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Molecular Mechanism of Neuroprotective Effect of Melatonin on Morphine Addiction and Analgesic Tolerance: an Update

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Abstract

Drug addiction is a global health problem and continues to place an enormous financial burden on society. This addiction is characterized by drug dependence sensitization and craving. Morphine has been widely used for pain relief, but chronic administration of morphine causes analgesic tolerance, hyperalgesia, and addiction, all of which limit its clinical usage. Alterations of multiple molecular pathways have been reported to be involved in the development of drug addiction, including mitochondrial dysfunction, excessive oxidative stress and nitric oxide stress, and increased levels of apoptosis, autophagy, and neuroinflammation. Preclinical and clinical studies have shown that the co-administration of melatonin with morphine leads to a reversal of these affected pathways. In addition, murine models have shown that melatonin improves morphine-induced analgesic tolerance and addictive behaviors, such as behavioral sensitization, reward effect, and physical dependence. In this review, we attempt to summarize the recent findings about the beneficial effect and molecular mechanism of melatonin on mitochondrial dysfunction, uncontrolled autophagy, and neuroinflammation in morphine addiction and morphine analgesic tolerance. We propose that melatonin might be a useful supplement in the treatment opiate abuse.

Keywords Analgesic tolerance · Autophagy · Melatonin · Morphine addiction · Mitochondrial dysfunction · Neuroinflammation

Abbreviations

3-MA	3-Methyladenine
ATG5	Autophagy related 5
ATG7	Autophagy related 7
ATP	Adenosine triphosphate
cAMP	Cyclic adenosine monophosphate
CPP	Conditioned place preference
CREB	CAMP response element-binding protein
ERK	Extracellular signal-regulated kinase
MD-2	Myeloid differentiation protein 2
MEG3	Maternally expressed gene 3
mtDNA	Mitochondrial DNA
NLRP3	NOD-like receptor protein 3
NMDA	N-Methyl-D-aspartate
NR1	NMDA subtype 1
NO	Nitric oxide
NOS	Nitric oxide synthase
Per1	Period 1
Per2	Period 2
PINK1	PTEN induced kinase 1
PKC	Protein kinase C
RACK1	Receptor for activated C kinase 1
ROS	Reactive oxygen species
SNC	Substantia nigra compacta
TLR4	Toll-like receptor 4
TNF-α	Tumor necrosis factor-α

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Introduction

Drug addiction is a chronic and relapsing brain disease [1, 2] with compulsive drug use, sensitization, tolerance, and dependence [2–7]. Drug addiction has become one of the biggest public health problems across the world and causes an enormous financial burden on society [1, 8]. As morphine is a typical opiate, exploring the molecular mechanism of morphine's effect on pain and addiction may provide helpful information for opiate withdrawal therapy. Morphine is still a gold standard medication for pain management in the clinical setting, although there are alternatives that can be used such as the synthetic drug, fentanyl. Morphine has a high potential for addiction, especially under chronic and repeated exposure [9]. Despite there are many studies to reveal the cellular and molecular mechanism of drug addiction, the exact mechanism of morphine addiction remains unresolved. It has been demonstrated that morphine induces brain damage and neuronal toxicity by inducing oxidative stress, nitric oxide (NO) stress, mitochondrial dysfunction, apoptosis, autophagy, and neuroinflammation [10–14]. A better understanding of the underlying mechanism of these deleterious effects will undoubtedly be of great benefit to public health and help to avoid the side effects of morphine treatment and drug addiction.

Melatonin (N-acetyl-5-methoxytryptamine) is the main neuroendocrine hormone secreted by the pineal gland. It is also produced in many other organs, including the liver, kidney, retina, stomach, gut, ovary, muscle, spleen, thymus, heart, intestine, and a variety of cells such as bone marrow cells, lymphocytes, and epithelial cells of mammals [15, 16]. Moreover, melatonin is widely available in many types of foods, such as fungi, plant products, eggs, and fishes [16]. Rich sources of melatonin are essential for the maintenance of normal biological functions, including antioxidant, antidiabetic, anti-inflammatory, anti-obesity, immunity booster, neuroprotective, and cardiovascular protective, anti-cancer, and anti-aging activities [17]. Initially, melatonin was described as a free-radical scavenger [18]. Melatonin can easily cross the blood–brain barrier and plays a major role in a variety of neuroprotective functions such as regulation of circadian rhythms, anti-nociception, anti-apoptotic, anti-autophagy, anti-inflammatory, and neuronal protection [19–22]. Emerging lines of evidence have suggested that melatonin can reverse morphine-induced conditioned place preference (CPP) [23], behavioral sensitization [10], and analgesic tolerance in mouse models [10, 24, 25].

When compared to healthy people, most drug abusers suffer disordered sleep patterns [26, 27]. Many studies have shown that melatonin supplementation improves the quality of sleep [28–31], although there is a conflicting study showing that administration of melatonin was no different from placebo in decreasing sleep problems in a cohort of alcohol abuser after 4 weeks of treatment [32]. There have been several studies that have evaluated the effects of melatonin supplementation on patients with drug addiction [32]. Most recently, Hemati et al. summarized some of these related studies about the role of melatonin to counteract the deleterious effect of morphine and advocated the co-use of melatonin and morphine [33].

In this review paper, we aim to summarize the literature regarding the molecular mechanism of melatonin's beneficial effects on morphine addiction and morphine analgesic tolerance, especially with reference to our own related studies [10, 14]. We believe a detailed overview of the current state of knowledge related to the role of melatonin in morphine addiction will help with the evaluation of melatonin's effects on symptoms and the molecular mechanisms underlying addiction, as well as the clinical treatment of drug abusers.

Changes in Melatonin Level and its Receptor Expression with Morphine Treatment

Acute administration of morphine resulted in a dose-dependent increase in the melatonin levels in rats [34] and bovine pinealocytes [35] when compared to the respective controls. Our previous study showed that drug abusers had a significantly lower levels of serum melatonin compared with healthy individuals, suggesting a downregulation of melatonin production by opioids [10]. Morphine administration also significantly decreased in the levels of plasma melatonin in rats [36] and pigs [37] exposed to constant light. Moreover, chronic morphine-tolerant rats had reduced expression level of the melatonin receptor 1A in spinal dorsal horn and significantly lower serum melatonin level compared to control animals [38]. Previous studies have also shown that melatonin receptor 1A was widely expressed in the prefrontal cortex, hippocampus, nucleus accumbens, and amygdala that are associated with drug addiction [39, 40]. As melatonin exerts its functions largely via the melatonin receptors [41, 42], it is possible that melatonin may play a neuroprotective role in modulating addictive behaviors.

Dysfunction of the circadian clock has been shown to be involved in drug addiction, with Per1 (period circadian regulator 1) and Per2 (period circadian regulator 2) being decreased in morphine-addicted rats [43, 44]. In contrast, clock genes have been found to modulate morphine-induced behaviors [45–48]. Mouse PER1 promotes morphine-induced locomotor sensitization and CPP via histone deacetylase activity [49] and extracellular signal-regulated kinase (ERK)–cyclic adenosine monophosphate (cAMP) response

element-binding protein (CREB) pathway [47, 50]. Reciprocally, mouse PER2 promotes the development of tolerance to the analgesic effects of morphine and enhances the development of withdrawal symptoms [48]. All together, these studies reveal the potential implication of the *Per1* and *Per2* genes and melatonin in modulating various morphine-induced effects in murine models.

Beneficial Effect of Melatonin on the Addictive Symptoms Induced by Morphine

Recent evidence suggests that melatonin is a potential antinociceptive adjuvant for use in the management of pain [22]. Moreover, melatonin plays an important role in regulating morphine action, enhancing the antinociceptive effect of morphine, and reversing morphine-induced hyperalgesia and tolerance (Table 1) [14, 51–54]. Melatonin attenuates repetitive morphine-induced hyperalgesia and tolerance by inhibiting protein kinase C (PKC) and N-methyl-D-aspartate (NMDA) receptors subtype 1 (NR1) in rats [51] and restores morphine antinociceptive effect in morphine-tolerant rats by inhibiting microglia activation and HSP27 expression [55]. Melatonin reduces morphine-induced hyperalgesia and exerts its antinociceptive action by increasing β-endorphin release in the substantia nigra compacta (SNC) of rats [56] and the hypothalamic arcuate nucleus of mice [57]. Melatonin can prevent morphine-withdrawal-induced hyperalgesia and glial reactivity in rats by inhibiting PKC activity and cAMP upregulation [53]. Further mechanistic study has revealed that the suppression of nitric oxide synthase (NOS) activity [52] and antioxidative enzymes [58] and modulation of peripheral benzodiazepine receptors [59] might have contributed to the mechanism of melatonin-induced reversal of morphine tolerance and dependence. Consistent with this beneficial role of melatonin, administration of ramelteon, a melatonin receptor agonist, attenuated the physical dependence and the blood levels of cortisol in rats treated with morphine [60].

In addition, co-administration of melatonin enhances the rewarding properties and proconvulsant effects of morphine via a mechanism that may have an involvement of the NO pathway in mice [13, 61]. On the contrary, another study showed that melatonin reverses the morphine-induced CPP through melatonin receptor 1B within the central nervous system in mice [23]. In our earlier study, we reported that melatonin ameliorated morphine-induced behavioral sensitization and analgesic tolerance by salvaging reactive oxygen species (ROS) and autophagy [10]. On the other hand, we have also recently reported that melatonin alleviates morphine analgesic tolerance in mice by decreasing NOD-like receptor protein 3 (NLRP3) inflammasome activation [14].

Improvement in Mitochondrial Function by Melatonin in Morphine Addiction and Analgesic Tolerance

As the center of energy production in eukaryotic cells [62], mitochondria have their own genetic material called mitochondrial DNA (mtDNA) [63]. Mitochondria play a crucial role in various cellular processes, including generation of adenosine triphosphate (ATP), ROS, regulation of calcium signaling, metabolism, inflammation, cell cycle, apoptosis, and mitophagy [64–66]. Normal mitochondrial function is important in the neurons [21, 67–69] and mitochondrial dysfunction may participate in the process of drug addiction [10] (Table 2). Accumulating evidence has shown that the ROS level was increased during morphine addiction and

Table 1 The effects of melatonin on the addictive symptoms induced by morphine

Animal model	Addictive symptoms	Pathway	Ref
Rat	Attenuates hyperalgesia and tolerance	Inhibiting PKC and NR1 activation	[51]
Rat	Restores antinociceptive effect	Inhibiting microglia and HSP27 activation	[55]
Mouse	Reduces hyperalgesia and exerts antinociceptive action	Increasing β-endorphin release	[57]
Rat	Prevent hyperalgesia	Inhibiting PKC and cAMP activity	[53]
Mouse	Reverses tolerance and dependence	Suppression of NOS activity	[52]
Rat	Reverses tolerance and dependence	Suppression of antioxidative enzymes	[58]
Mouse	Reverses tolerance and dependence	Modulation of benzodiazepine receptors	[59]
Mouse	Enhances rewarding properties	Involvement of the NO pathway	[13]
Mouse	Enhances anti- and proconvulsant effect	Involvement of the NO pathway	[61]
Mouse	Reverses conditioned place preference	Activation of melatonin receptors 2	[23]
Rat	Ameliorates behavioral sensitization	Salvaging ROS and autophagy	[10]
Mouse	Alleviates analgesic tolerance	Decreasing NLRP3 inflammasome activation	[14]

Table 2 Mitochondrial dysfunction in mouse and rat tissues and cells treated with morphine

Models	Effect	Tissue or cell	Ref
Mouse and rat	↓ mtDNA copy number, ↑ mtDNA damage	Hippocampus and peripheral blood	[10]
Rat cell	↑ ROS/mtDNA damage, ↓ mtDNA copy number/respiratory chain capacity	Rat PC12 cells	[10]
Heroin addicts	↓ mtDNA copy number, ↑ mtDNA damage	Peripheral blood	[10]
Human cell	↑ ROS	SH-SY5Y cells	[80]
Human cell	↑ mitochondria-dependent apoptosis	SH-SY5Y cells	[73]
Mouse	↑ ROS/mitophagy	Spinal cord	[71]
Mouse cell	↑ ROS	BV2 and microglia	[14]
Rat	↑ mitochondria-dependent apoptosis	Cortical neuron	[11]

tolerance [10, 14, 70]. Morphine-induced ROS are generated in a concentration- and time-dependent manner in SH-SY5Y and PC12 cells [10, 70]. Chronic intrathecal administration of morphine induced excessive generation of ROS and causes accumulation of damaged mitochondria in spinal cord [71]. Mitochondrial ROS induced by morphine promotes the NLRP3-dependent lysosomal damage and inflammasome activation [14, 72]. Chronic morphine treatment also results in mitochondrion-dependent apoptosis [73].

The main source of cellular ROS is mitochondrion [72]. Chronic morphine treatment also results in mitochondrial dysfunction [11]. In our previous study, we found that chronic morphine exposure led to a decrease in the mtDNA copy number and an increase in mtDNA damage in hippocampal tissues and the peripheral blood of the rat and mouse models [10]. Similarly, a decreased mtDNA copy number and elevated levels of both mtDNA damage and ROS, together with impaired respiratory chain capacity were observed in PC12 cells treated with morphine [10]. We also found that heroin addicts had a lower mtDNA copy number and decreased melatonin in the peripheral blood compared to healthy individuals. But additional melatonin blocked the ROS elevation, ameliorated the impaired respiratory capacity, and salvaged the increased mitochondrial mass induced by morphine in PC12 cells. Importantly, the pretreatment with melatonin restored the mtDNA copy number and reduced the amount of mtDNA damage in PC12 cells and mice in response to morphine treatment [10].

The high level of ROS not only leads to oxidative damage of the mtDNA, but also affects energy-dependent neuronal function including neurite outgrowth and synaptic plasticity [75, 76]. Melatonin restores the morphological changes seen in neurons induced by morphine. Moreover, co-administration of melatonin with morphine ameliorated morphine-induced behavioral sensitization and analgesic tolerance in mice [10]. Most recently, using the mouse models, we found that a treatment with melatonin attenuates established morphine tolerance and facilitates the pain relief by morphine in the morphine-tolerant mice [14]. This observation suggested that melatonin was involved in morphine tolerance and pain relief in our murine models. Further study of the underlying mechanism showed that melatonin alleviates morphine analgesic tolerance in mice by decreasing NLRP3 inflammasome activation through blocking cathepsin B (CTSB) release and oxidative stress [14].

Note that melatonin is produced in mitochondrial matrix, which means that neurons have the capacity to synthesize melatonin for self-protection [77]. It has been reported that the neuroprotective effects of melatonin are mainly mediated by mitochondria and mitochondrial-produced melatonin [77, 78]. Therefore, it would be rewarding for future studies to determine the mechanism by which melatonin mediates neuroprotective effects on morphine addiction and analgesic tolerance.

Regulation of the Autophagy Pathway by Melatonin in Morphine Addiction and Analgesic Tolerance

Autophagy plays an important role in the pathogenesis of brain diseases, such as Alzheimer disease [79], Parkinson disease [74], and drug addiction [10, 80–83] (Table 3). Previous study has indicated that autophagy was involved in the cell death induced by morphine [80]. Morphinone, an oxidative metabolite of morphine, induced autophagy and led to non-apoptotic cell death in HL-60 cells, and this effect could be reversed by a pretreatment of the autophagy inhibitor 3-methyladenine (3-MA) [84]. The Beclin 1-dependent and autophagy related gene 5 (ATG5)-dependent autophagy were involved in SH-SY5Y cells being treated with chronic morphine, which may contribute to morphine-induced neuronal injury [80]. In addition, chronic treatment with morphine induces cell death, which is increased by autophagy inhibition [80]. Activation of autophagy in hippocampal cells alleviates the morphine-induced memory impairment [81]. A recent study has shown that activation of RACK1 (receptor for activated C kinase 1)-dependent autophagy

Table 3 Autophagy in morphine-addicted mouse or rat models and cells with morphine treatment

Model	Effect	Tissue or cell	Ref
Human cell[a]	Autophagy and apoptotic cell death	HL-60 cells	[84]
Human cell	Beclin 1- and ATG5-dependent autophagy	SH-SY5Y cells	[80]
Human cell	RACK1-dependent autophagy	SH-SY5Y cells	[85]
Mouse cell	Autophagy	HT22 cells	[87]
Mouse	PINK1/Parkin-mediated mitophagy	Spinal cord	[71]
Mouse	*Atg5*- and *Atg7*-dependent autophagy	Midbrain tissue and midbrain neuron	[12]
Mouse	CTSB-dependent autophagy	Spinal cord	[82]

[a]Cells were treated with morphinone, a derivate of morphine

induced by morphine contributed to the maintenance of CPP memory in mice [85]. The induction of endoplasmic reticulum (ER) stress and subsequent initiation of autophagy by morphine ultimately culminated in activation of astrocytes [86]. Long non-coding RNA MEG3 (maternally expressed gene 3) promotes morphine-induced autophagy through modulating the ERK pathway in HT22 cells [87]. Morphine treatment facilitated lipopolysaccharide-induced autophagy and inhibited autophagolysosomal fusion, leading to decreased bacterial clearance and increased bacterial load [88]. Morphine induced dysfunction of PINK1 (PTEN induced kinase 1)/Parkin-mediated mitophagy in spinal cord neurons, which is involved in antinociceptive tolerance [71]. Intracerebroventricular pretreatment with the autophagy inhibitor wortmannin or 3-MA significantly attenuated the anti-nociception effects from morphine [82] and aggravated morphine-induced memory impairment [81]. In our previous study, we also found that intracerebroventricular injections of 3-MA prevented the behavioral sensitization, whereas induction of autophagy by rapamycin promoted the behavioral sensitization induced by morphine [12].

The available evidence has shown that autophagy plays an active role in morphine-induced effect, possibly via the induction of ROS and mitochondrial damage [89]. At the present time, we have no answers for the question as to whether the autophagy induced by morphine has a cell-specific pattern and what may be the downstream biological implication. Chronic morphine treatment causes mitochondrial dysfunction and leads to *Atg5*- and *Atg7*-dependent autophagy in the midbrain dopaminergic neurons, which participated in the development of addictive behaviors [10, 12]. Mice deficient for *Atg5* or *Atg7* specifically found in the dopaminergic neurons impaired the CPP, development of behavioral sensitization, and antinociceptive tolerance in response to morphine [12]. The total dendritic length and dendritic complexity were significantly reduced in morphine-treated dopaminergic neurons relative to untreated neurons. These neuronal morphological changes triggered by morphine could be reversed by knockdown of *Atg5* and *Atg7* in primary neuron or knockout of *Atg5* and *Atg7* specific for dopaminergic neurons in mice [12]. We found that pretreatment with melatonin could protect mitochondrial oxidative stress induced by morphine and further prevented autophagy, resulting in mtDNA recovery. Furthermore, pretreatment with melatonin rescued the neuromorphological changes and counteracted the deleterious effects of morphine, such as behavioral sensitization and analgesic tolerance [10]. It would be rewarding to test whether melatonin can regulate autophagy in a cell-specific and tissue-specific pattern, and which circuit is heavily affected.

Melatonin Reduces Neuroinflammation in Morphine Addiction and Analgesic Tolerance

It is known that heroin addicts are prone to many infections [90]. Neuroinflammation plays an important role in morphine addiction [91, 92] and antinociceptive tolerance [93, 94] (Table 4). Early studies found that chronic morphine treatment increased the astrocyte and microglial activation [95–97]. During neuroinflammation, both astrocytes and microglia can release tumor necrosis factor-α (TNF-α). Several investigations have revealed that the expression levels of TNF-α, interleukin 6 (IL-6), and IL-1β were increased both in rodents and patients with morphine tolerance [14, 98, 99]. Furthermore, knockdown of IL-1β in the dorsal root ganglion prolonged morphine analgesia [98], whereas inhibition of microglial P2X4 receptors [100] or TNF-α receptor [101] attenuated the morphine tolerance. Morphine paradoxically prolonged the neuropathic pain in rats by amplifying spinal NLRP3 inflammasome activation [93]. Morphine bound to an accessory protein of the toll-like receptor 4 (TLR4) and the myeloid differentiation protein 2 (MD-2), thereby inducing TLR4 oligomerization and triggering proinflammation [91]. The morphine-evoked neuroinflammation is very important for morphine tolerance, which mediated by astrocyte activation [96], microglia activation [55], and the TLR4-NLRP3 inflammasome [102].

Table 4 Neuroinflammation in morphine-addicted rodent models and cell lines

Model	Effect	Tissue or cell	Ref
Mouse	Microglia activation	Spinal cord	[93, 98]
Mouse	Microglia activation	Cortex	[14]
Mouse	Astrocyte activation	Spinal cord	[98]
Rat	Microglia activation	Spinal cord	[55]
Rat	Astrocyte activation	Spinal cord, posterior cingulate cortex, hippocampus	[97]
Rat	Astroglia activation	Spinal cord	[53]
Mouse cell	TLR4 oligomerization	BV2 cells	[91]
Mouse	NLRP3 inflammasome activation	Spinal cord	[93]
Mouse and human cell	NLRP3 inflammasome activation	BV2 cells and SH-SY5Y cells	[102]
Mouse	NLRP3 inflammasome activation	Cortex tissue, BV2 cells, microglia cells	[14]

Multiple studies have suggested that melatonin attenuated morphine-induced antinociceptive tolerance [14, 24, 25] by inhibiting the canonical pathway of ion channels [103], the ROS and autophagy [10], the protein kinase C (PKC) and N-methyl-D-aspartate receptors activity [51], the peripheral GABAergic system [59], astroglia activation [53], microglia activation, and HSP27 expression [55]. In our recent study, we found that chronic morphine exposure induces excessive ROS production and NLRP3 inflammasome activation in microglia [14]. Deficiency of *Nlrp3* in mice blunts morphine-induced analgesic tolerance and acetic acid-induced pain. Pretreatment of melatonin blocks NLRP3 inflammasome activity by diminishing ROS and CTSB release to alleviate morphine analgesic tolerance in mice [14]. Therefore, melatonin can be useful as a promising therapeutic adjuvant for patients under long-term opioid treatment for pain relief by inhibiting morphine-induced neuroinflammation.

Melatonin as an Ideal Adjuvant to Morphine Treatment for Curing Pain

Morphine has been widely used to relieve pain, but has side effects of analgesic tolerance and hyperalgesia in those patients given frequent injections [104, 105]. Melatonin has

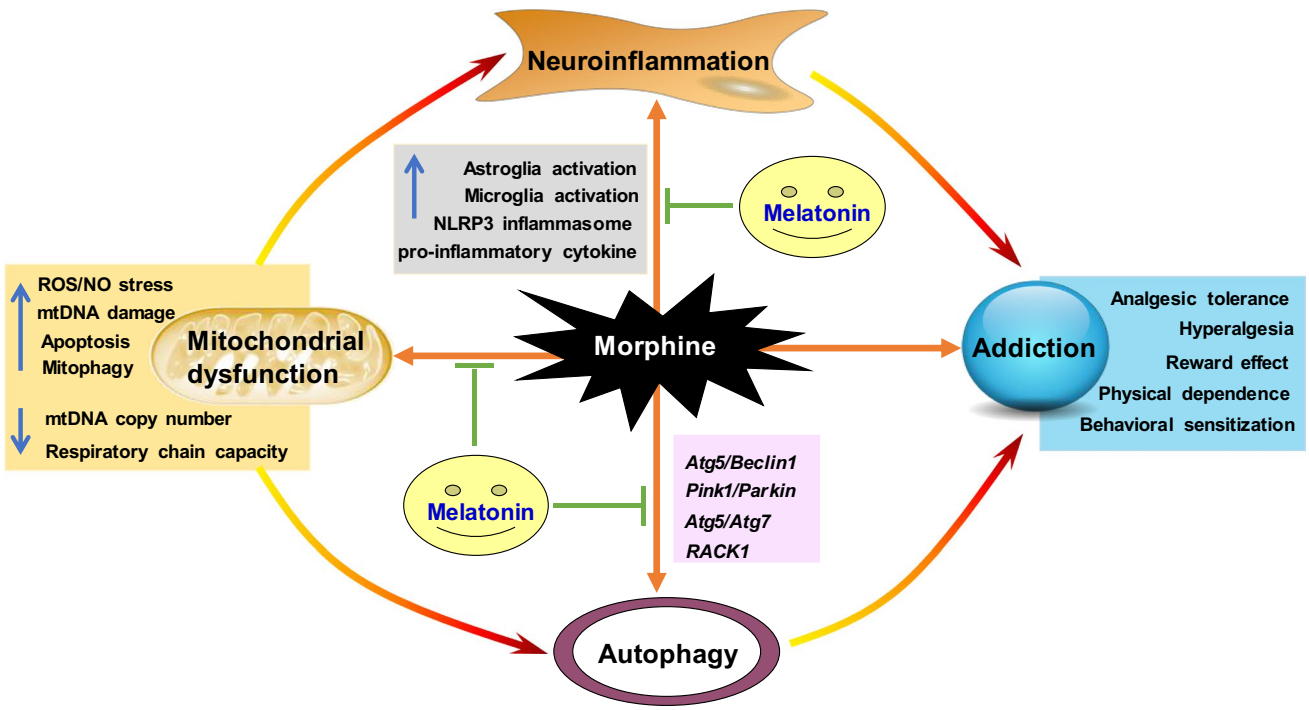

Fig. 1 Cellular biological processes and molecular pathways involved in the beneficial effects of melatonin on morphine-induced addiction and analgesic tolerance. Upregulation and downregulation effects are marked with an upwards arrow and a downwards arrow, respectively

different interactions with opioids including enhancement of analgesic effects of morphine, reversal of tolerance, and dependence to morphine [10, 14, 55]. It is an interesting point to note that the combination of melatonin with morphine was more effective than the monotherapy of using morphine alone. Our recent study indicated that melatonin combined with a low dose of morphine (1 mg/kg) had a better analgesic effect than morphine alone in a murine pain model induced by acetic acid [14]. Melatonin administration was associated with a significant decrease in total morphine analgesia consumption for controlling the pain in patients with bilateral multiple fracture ribs [106] and in patients undergoing abdominal hysterectomy [107]. Therefore, melatonin may be a perfect and ideal adjuvant to treatment when morphine is needed to treat acute and chronic pain. Focused clinical trial for this proposal should be carried out to clarify the exact role of a combination of melatonin with morphine in curing pain.

Conclusion

Addiction, tolerance, and the associated hyperalgesia induced by long-term morphine administration substantially restrict the clinical use of morphine in the treatment of pain. An increasing amount of evidence suggests that melatonin has a profound influence on morphine addiction. There are many beneficial effects from the use of melatonin and they mainly work against the mitochondrial dysfunction, abnormal autophagy, and neuroinflammation that are all features associated with morphine addiction and morphine analgesic tolerance (Fig. 1). In addition, melatonin improves the behavioral sensitization, analgesic tolerance, reward effect, and physical dependence in morphine-addicted rodents. Moreover, preclinical studies shown that melatonin may be a perfect and ideal adjuvant to the treatment with morphine against acute and chronic pain. Our increasing knowledge obtained from these reported cellular assays and animal model studies [10, 14, 23, 33, 51, 55–57, 61] indicate the need for clinical trials of melatonin in preventing the deleterious effects of long-term morphine exposure.

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Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication All authors have seen and approved the manuscript and contributed significantly to this work.

Conflict of Interest The authors declare no competing interests.

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