodegenerative diseases such as Parkinson's, Alzheimer's and Huntington's diseases, misfolding and aggregation of cellular proteins are considered as one of their main features [25]. These altered proteins have to be vanished otherwise they may become toxic. Hence, it is speculated that autophagy plays an important role in initiation and progression of such neurodegenerative diseases.

Prion disease is a neurodegenerative disease. During infection, prion proteins induce misfolding of normal cellular proteins. SH-SY5Y neuroblastoma cells exposed to prion

protein (PrP) resulted in mitochondrial dysfunction leading to apoptosis [26]. Co-treatment of these cells with melatonin enhanced the LC3-II levels and attenuated Bax translocation to the mitochondria and cytochrome c secretion. This suggested that melatonin increased autophagy but decreased apoptosis in the SH-SY5Y cells. Further experiments demonstrated that in the presence of autophagy inhibitors such as bafilomycin A1, 3-MA or Atg5 siRNA, the protective effect of melatonin was attenuated. This study demonstrated that melatonin-induced autophagy protected SH-SY5Y cells from PrP-induced neurotoxicity [26]. Similarly, the results of a more recent study showed that melatonin reduced mitochondrial neurotoxicity by activation of alpha-7 nicotinic acetylcholine receptors and subsequently increased the autophagic response in PrP-treated cells [27].

Taken together, the above studies suggest that melatonin reduced neurotoxicity and autophagic cell death by acting as an autophagy activator.

Gradual degeneration of dopaminergic neurons in certain parts of the brain is the main pathological finding of Parkinson's disease. However, the mechanism responsible for the selective destruction of the dopaminergic cells is not well understood. Previous studies have suggested that melatonin had protective effects in several experimental models of Parkinson's disease [28-30]. To investigate the role of autophagy, Su et al. used 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) for selective destruction of dopaminergic neurons in the substantia nigra [31]. MPTP has long been used as an agent for the development of Parkinson's disease in animal models. Exposure of C6 cells and mice

striatal cells to MPTP increased LC3-II that was mediated by upregulation of CDK5. Pretreatment of mice with melatonin, similar to Cdk5 siRNA, reduced MPTP-induced α-synuclein aggregation in mice as the main step in the pathogenesis of Parkinson's disease [31].

For a long time, kainic acid has been used to induce experimental model of Parkinson's disease [32]. A study showed that it increased α-synuclein and the level of LC3-II and induced neuronal loss in the hippocampus of mice. All these changes were reversed by Atg7 siRNA transfection [33]. The researchers showed that melatonin had significant protective effect which was demonstrated by enhanced α-synuclein ubiquitination and reduced LC3-II, cathepsin B and lysosomal-associated membrane protein 2 (LAMP-2) [33].

Zhou and colleagues [34] used rotenone-induced neuronal cell death to explore the effect of melatonin on Parkinson's disease. They showed that rotenone promoted autophagic cell death and that its toxic effect was mediated by Bax and Omi release into the cytoplasm. Pre-treatment of Hela cells with melatonin decreased cell death which was concomitant with decreased expression of Bax and the release of omi into the cytoplasm [34].

Melatonin has been reported to have significant beneficial effects in other models of neurodegenerative diseases. Another neurological disorder, which is recognized mainly in the elderly, is Alzheimer's disease. Similar to Parkinson's disease, it is a neurodegenerative disease and is, if not the main cause of dementia, one of the main causes [35]. Melatonin has been reported as a protective agent in Alzheimer's diseases [36, 37]. For instance,

Zhang et al. [38] demonstrated that melatonin reduced amyloid β generation in N2a/APP cells. Their study further showed that melatonin increased autophagy at low levels. These researchers concluded that regulation of reactive oxygen species (ROS) and inflammation had a more important role than autophagy in the beneficial effects of melatonin on amyloid β generation [38]. It is worth noting that uncontrolled formation of ROS in the cells may lead to destruction of mitochondrial proteins, lipids and DNA and initiation of autophagy [39]. A recent study showed that mitochondria along with the endoplasmic reticulum have a critical role in the formation of autophagosomes. The study showed that autophagosomes are formed at the endoplasmic reticulum-mitochondria contact site [40]. It is well known that a number of targets that participate in the endoplasmic reticulum stress process are modulated by melatonin. Through this interaction, melatonin is able to affect both autophagy and apoptosis. For review, see the following source [41]. On the other hand, melatonin has been reported as a mitochondria-targeted antioxidant. It induces its beneficial effects on mitochondria by decrease in oxygen consumption, inhibition of oxygen flux, membrane potential reduction, and finally suppression of superoxide anion and hydrogen peroxide production [42]. Evidence is building to support the claim that melatonin has a neuroprotective effect in the CNS [43]. Studies have shown that arsenite is a neurotoxic agent. Studies undertaken to investigate the protective effect of melatonin on arsenite-induced neurotoxicity via regulation of autophagy showed that arsenite increased autophagy was reversed in the presence of melatonin [44]. This study indicated that melatonin inhibited arsenite-induced autophagy and autolysosome formation in rat primary cultured cortical neurons. Melatonin also increased α-synuclein level that was

decreased by the arsenite. It reversed the decrease in peroxisome proliferator-activated receptor gamma co-activator 1α which is involved in the biosynthesis of mitochondria. These researchers concluded that the reduced autophagy following melatonin treatment prevented the subsequent degradation of mitochondria [44]. Accordingly, it is possible that melatonin, through maintenance of mitochondrial functions, induced its neuroprotective effects.

Cadmium is another neurotoxic agent that may adversely affect health following exposure. It induces serious side effects including headache, polyneuropathy, vertigo, memory deficits, and Parkinsonism-like symptoms [45, 46]. There are reports showing that autophagy impairment has a crucial role in cadmium-induced neurotoxicity [47, 48]. For example, Li and colleagues showed that cadmium increased the LC3- II/LC3- I ratio and decreased SQSTM1 levels implying that it induced autophagy in Neuro-2a cells [48]. They also reported that cadmium decreased autophagosome–lysosome fusion, the level of transcription factor EB (TFEB), inhibited lysosomal function and induced cell death. Treatment with melatonin increased TFEB expression and the levels of lysosomal-associated membrane protein, preserved lysosomal protease activity, maintained the lysosomal pH level, and enhanced autophagosome–lysosome fusion. These findings strongly support the finding that melatonin reduced cadmium-induced neurotoxicity by regulation of autophagic-related pathways and proteins [48].

Severe peripheral neuropathy is an untoward effect of oxaliplatin therapy. Oxaliplatin is a chemotherapeutic agent widely used in the treatment of different cancers. Recently, in an

experimental model of neuropathic pain, researchers evaluated the role of autophagy in oxaliplatin-induced neuropathy in rats [49]. The results showed that melatonin treatment decreased oxaliplatin-induced neuropathy and pain. Moreover, the basal levels of LC3A/3B-I and II, beclin, Atg3, Atg5, and Atg7 were significantly attenuated in the sciatic nerve and dorsal root ganglion of oxaliplatin-treated animals indicating the impairment of autophagy. Melatonin treatment significantly reversed these changes and increased basal autophagy proteins [49].

Melatonin has been reported as good alternative for benzodiazepines and similar hypnotic drugs. It has a wide therapeutic index and is tolerated well with low abuse potential [50]. Drug addiction is a complex, multifactorial dependent disease following repeated consumption of a drug or other addictive substances. It is a major social and economical problem worldwide. Opioid drugs have been used either for analgesia or recreation purposes for decades. However, their toxic effects and high abuse liability limit their clinical usefulness. It has been reported that morphine induced mitochondrial degradation by autophagy induction in C6 cells. Moreover, morphine elevated the mRNA expression levels of autophagy-related genes including Atg3, Atg5, Atg7 and Atg12 in C6 cells. Melatonin reversed the LC3-II level to normal and decreased the number of secondary lysosomes in morphine-treated C6 cells. Melatonin also reversed the increased Atg3, Atg5, Atg7 and Atg12 mRNA expression [51]. Using PC12 cells, the researchers showed that melatonin could reverse ROS production and alleviated the impaired respiratory capacity induced by morphine. This may be an additional mechanism for melatonin that protects

mitochondria against toxic effect of opioids. Methamphetamine (Meth) is a psychostimulant that has various neurotoxic effects. It was demonstrated that neurons exposed to Meth had higher levels of autophagy [52]. The potential protective effect of melatonin on Meth-induced neurotoxicity was evaluated in two studies. Both studies reported that melatonin, by increasing mTOR activity and dissociation of the Bcl-2/Beclin 1 complex, reduced Meth-induced autophagy and induced a significant protective effect against Meth-induced neurotoxicity in a SK–N–SH dopaminergic cell line [53, 54].

Inflammation of the neuronal system is considered as the basis of many neurologic disorders such as stroke and brain injury. The role of autophagy and the protective effects of melatonin in the central nervous system were investigated recently. A study by Ding et al. [55] revealed that melatonin attenuated secondary brain injury following traumatic brain injury (TBI) in rats. The results showed that melatonin decreased Bax translocation to the mitochondria and the release of cytochrome c to the cytoplasm indicating an increased autophagy response following TBI. Moreover, some cognitive deficits and histopathological changes following TBI have been associated with mitochondrial damage which promotes metabolic abnormalities after TBI [56]. Hence, it is feasible that melatonin could protect animals from secondary brain injury after TBI through autophagy promotion [55]. In another study, the role of mitophagy in the TBI-induced release of pro-inflammatory cytokines was investigated. These results showed that inhibition of either autophagy or mitophagy increased IL-1β secretion. On the other hand, administration of rapamycin, as an autophagy inducer, attenuated the TBI-induced release of pro-

inflammatory cytokines. Mitophagy, by elimination of damaged mitochondria, has an important role in the amelioration of inflammation in the brain following TBI [57].Similarly, administration of melatonin reduced the ratio of mitochondrial to genomic DNA implying that melatonin could elicit mitophagy. Interestingly, these researchers also reported that melatonin, by preventing phosphorylation of mTOR Ser2448, suppressed the mTOR pathway and induced autophagy [57].

Stroke, another neurologic disorder, is attributed to an acute focal injury of the CNS following subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction. Stroke is considered the primary cause of disability and death worldwide [58]. Current drug therapies have limitations with numerous side effects. Therefore, finding new alternatives for treatment of stroke is needed. Melatonin is a potential candidate for serious consideration. The role of autophagy and melatonin during stroke was evaluated by Feng et al. [59]. They showed that pre-ischemic treatment with melatonin reduced acute neuronal injury following ischemic stroke by inhibiting endoplasmic reticulum stress-dependent autophagy via protein kinase RNA-like endoplasmic reticulum kinase (PERK) andinositol-requiring enzyme 1 (IRE1) signaling inhibition [59]. Similarly, melatonin reduced early brain injury by upregulation of mitophagy-associated proteins, PTEN-induced putative kinase 1 (PINK1) and Parkin, and reduction of mitochondrial damage (Figure 1). It also reduced inflammation by inhibition of NLRP3 inflammasome activation after subarachnoid hemorrhage [60]. The researchers also demonstrated that ischemic stroke activated PERK/ATF4/CHOP pathway implying that endoplasmic reticulum stress was

induced. In addition, mitochondrial dysfunction has been associated with endoplasmic reticulum stress via phosphorylation of PERK [61]. The study showed that melatonin also blocked endoplasmic reticulum stress. Therefore, it may be suggested that melatonin via this mechanism may have additional protective effects on mitochondrial function and consequently ischemic stroke. Another study by Chen et al. [62] suggested that melatonin reduced early brain injury following a subarachnoid hemorrhage in rats by autophagy enhancement and reduction of subsequent apoptosis [62]. These studies show that melatonin has a significant protective effect on the cerebrovascular system and may alleviate some permanent and serious side effects of such disorders. In another study, it was demonstrated that neonatal brain inflammation reduced autophagy that was reversed by maternal administration of melatonin [63]. They also reported that melatonin reduced brain damage in neonatal rats subjected to hypoxia–ischemia. The results showed that melatonin reversed hypoxia–ischemia-induced Sirt1 suppression and reduced endoplasmic reticulum stress [64]. In contrast to these studies, Hu and colleagues, in their recent study, showed that melatonin via inhibition of autophagy and apoptosis reduced brain damage in an experimental model of neonatal hypoxic-ischemic brain injury [65]. The researchers suggested that this controversy could be due to differences in animal models of neurological disorders. Similar to this study, melatonin by activation of PI3K/Akt signaling and inhibition of autophagy ameliorated brain injury in transient middle cerebral artery occlusion model in rats [66]. Therefore, melatonin should be considered as a potential candidate for prevention of some pathological conditions following inflammation in term and preterm infants. It is worth noting that autophagy is essential for the development and

survival of neonatal tissues soon after birth [67]. The role of melatonin in an experimental model of aging was evaluated in a recent study [68]. Noparat et al. evaluated the effect of melatonin on H2O2-induced senescence in SH-SY5Y cells. The results showed that melatonin increased autophagy and reduced aging through Sirt1 protein enhancement and decrease in p65 subunit of NF- κB [68]. Accordingly, the researchers concluded that melatonin may be an effective therapeutic agent in the aging processes. In accordance, the role of melatonin in aging, through the modulation of autophagy and apoptosis, has been discussed in details in the following review article [69].

Glioblastoma multiforme is a highly aggressive tumor with a high mortality rate in less than one year. Treatment of glioblastoma-initiating cells (GICs) with melatonin showed that melatonin increased LC3-II and induced a progressive accumulation of autophagosome vacuoles [70]. These results showed that treatment of GICs with melatonin attenuated Akt activation that resulted in autophagic cell death. Melatonin had antitumor activity that was elicited by affecting stem cell properties in GICs subpopulation and by inducing autophagic cell death [70]. In accordance, the effect of melatonin on the viability, proliferation and differentiation of stem cells has been documented well [71]. This finding supports the hypothesis that melatonin should be investigated as an alternative or an adjuvant in the treatment of CNS cancers.

Melatonin and the cardiovascular system

Basal autophagy has been reported to have a role in protecting the heart during various cardiovascular disorders including heart failure [72], ischemic cardiomyopathy [73, 74],

and cardiac hypertrophy [72, 75]. On the other hand, excessive autophagy induces cell death and promotes cardiac atrophy [76]. Rapid development of cardiac hypertrophy [75] and heart failure [77] also were reported as consequences of impaired autophagy. There are reports showing that myocardial infarction (MI) upregulates autophagy but insufficiently [78]. So, enhancement of autophagy has been proposed as a strategy for treatment of MI [78]. Melatonin has been reported to induce a significant protective effect in ischemia/reperfusion (I/R) injury, atherosclerosis, and hypertension [79-81]. This hormone can attenuate left ventricular remodeling and cardiac dysfunction following MI [82]. The involvement of autophagy in the beneficial effects of melatonin on the cardiovascular system has been the subject of a number of recent studies. For example, Hu and colleagues explored the role of Mst1/Sirt3 signaling as a protective action of melatonin against post-infarction cardiac remodeling and dysfunction [82]. in an experimental model. They showed that melatonin reduced mammalian Ste20- like kinase 1 (Mst1) phosphorylation and enhanced Sirt3 expression in heart tissue. These researchers concluded that Mst1/Sirt3 signaling had an important role in the protective effect of melatonin against post-infarction cardiac remodeling and dysfunction [82].

Cardiovascular events are much higher in diabetic patients and are a major cause of mortality in diabetic patients [83]. More specifically, diabetic cardiomyopathy is considered as the major cause of heart failure in these patients. Using an experimental model, Zhang et al. [84] showed that administration of melatonin for four weeks enhanced autophagy, alleviated adverse left ventricle remodeling and reduced cardiac dysfunction in

diabetic animals [84]. Further experiments indicated that melatonin reduced Mst1 phosphorylation and enhanced Sirt1 expression following diabetic cardiomyopathy. These effects of melatonin were abolished completely in Mst1 knock-out (KO) mice subjected to diabetic cardiomyopathy. The authors concluded that Mst1/Sirt1 signaling had a pivotal role in both autophagy induction and the cardioprotective effects of melatonin [84]. Sirt1 modulates different intracellular proteins such as adenosine monophosphate-activated protein kinase, peroxisome proliferator-activated receptor gamma coactivator-1a, mTOR, and FOXO3 to maintain the mitochondrial functions [85-88].

The physiological effects of melatonin are often mediated through activation of two classical transmembrane melatonin receptors namely MT1 and MT2. However, other receptors have also been implicated for melatonin. Accordingly, the retinoid-related orphan receptor-α (RORα) has been suggested as a nuclear melatonin receptor [89, 90]. This receptor is involved in the regulation of metabolism, development and circadian rhythm [91, 92]. The role of this receptor in the protective effect of melatonin on the cardiovascular system was the subject of a recent study [93] where it was hypothesized that this receptor may mediate, at least in part, some of the beneficial effects of melatonin on the cardiovascular system. Zhao et al. [93] using RORα inactive staggerer mice and transgenic mice with cardiac-specific RORα overexpression and also by using RORα agonist and inhibitor, examined the role of melatonin in diabetic cardiomyopathy [93]. The results of their study showed that RORα deficiency aggravated diabetes-induced cardiomyopathy and autophagy dysfunction. Furthermore, the levels of p-AMPK and mTOR were mitigated

and enhanced by RORα deficiency in the hearts of diabetic sg/sg mice. Besides, activation of RORα, melatonin normalized autophagosome numbers, reduced cardiomyocyte hypertrophy and fibrosis and improved cardiac diastolic function. In a similar way, it was demonstrated that mice with RORα deficiency had increased myocardial infarct size during myocardial I/R injury compared with wild type mice [89]. These researchers showed that these mice had mitochondria mediated autophagy dysfunction that was reversed by melatonin. In addition, it was reported that RORα deficiency enhanced myocardial I/R injury-induced mitochondrial cytochrome c release to the cytoplasm, mitochondria swelling, and increased endoplasmic reticulum stress. All of these changes were reversed following melatonin administration. This finding is suggesting that RORα mediated the beneficial effects of melatonin on mitochondria. Altogether, the results suggested that RORα has an important role in the protective effect of melatonin on myocardial I/R injury [89].

Obstructive sleep apnea syndrome (OSAS) is presented following repeated collapse of the upper airway during sleep. OSAS causes chronic intermittent hypoxia (CIH) [94]. CIH, in turn, causes multiple cardiovascular disorders such as coronary heart disease [95], hypertension [96] and myocardial hypertrophy [97]. In accordance, rats exposed to CIH had myocardial hypertrophy and a higher LC3II/I ratio and greater Beclin-1 expression in the myocardial tissue suggesting an increased autophagic response. Administration of melatonin during CIH reversed CIH-induced myocardial hypertrophy and induced more autophagy. The results showed that the expression of p-AMPK in the melatonin-treated

group was much higher than control CIH rats. In addition, pharmacological inhibition of AMPK or autophagy increased apoptosis and reduced the protective effect of melatonin in these animals [98]. This finding suggests that melatonin, via activation of AMPK, induced autophagy and had a protective effect in CIH rats.

One of the major adverse drug reactions following administration of doxorubicin (DXR), an important chemotherapeutic agent, is cardiotoxicity. Various signalings and targets have been reported to be involved in DXR-induced cardiotoxicity. Autophagy was reported to be upregulated during DXR-induced cardiotoxicity [99]. These same researchers also demonstrated that increased autophagy was concomitant with lower cell death. Moreover, melatonin has been reported to reduced the deteriorative effects of DXR on mitochondria by reversal of decreased ATP production and inhibition of cytochrome c release in an experimental model of cardiorenal syndrome [100]. On the other hand, there are reports suggesting that melatonin has protective effects on the mitochondria by preventing cardiolipin oxidation which promotes mitochondrial transition pore opening and induces cell death [101]. So, it was suggested that melatonin attenuated the cardiotoxic effect of doxorubicin by regulation of mitophagy [102]. Altogether, it appears that melatonin has significant protective effect on the cardiovascular system by modulation of autophagy [mitophagy].

Melatonin and the gastrointestinal system

The mechanism underlying the potential benefit of melatonin on the gastrointestinal system via regulation of autophagy has been the subject of considerable research. Liver is the main

organ for detoxification of hazard agents and its function may be dysregulated by toxic agents such as cadmium [103]. On the other hand, autophagy is a determinant factor in cadmium-induced hepatotoxicity [104]. Excess autophagy has been suggested as one possible mechanism that is responsible for mitochondrial loss, cellular energy mitigation and cell death following cadmium-induced hepatotoxicity [104]. So, it was hypothesized that melatonin, by regulation of autophagy, has the ability to attenuate the destructive effect of cadmium in the liver [105]. The results of the Pi et al. study showed that melatonin protected HepG2 cells against cadmium-induced autophagic cell death. The results also demonstrated that the underlying mechanism for the protective effect of melatonin was activation of SIRT3-SOD2 signaling. By activation of this pathway, melatonin significantly reduced mitochondrial reactive oxygen species [ROS] and subsequnetly reduced autophagy and cell death in HepG2 cells [105].

Hepatic fibrosis is a reversible wound-healing response to long-lasting liver injury. Carbon tetrachloride (CCL_4) has been used widely to induce experimental hepatic fibrosis. Following CCL_4-induced hepatic fibrosis, mRNA levels for beclin-1, Atg12, Atg5, Atg16L1, PERK, ATF6, IRE1, ATF4, and XBP1s were increased significantly [106]. These changes were reversed by co-administration of melatonin [with CCL_4]. The role of autophagy during I/R has been reported. Accordingly, it was suggested that the role of autophagy during I/R-induced injury is organ and model dependent [107-109]. In a study by Kang and coworkers [110] it was demonstrated that ischemia for 60 min did not change the LC3-II/LC3-I ratio, while reperfusion for 1 and 5 h enhanced the ratio [110]. These

researchers linked the enhanced autophagy to liver dysfunction and damage during I/R. In their study, melatonin promoted significant protective effect against I/R-induced hepatocellular damage. Melatonin also decreased the elevated number of autophagic vacuoles. Further experiments revealed that melatonin by increasing the phosphorylation of mTOR and its downstream molecules, 4E-BP1 and 70S6K, induced its protective effects [110]. In an animal model of acute liver failure (ALF), which results from rapid loss in hepatocyte function, San-Miguel et al. [111] evaluated the protective role of melatonin. San-Miguel and his colleagues inoculated rabbits with the rabbit hemorrhagic disease virus (RHDV) and thereby produced an animal model with properties that resemble ALF [111]. They showed that RHDV induced autophagosome and autophagolysosome formation, with upregulation of the LC3-II/LC-I ratio, and increased levels of beclin-1, and Atg5, Atg12, and Atg16L1 implying that RHDV exerted an autophagic response. All these changes were reversed by melatonin suggesting that this molecule has the potential to inhibit acute liver diseases including ALF [111].

At present, cold storage of organs to be transplanted suppresses cell metabolism and limits tissue injury. Zaouali et al. [112] evaluated the effect of a combination of melatonin and trimetazidine in a cold-storage solution for increasing steatotic liver graft preservation. They showed that cold preservation of liver reduced beclin-1, Atg7 and LC3-II implying that cold-storage reduced autophagy. However, addition of melatonin and trimetazidine also increased autophagy and induced significant protective effects that vanished in the

presence of an autophagy inhibitor. They further demonstrated that autophagy induction was mediated through AMPK activation [112].

Obesity is a global problem. Moreover, the liver undergoes many changes in obese subjects including progression of fatty liver. The results of a study of obesity on autophagy and the role of melatonin reported that in the liver of obese, leptin deficient mutant mice (ob/ob mice), melatonin decreased autophagy as reflected in a decrease in beclin1 and an increase in p62 [113]. Furthermore, it was reported that p62 KO mice had higher levels of PPARγ mRNA with increased adipogenesis and obesity [114]. So, it can be interpreted that melatonin through increment of p62 concentration reduced adipogenesis in ob/ob mice. Another study reported that ob/ob mice had lower levels of autophagy, and melatonin treatment attenuated these levels [115]. The study also revealed that ob/ob mice had much higher levels of mTOR that was reduced by melatonin.

Several studies have reported that melatonin has anti-proliferative, pro-apoptotic, and anti-angiogenic effect on HepG2 cells [116, 117]. To pursue the mechanism of melatonin-induced toxicity on hepatocellular carcinoma, HepG2 cells were exposed to melatonin and autophagic and apoptotic parameters were measured [118]. The results revealed that melatonin through activation of JNK but not mTOR induced autophagy, increased ceramide levels and finally induced apoptotic cell death [118]. The effect of melatonin plus valproic acid on bladder cancer cells was also investigated. The results showed that this combination had a higher toxicity against bladder cancer cells. The drug combination

enhanced autophagy but through different mechanisms [119]. The mechanism underlying enhanced cytotoxicity of this combination needs to be evaluated in more details.

It was reported that treatment of human colorectal cancer cells (HCT116 cells) with melatonin reduced p-Akt and upregulared autophagy with enhanced cell death that was maintained for 24 h, suggesting that melatonin has the ability to be used as a chemotherapeutic in the treatment of colon cancer [120]. Patients with ulcerative colitis have a higher risk of colitis-associated colon carcinogenesis (CACC) [121]. Oral treatment of mice with 1, 2-dimethylhydrazine dihydrochloride induces colitis that resembles CACC. It was hypotethized that administration of melatonin could reduce the risk of CACC [122]. Melatonin reduced the progression of CACC by reducing different inflammatory markers such as IL-6, TNF-α, NF-κB and cyclooxygenase-2. It also reduced CACC-induced autophagy and increased Nrf-2 expression. These researchers concluded that melatonin acted by regulation of both autophagy and Nrf-2 signaling, thus inducing its protective role during progression of CACC. Thus suggesting the hypothesis that melattonin may be a new approach for prevention of CACC progression [122]. However, in contrast to previous studies, melatonin decreased cisplatin-induced cell death by inducing an autophagy survival signal pathway [123]. These researchers reported that melatonin decreased p-mTOR and ERCC1 when added to cisplatin. ERCC1 is a marker of DNA repair and its over-expression has been linked to cisplatin resistance [124]. In the same way, melatonin also enhanced autophagy in H22-bearing mice by inhibition of Akt and mTOR pathways. Pretreatment of H22 cells with beclin-1 RNAi or 3-MA as an autophagy inhibitor before

melatonin protected mouse hepatoma H22 cells from undergoing apoptosis by induction of protective autophagy through the PI3K/Beclin-1 pathway [125]. Melatonin has both protective autophagy and protective-apoptotic effects on tongue squamous cell carcinoma [126]. The results of a recent study revealed that melatonin induces protective autophagy via the MT2/mTORC1/TFE3 pathway. This property protects tongue squamous cell carcinoma from death. Accordingly, suppresion of the protective autophagy increased apoptosis and has been suggested as a new strategy to boost the anti-tumor effects of melatonin [126]. Interesingly, it has been reported that endoplasmic reticulum stress also increases the effects of melatonin on melanoma cell death [127].

All these studies suggest that melatonin has beneficial effects on the gastrointestinal system, especially the liver. In cancers, autophagy has both pro-survival and death promoting effects and melatonin by modulation of autophagy exerts its beneficial effect both on cancer treatment and chemotherapy-induced side efects.

Melatonin and the endocrine system

There is cross-talk between melatonin secretion from the pineal gland and the endocrine system. Indeed, melatonin, as an endogenous hormone, has various modulatory roles on the endocrine system. For example, it can suppress insulin secretion [128] and its MT1 receptor removal induces glucose metabolism dysfunction and promotes insulin resistance. Interestingly, lower urinary melatonin secretion was attributed to increased risk of type 2 diabetes [129]. Moreover, melatonin has significant effects on adipose tissue [130] and

modulates hair growth and pigmentation [131]. Therefore, the role of autophagy and melatonin on the endocrine system was investigated in the following studies.

Pancreatic β cells are the only source of insulin in the body. The endoplasmic reticulum (ER) has an important role in insulin production and its dysfunction has been attributed to ER stress which is involved in type 2 diabetes [132]. ER stress also promotes autophagy in pancreatic β cells [132]. Autophagy is necessary to preserve normal morphology, cell mass, and function of β cells and is considered as an important protectant against stress during resistance to insulin [133]. In addition, there are literature reports showing that melatonin can modulate insulin secretion [134, 135]. The glucose analog, 2-DG, is a glycolytic inhibitor which promotes ER stress. Kim et al. [136] in their study evaluated the effect of 2-DG on autophagy in β cells. They showed that 2-DG increased p-AMPK and decreased p-mTOR showing an autophagic response. However, addition of melatonin did not modulate this effect of 2-DG significantly [136]. The protective role of melatonin on the pancreas was reported in an experimental model of acute pancreatitis [137]. The results showed that acute pancreatitis increased autophagy that was further enhanced by melatonin administration.

The effect of melatonin on diabetes-induced osteoporosis was also investigated [138]. The researchers showed that melatonin had beneficial effects on osteoporosis in rats. Using an *in vitro* preparation, they demonstrated that increased glucose in hFOB1.19 cells promoted autophagy in the osteoblasts. They also showed that melatonin, both at low and high concentrations of glucose, reduced autophagy through inhibition of the ERK pathway

[138]. Microgravity during space flights attenuates bone matrix production, mineral content of the bones and bone formation. These changes promote osteoporosis. Clinostat has been reported to induce microgravity and thus has been implicated in microgravity laboratory studies [129]. Clinostat rotation promoted autophagy in preosteoblast MC3T3-E1 cells without changes in cell survival. Exposure of cells to melatonin reduced autophagy significantly. In addition, it was demonstrated that clinostat rotation reduced the levels of p-ERK, p-Akt, and p-mTOR that were reversed by melatonin. The study also showed that melatonin, through activation of its MT1 and MT2 receptors, enhanced autophagy in preosteoblast MC3T3-E1 cells [139]. However, in contrast to these findings, it was reported that in the presence of melatonin, through p-ERK and p-Akt elevation, and inhibition of p-mTOR, autophagy was increased in C2C12 myoblast cells [140]. It should be noted that melatonin-induced autophagy participates in partial lysosomal degradation of MyoD protein that acts as a master switch for skeletal muscle differentiation. Melatonin plus exercise was also able to accelerate gastrocnemius muscle remodeling of rats with collagenase-induced knee instability. The study showed that melatonin, through inhibition of endoplasmic stress and subsequently suppression of autophagy, accelerated muscle adaptation [141].

Syrian hamster Harderian gland has different cell types with different porphyrin production levels. The gland of female hamsters has a single secretory cell type while the glands of males have two different cell types. More importantly, the glands of the females have much more porphyrin deposits in comparison to males [142]. Naturally, the gland is exposed to

oxidative stress, especially, in females [143]. Therefore, the cells of the gland undergo the autophagic process to adapt to environmental stress and to maintain their functionality. In some cases they undergo detachment-related cell death that has characteristics intermediate between apoptotic and autophagic cell death [144, 145]. Administration of melatonin for 1-2 month to female Syrian hamsters reduced the destructive effects of free radicals via different mechanisms including amelioration of detachment-induced autophagic cell death [144].

There are other reports showing that melatonin has beneficial effects on the maturation of oocytes and development of embryos in different animals [146-148]. The mechanisms behind the beneficial effects of melatonin on oocyte maturation was investigated by Chen et al. [149] who showed that melatonin improved maturation of small follicle-derived oocytes and artificially denuded oocytes and subsequent embryo development. Their study revealed that melatonin enhanced different genes expression including *ATG7* and *BECLIN1* in pig oocytes and cumulus cells. This implies that melatonin, at least in part, by induction of autophagy exerted its beneficial effects on oocytes maturation [149].

Ovarian aging has been reported with significant decline in oocyte quality and quantity. Tamura and colleagues showed that melatonin increased the number of ovulated oocytes in aged female ICR mice [150]. Melatonin administration enhanced mRNA expression of Sirt1 and increased autophagy. The authors concluded that suppression of autophagy by melatonin was involved in the beneficial effects of melatonin on ovarian aging [150].

Corneal keratocytes are specific fibroblasts that exist in the stroma. This layer consists 85-90% of the corneal thickness. The deposition of mutant transforming growth factor-b (TGF-b)-induced protein (TGFBIp) in the cornea is the main feature of granular corneal dystrophy type 2 (GCD2). A study showed that there was a delay in autophagic degradation of mutant-TGFBIp via impaired autophagic flux in GCD2 corneal fibroblasts [151]. Therefore, it was hypothesized that melatonin may increase autophagy and subsequently promotes mutant-TGFBIp degradation. Choi et al. in their study examined this hypothesis and found that melatonin elevated autophagy in both GCD2-homozygous and wild-type corneal fibroblast cell lines [152]. In addition, melatonin attenuated mutant-TGFBIp concentration. The study showed that melatonin via inhibition of mTOR-dependent signaling promoted autophagy. Melatonin in the presence of luzindole also induced autophagy suggesting that melatonin exerted its effect via targets or receptors other than MT1 or MT2 receptors. Therefore, it was concluded that melatonin has the potential to be used as a treatment for GCD2 [152].

Atrazine, a herbicide, has been reported to be a potent endocrine and immune system disruptor [153, 154]. An increased risk of bronchitis with humoral and immune system dysregulation was reported in applicators of atrazine [155]. Sharma et al. [156] showed that atrazine dysregulated autophagy in splenocytes. Melatonin when added to these cells increased *BECN-1* expression and ameliorated LC3B-II and p62 levels indicating that melatonin attenuated atrazine-induced autophagy impairment [156]. The number of studies concerning the role of melatonin and autophagy on the endocrine system is limited.

However, the available literature reports seem to suggest that autophagy may mediate the modulatory role of melatonin on the endocrine system.

Conclusion and perspectives

Melatonin is potentially a very important drug candidate. A growing number of articles continues to be published in the peer reviewed literature that support the beneficial effects of melatonin. Activation or inhibition of melatonin signaling is a novel area to consider as a potential therapeutic approach for treating some important diseases including neurodegenerative diseases. On the other hand, there can be little doubt that autophagy has a crucial role in homeostasis and in human diseases. A large number of molecules are under evaluations in drug development for treatment of cancer and neurodegenerative disease. In the present paper, some of the significant protective and beneficial effects of melatonin have been reviewed. Melatonin appears to induce its beneficial effects through autophagy promotion and/or autophagy suppression. This finding confirms the double role of autophagy in cells and implies that melatonin can balance the autophagy process. This balance is, at least in part, responsible for the protective role of melatonin in the central nervous, cardiovascular, endocrine and gastrointestinal systems. As presented in figure 1, melatonin through very different mechanism, activates or inhibits the autophagy process, suggesting that melatonin give us the opportunity to change the function of different organs by autophagy. Melatonin also has significant antioxidant and anti-apoptotic effects. Besides activation of classical MT1 and MT2 receptors, activation of RORα by melatonin is another alternative receptor and an important target for melatonin that should be

considered in future studies. Development and the successful use of the selective MT1 and MT2 receptors agonists for treatment of sleep disorders open the opportunity to use these drugs in the treatment of diseases other than insomnia with limited side effects. Moreover, its synergistic effects with other molecules including valproate indicate that melatonin in combination with other therapeutic agents may elicit better therapeutic responses with lower toxicities. This review offers a new look at melatonin and its potential therapeutic effects through its effects on autophagy. Melatonin should be given serious consideration in the future.

Acknowledgments

The authors appreciate Mashhad University of Medical Sciences for financial support.

Table 1: Summary of melatonin effects through modulation of autophagy pathways.

Disease or experimental model	**Target**	**The effect on autophagy**	**Mechanism of action**	**The effect on target tissue or cells**	**Ref.**
Alzheimer's disease	Neuro-2a cells	No significant effect	-	Antiamyloidogenic activity	[38]
Opiate addiction	Primary cells from the hippocampus of rats	Decreased autophagy	-	Increased mtDNA content andneuronal outgrowth	[51]
Malignant glioblastomas	Human glioblastoma cells	Increased autophagy	Inhibition of Akt	Increased cell death	[70]
Arsenite-Induced Neurotoxicity	Primary culture of rat cortical neurons	Decreased autophagy	-	Reduced neurotoxicity	[44]

Cadmium-induced neurotoxicity	Mouse neuroblastoma cells	Increased autophagy	Enhanced TFEB expression	Reduced neurotoxicity	[48]
Kainic acid-induced neurotoxicity	Mouse hippocampal tissues	Decreased autophagy	-	Reduced kainic acid-induced neurotoxicity	[33]
Methampheta mine-induced neurotoxicity	SK-N-SH cells	Decreased autophagy	Inhibition of mTOR and decrease in 4EBP1 activity	Reduced methamphetamine-induced neurotoxicity	[53]
MPTP-induced neurotoxicity	Striatum of mice	Decreased autophagy	Decrease in CDK5 activity and α-synuclein aggregation	Reduced MPTP-induced neurotoxicity	[31]
Rotenone-induced neurotoxicity	Hela cells	Decreased autophagy	Inhibition of Bax expression and release of Omi	Decreasedrotenone -induced neurotoxicity	[34]
Prion-mediated neurotoxicity	Human neuroblastoma cell lines (SH-SY5Y)	Increased autophagy	Upregulatio n of α7nAchR signals	Reducedprion-mediated neurotoxicity	[27]
Traumatic brain injury	Cortex of the rats	Increased autophagy	Inhibition of mTOR	Decreased traumatic brain injury	[57]
Neonatal hypoxia–ischemia	Hippocampus and cerebral cortex and PC12 cells	Decreased autophagy	-	Reduced brain damage	[65]
Ischemic stroke	Brain	Decreased autophagy	Activation of PI3K/Akt	Reduced brain damage	[66]
Aging	SH- SY5Y cells	Increased autophagy	Increase in SIRT1 and suppresion of NF-κB	Increased aging	[68]
Fatty liver graft preservation	Steatotic livers	Increased autophagy	AMPK activation	Improved steatotic liver graft preservation	[112]
Liver cancer	HepG2 cells	Increased autophagy	JNK phosphoryla tion	Decreased cell viability	[118]

Hepatocellular carcinoma	Mouse hepatoma cell line H22	Increased autophagy	Inhibition of mTOR and activation of Akt	Reduced cell toxicity	[125]
Obesity	Liver of ob/ob mice	Decreased autophagy	Increased p62 and decrease in PPAR-γ	Reduced adiposity	[113]
Hepatocellular carcinoma	Hepatocellular carcinoma HepG2 cells	Increased autophagy	Inhibition of mTOR and ERCC1	Attenuated cisplatin-induced cell death	[123]
Hepatic fibrosis	Liver of mice	Decreased autophagy	Inhibition of mTOR	Protective effects against CCL-4-induced fibrosis	[106]
Liverischemia/ reperfusion	Liver of C57BL/6 mice	Decreased autophagy	Activation of mTOR and 4EBP1 activity	Protective effects in liver I/R injury.	[110]
Cadmium-induced hepatotoxicity	Liver of C57BL/6 mice	Decreased autophagy	Increased Sirt1, Sirt3 and SOD2 activity	Protected against cadmium-induced hepatotoxicity	[105]
Colitis-associated colon carcinogenesis	Colon of Swiss albino mice	Decreased autophagy	-	Attenuated the progression of CACC	[122]
Myocardial infarction	Heart of C57BL/6 wild-type mice	Increased autophagy	Inhibited Mst1 phosphorylti on and increased Sirt1 expression	Reduced postinfarction cardiac remodeling and dysfunction	[82]
Chronic intermittent hypoxia	Heart of Sprague-Dawley rats	Increased autophagy	AMPK activation	Ameliorated cardiac hypertrophy induced by CIH	[98]
Diabetic cardiomyopath y	Heart of C57BL/6 wild-type mice	Increased autophagy	Decreased p-Mst1and increased Sirt3 expression	Attenuated diabetic cardiomyopathy	[84]
Cerebral ischemia	N2a cells	Increased autophagy	Inhinition of Akt	Protected against cerebral ischemia	[157]
Skeletal muscle atrophy	C2C12 myoblast cells	Increased autophagy	Activation of mTOR,	Degradation of MyoD protein in	[140]

			ERK and Akt signaling	C2C12 myoblast cells	
Muscle remodeling	Gastrocnemius muscle	Decreased autophagy	Inhibition of endoplasmic stress	Accelerated muscle adaptation	[141]
Osteoporosis	The human fetal osteoblastic cell line hFOB 1.19	Decreased autophagy	Inhibition of ERK pathway	Suppression of osteoporosis	[138]
Microgravity induced abnormalities	Preosteoblast MC3T3-E1 cells	Decreased autophagy	Activation of mTOR, ERK and Akt signaling	Reduced microgravity-induced abnormalities	[139]
Ovarian aging	Oocytes of aged female ICR mice	Increased autophagy	Increase in Sirt1 gene expression	Delay in ovarian aging	[150]
Granular corneal dystrophy type 2	Primary corneal fibroblasts	Increased autophagy	-	promoted mutant-TGFBIp degradation	[151]

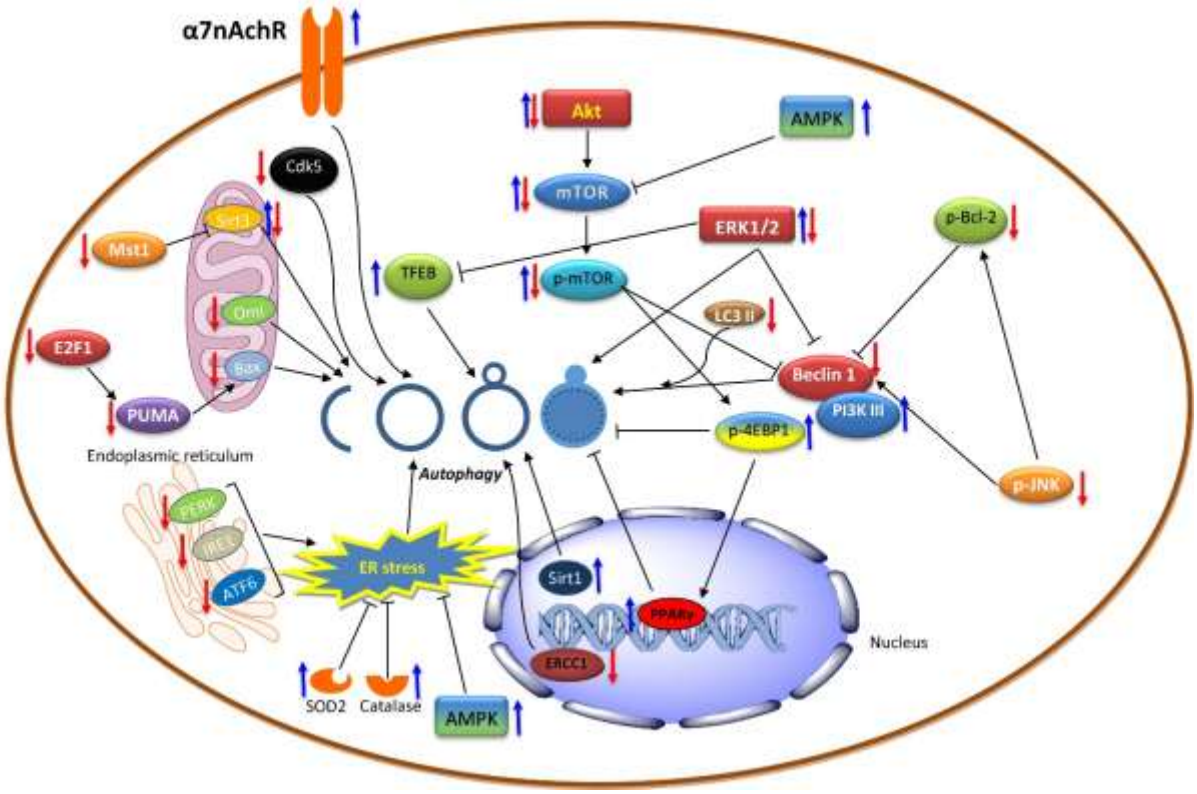


Figure 1. Melatonin and autophagy. Cellular targets for melatonin are illustrated. ↑, promote/activate; ↓, inactivate/inhibit. Melatonin via various targets suppresses or activates autophagy based on experimental model, cell type, time of intervention, and many more parameters. However, in many of the studies, melatonin induced protective and beneficial effects either by suppression or by activation of autophagy.

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