

Role of Melatonin in the Regulation of Pain

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Abstract: Melatonin is a pleiotropic hormone synthesized and secreted mainly by the pineal gland in vertebrates. Melatonin is an endogenous regulator of circadian and seasonal rhythms. Melatonin is involved in many physiological and pathophysiological processes demonstrating antioxidant, antineoplastic, anti-inflammatory, and immunomodulatory properties. Accumulating evidence has revealed that melatonin plays an important role in pain modulation through multiple mechanisms. In this review, we examine recent evidence for melatonin on pain regulation in various animal models and patients with pain syndromes, and the potential cellular mechanisms.

Keywords: melatonin, pain, cellular mechanisms

Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine), a derivative of serotonin, is an endogenous neurohormone synthesized and secreted mainly by the pineal gland. Secretion increases at night and decreases during the day, following a rhythm of diurnal and nocturnal fluctuation.¹ Melatonin is produced with tryptophan as a precursor.² In addition, melatonin is considered to be synthesized locally.³ Traditionally, melatonin is known for its neurobiological role in sleep.^{4,5} However, melatonin has antioxidant and anti-inflammatory properties, acting as a free radical scavenger during inflammation and injury.^{6,7} For example, melatonin reduced the elevated expression of nuclear factor-kappa B (NF-κB) and inhibited the enhanced level of proinflammatory cytokines IL-6 or TNF-α to modulate neuroinflammation in a model of diabetic neuropathy.⁸ Some evidence suggests that melatonin also has immunomodulatory properties.⁹ Study shows that melatonin decreases peripheral and central Th1/Th17 cells responses protecting against experimental autoimmune encephalomyelitis.¹⁰

The efficacy of melatonin as an analgesic and anxiolytic agent has been demonstrated in animals and humans.^{11–13} It has been suggested that melatonin regulates pain via membrane receptors, nuclear receptors, and simple diffusion.^{14–17} Given these properties with few adverse side effects, melatonin has potential as a painkiller. The aim of this review is to discuss and analyze different lines of evidence for the effects of melatonin on pain modulation as well as to describe the cellular mechanisms of melatonin as a potential analgesic.

Melatonin Synthesis and Metabolism

Synthesized and secreted by the pineal gland, melatonin follows a circadian rhythm controlled by the hypothalamic suprachiasmatic nucleus (SCN).¹⁸ In vertebrates, the precursor of melatonin synthesis is the essential amino acid tryptophan.² The classical pathway of melatonin synthesis in mammals is a four-step enzyme-catalyzed reaction.¹⁹

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The first step is catalyzed by tryptophan hydroxylase (TPH) and synthesizes 5-hydroxytryptophan (5-HT).^{20,21} Next, the aromatic amino acid decarboxylase (AAAD) synthesizes serotonin.²² At this point, the melatonin synthesis pathway divides. Under one branch, N-acetylserotonin (NAS) is produced under the catalysis of serotonin N-acetyltransferase (SNAT).²³ In the other branch, 5-methoxytryptamine (5-MT) is synthesized by acetylserotonin O-methyltransferase (ASMT).²⁴ In the final step, melatonin is synthesized either by the catalysis of ASMT with NAS as a substrate or by SNAT with 5-MT as a substrate²⁵ (Figure 1). Research has revealed that SNAT is the rate-limiting enzyme for controlling the amount of melatonin synthesis.²⁶

Melatonin is an indoleamine with two functional groups, a 5-methoxy group and a 3-amide group.²⁷ Due to the hydrophilicity and lipophilicity conferred by these functional groups, melatonin can travel throughout the body. Once secreted by the pineal, melatonin crosses the blood-brain barrier and enters the circulation system, through which it reaches various tissues and cells of the body. In addition to the pineal gland, melatonin can be synthesized locally by the skin,²⁸ bone marrow,²⁹ oocytes,³⁰ macrophages,³¹ gastrointestinal tract,³² and retina³ exerting specific intracrine, autocrine, and paracrine effects.

In vertebrates, hepatic cytochromes are the primary enzymes responsible for melatonin catabolism. The hepatic cytochromes (primarily CYP1A1, CYP1A2) catalyze melatonin to form 6-hydroxymelatonin (6-HMT).^{33,34} CYP1B1, another important enzyme, can catalyze melatonin to produce NAS.³⁵ 6-HMT and NAS are further degraded to form sulfate- or glucuronide-conjugated compounds that are subsequently excreted with urine.³⁶ In the pineal gland and retina, melatonin is deacetylated to 5-MT, which contains a pyrrole ring that is further cleaved by either myeloperoxidase, indoleamine 2,3-dioxygenase, or reactive oxygen particles to form the metabolites N1-acetyl-N2-formyl-5-methoxykynurenamine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK).³⁷ AFMK and AMK are considered major catabolic products of melatonin in the central nervous system. AFMK and AMK act as free radical scavengers and have a synergistic effect with melatonin that further enhances the antioxidant capacity of melatonin in the brain.^{38,39}

The indolic and kynuric pathways are the main metabolic pathways of melatonin in skin; melatonin metabolites 6-HMT, AFMK, and 5-MT are detected in different skin cells.⁴⁰ Furthermore, researchers have revealed that aryl acylamidases (AAAs) catalyze melatonin to produce

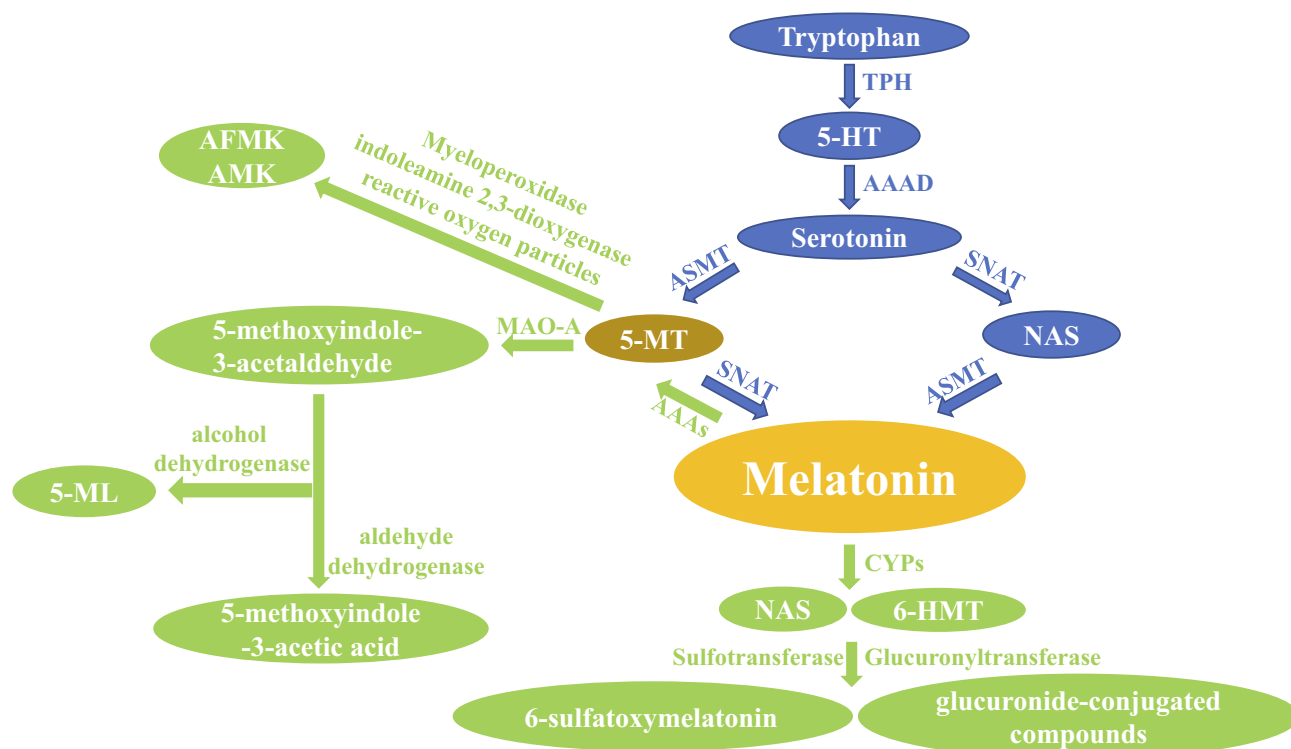


Figure 1 The main synthesis and catabolic route of melatonin in vertebrates. **Note:** The blue arrows represent the anabolic pathway of melatonin and the green arrows represent the catabolic pathway of melatonin.

Abbreviations: 5-HT, 5-hydroxytryptophan; TPH, tryptophan hydroxylase; AAAD, aromatic amino acid decarboxylase; SNAT, serotonin N-acetyltransferase; ASMT, acetylserotonin O-methyltransferase; NAS, N-acetylserotonin; 5-MT, 5-methoxytryptamine; AAAs, aryl acylamidases; CYPs, hepatic cytochromes; 6-HMT, 6-hydroxymelatonin; MAO-A, monoamine oxidase A; AFMK, N1-acetyl-N2-formyl-5-methoxykynurenamine; AMK, N1-acetyl-5-methoxykynuramine; 5-ML, 5-methoxykynuramine.

5-MT. In vertebrates, 5-MT is further catabolized by monoamine oxidase-A (MAO-A) to form 5-methoxyindole-3-acetaldehyde. 5-methoxyindole-3-acetaldehyde is then converted to 5-methoxychromitol (5-ML) by alcohol dehydrogenase or 5-methoxyindole-3-acetic acid by aldehyde dehydrogenase⁴¹ (Figure 1).

Melatonin Receptors and Transduction Systems

Melatonin-mediated effects occur through receptor-dependent and -independent pathways. In the receptor-dependent mechanism, melatonin receptors are primarily divided into cell membrane receptors or nuclear orphan receptors from the superfamily RZR/ROR. Membrane receptors (MT1 and MT2) belong to the G-protein-coupled receptor (GPCR) family containing seven transmembrane receptors.⁴² MT3 receptor once existed in theory, and then was proved to be quinone reductase II enzyme.^{43,44} MT1 and MT2 receptors are formed by 350 and 362 amino acids, respectively, and shows 60% homology. The nuclear orphan receptor GPR50, also known as the melatonin-related receptor, has high sequence homology to membrane receptors. However, melatonin or any other known ligand does not bind to GPR50.⁴⁵ Membrane receptors have been identified and cloned in a great number of tissues in humans and rodents, such as the retina,⁴⁶ brain, pituitary,⁴⁷ gastrointestinal tract,⁴⁸ oocytes,⁴⁹ and pancreatic islet.⁵⁰ Changes in MT1/MT2 and RZR/ROR receptor density fluctuate in relation to serum and intracellular melatonin levels following the circadian rhythm of melatonin secretion.^{48,51}

Variation of sunshine exposure owns a selective pressure in melatonin receptors.⁵² *MTNR1a* is the gene for MT1 and *1b* for MT2, whose genes mutation and expression variation may contribute to cancer susceptibility.^{53,54} In the central and peripheral nervous systems, MT1 and MT2 receptors both are localized on neuronal membranes.⁵⁵ The two subtypes of membrane receptors rarely co-exist in the same cell. When they do, one of them dominates the cell membrane.⁵⁶ MT1 may play an important role in the signaling pathway transduction of the nervous system. Recent research indicates that MT1 receptor is involved in neural pathways modulating depression and diurnal rhythms.^{57–59} Interestingly, little study demonstrated the involvement of MT1 in nociception modulation, and whether MT1 is involved in the transduction of nociceptive signals requires more research to validate.

Melatonin Effects on Nociception

Melatonin has been demonstrated to attenuate nociceptive responses to various noxious stimulus and is considered as a potential analgesic drug in the clinic. Administration of melatonin or its analogs through peripheral or central pathways has dose-dependent long-term antinociceptive effects in models of acute, neuropathic, and inflammatory pain. (Table 1)

Acute Pain

It has been shown that melatonin (25–100mg/kg, i.p.) administration dose-dependently attenuates the hyperalgesic response and has ameliorative potential in reducing inflammation in a well-established model of hyperalgesia associated with inflammation.¹¹ In addition, melatonin was shown to reduce the flinching response during Phase 1 and Phase 2 of formalin-evoked acute pain.⁶⁰ Melatonin has also been found to play an important role in neuroprotection in acute pain caused by complete Freund's adjuvant (CFA).⁶¹ Interestingly, other data suggest that dental pulp damage could cause acute pulpitis and reduce serum melatonin levels. Supplementation with exogenous melatonin via intraperitoneal injection induced pain relief.⁶² In morphine-exposed rodents, melatonin counteracted the resulting hyperalgesia and tolerance through inhibition of microglia activation and protein kinase C γ (PKC γ) activities.^{63–65}

In the past 10 years, researchers have conducted an increasing number of studies on the antinociceptive effects of melatonin. In addition to animal experiments, clinical trials have been carried out in this field. A meta-analysis of current trials of pharmacotherapy for cluster headache suggests that 10 mg of melatonin daily could be given for both acute treatment and preventive therapy.⁶⁶ Melatonin displays a definite dose-dependent antinociceptive effect, which may be correlated with changes in pain threshold.⁶⁷ Melatonin can also effectively relieve pain induced by anodal stimulation applied over the primary motor cortex.⁶⁸ However, if the level of melatonin in the body is disordered, it may cause post-traumatic stress disorder.^{69,70} Interestingly, another clinical trial shows that the treatment effect on pain of melatonin is not observed in patients undergoing abdominal hysterectomy with mildly anxiety.⁷¹ Whether melatonin owns analgesic effect on acute pain seems to be controversial and needs further study.

Chronic Inflammatory Pain

In the last decade, an increasing number of clinical trials on the analgesic effect of melatonin have been carried due

Table 1 Antinociceptive Activity of Melatonin and Its Analogs

Pain Model	Species	Dose & Administration	Effect	References
O ₂ ⁻ -evoked hyperalgesia	Rat	Melatonin, 25–100mg/kg, i.p.	Antinociceptive activity	11
Formalin test	Rat	Melatonin, 30µg/10µL, intrathecally	Reduce flinching response	60
CFA	Rat	Melatonin, 50,60mg/kg, i.p.	Neuroprotective effects	61
		Melatonin, 50mg/kg, i.p.	Alters mechanical and thermal hyperalgesia	76
Morphine exposure	Rat	Melatonin, 10mg/kg, i.p.	Counter mechanical and thermal hyperalgesia	63
		Melatonin, 50mg/kg, i.p.	Reverse hyperalgesia	64
RIM	Rat	Melatonin, 2.5,5mg/kg, p.o.	Dose and/or time dependently analgesic effects	72
		Melatonin, 5mg/kg, p.o.	Improve motor activity	73
Arsenic	Rat	Melatonin, 10mg/kg, p.o.	Neuroprotective effects	83
Oxaliplatin	Rat	Melatonin, 20mg/kg, i.p.	Alleviate mechanical and thermal hyperalgesia	85
		Melatonin, 10mg/kg, i.p.	Alleviate pain behavior	86
Tail Flick Test Writhing Test Formalin Test	Mouse	Melatonin, 10mg/kg, s.c. Benzoyl-melatonin (BMT), 25mg/kg, s.c. Acetyl-melatonin, 50mg/kg, s.c.	BMT increases tail flick latency time, decreases number of writhes and reduces nociceptive response	87
CCI of sciatic nerve	Rat	Melatonin, 2.5, 5mg/kg, i.p.	Attenuate thermal hyperalgesia, cold allodynia	88
		Melatonin, 100mg/kg, i.p.	Increase pain threshold of mechanical allodynia and slightly increase threshold of thermal hyperalgesia.	89
		Melatonin, 5–10mg/kg, i.p.	Reduce thermal hyperalgesia	90
Oxaliplatin Streptozocin CCI of sciatic nerve	Rat	Agomelatine, 45 mg/kg, i.p.	Dose dependently reduce mechanical hypersensitivity	92
CCI of median nerve	Rat	Melatonin, 37.5, 75, 150, 300 mg/kg, p.o.	Dose dependently reduce mechanical hypersensitivity	95
CCI of sciatic nerve	Rat	Extracorporeal shock wave-assisted melatonin, 50,20mg/kg, i.p.	Superior to either one alone to improve pain	96,97
Sciatic nerve cuff-implanted	Mouse	Melatonin, 100mg/kg, i.p.	Suppress mechanical allodynia and thermal hyperalgesia	17
PSL	Mouse	Piromelatine, 25, 50, or 100 mg/kg, i.p.	Antinociceptive	93

to the minor side effects and sequelae of melatonin. For instance, chronic musculoskeletal pain and generalized tenderness including allodynia or hyperalgesia from fibromyalgia syndrome are alleviated by melatonin treatment. Melatonin administration (3 mg or 5 mg/day) alone or combined with fluoxetine (20 mg/day) shows a significantly therapeutic effect in patients with

fibromyalgia syndrome.¹² Melatonin also attenuates inflammation and oxidative stress and is reported to be effective in repairing morpho-functional damage in a fibromyalgia syndrome model.^{72,73} A clinic trial suggests that reduction of melatonin synthesis and significant increase in 6-sulfatoxymelatonin secretion are positively correlated with clinical symptoms of fibromyalgia

syndrome.^{74,75} Melatonin treatment also causes moderately increased expression of mitofusin2 and proliferator-activated receptor gamma coactivator-1alpha (PGC-1 α) in reserpine-induced myalgic (RIM) rodents meant to mimic mitochondrial function.⁷³

In the orofacial pain test, acute melatonin administration alters mechanical and thermal hyperalgesia with long-term effects.⁷⁶ Post-hoc analysis also shows that melatonin treatment increases the mechanical pain threshold and improves sleep quality in chronic inflammatory pain patients.^{77–79} Another study provides evidence that melatonin could reduce pain scores, lower analgesic use, and improve sleep quality.⁷⁸ Interestingly, melatonin achieved complete pain alleviation in the first post-traumatic/secondary case of long-lasting autonomic symptoms with hemicrania (LASH) syndrome.⁸⁰ Moreover, exogenous melatonin supplementation can significantly relieve abdominal pain caused by irritable bowel syndrome (IBS).⁸¹ Furthermore, melatonin reduces indomethacin dosage during the treatment period of hemicrania continua and shows better pain relief effect.⁸²

In sub-chronic arsenic-induced animals, exogenous melatonin administration exerts properties of scavenging oxidative and nitrosative radicals, inhibiting pro-inflammatory cytokines and repairing neuropharmacological disturbance.⁸³ The hyperalgesic and inflammatory responses induced by CFA could be effectively attenuated by melatonin.⁸⁴ In an animal model of oxaliplatin-induced pain, melatonin alleviates nociceptive response via repression of glial fibrillary acidic protein (GFAP) and inflammatory cytokines such as IL-1 and TNF- α , and neuropathic deficits via reduction of the loss of mitochondrial membrane potential.^{85,86} Moreover, melatonin derivatives such as benzoyl-melatonin (BMT) and acetyl-melatonin (AMT) perform the anti-inflammatory activities in lipopolysaccharide (LPS)-stimulated macrophage cells and exert antinociceptive effects, which result in the reduction of nitric oxide (NO) and prostaglandin E2 (PGE2).⁸⁷

Neuropathic Pain

Thermal hyperalgesia, cold allodynia, and oxidative stress induced by chronic constriction injury (CCI) of the sciatic nerve are significantly attenuated by administration of melatonin (2.5 or 5 mg/kg, i.p.). L-arginine pretreatment can reverse the melatonin-induced protective effect suggesting the nitric oxide pathway is involved.⁸⁸ Other researchers have found that melatonin could increase the mechanical pain threshold and slightly increase thermal hyperalgesia threshold. However, naloxone pretreatment abolishes the

mechanical antinociceptive but not the thermal protect effect of melatonin.⁸⁹ In addition, melatonin also increases the withdrawal latency during plantar tests in CCI rodents.⁹⁰ Interestingly, agomelatine, a melatonin analog, administration alone had no effect on mechanical allodynia induced by chronic constriction (ligation) injury to the sciatic nerve (CCI-SN) or the infraorbital nerve (CCI-ION) rats but produced an anti-allodynic effect when combined with gabapentin.⁹¹ However, in another study, agomelatine dose-dependently decreased mechanical hypersensitivity in three neuropathic pain models (oxaliplatin, streptozocin, and CCI).⁹² The analgesic effect of agomelatine remains controversial and needs to be validated. While, piromelatine, another melatonin analog, is reported to significantly prolong thermal and mechanical latency and improve sleep of partial sciatic nerve ligation (PSL) mice.⁹³ Furthermore, neuropathic pain is worse due to the reduction of endogenous melatonin from sleep deprivation or pinealectomy, while exogenous supplement of melatonin can alleviate the behavioral hypersensitivity.^{94,95} Otherwise, adjuvant therapy with melatonin has a superior anti-hyperalgesia effect. For instance, melatonin combined with an extracorporeal shock wave has a synergistic effect with short- and long-term improvement of neuropathic pain.^{96,97}

Misaligned diet and sleep deprivation during the peri-CCI surgery and post-CCI distinctly decrease the paw withdrawal mechanical threshold, whereas melatonin pretreatment ameliorates the hypersensitivity and reverses the disturbed sleep rhythm.^{94,98} In other neuropathic pain models, such as cuff implantation, valproic acid, and paclitaxel, melatonin ameliorates mechanical and thermal allodynia by preventing the increases in NO levels, down-regulating c-fos, and increasing C-fiber activity.^{17,99,100} Growing evidence suggests that melatonin administration may reverse the nociceptive threshold in spinal nerve ligation (SNL) rodents.^{101,102} Meanwhile, MT2 receptor-selective antagonist treatment reverses the effect caused by melatonin, suggesting that MT2 receptors may be a novel target in treating neuropathic pain.^{15,103,104}

Mechanisms of Action on Animal Models

Melatonin Receptors

Melatonin receptors in both central and peripheral nervous system have been considered antinociceptive, due to mounting evidence in many rodent models of neuropathic pain.^{89,93,105,106} In rat L5–L6 SNL and spared nerve injury models, a selective MT2 partial agonist, UCM924, exerted

anti-allodynic effects by modulating the ON/OFF cells of the antinociceptive system, suggesting that MT2 receptor may be an important target in analgesic drug development.¹⁵ Meanwhile, in the hot-plate and formalin tests, UCM765 (another selective MT2 partial agonist) and UCM924 also exert an antinociceptive effect.¹⁴ Another study shows that MT2 receptor agonist, IIK-7, can relieve neuropathic pain through the inhibition of glial activation and downregulation of proteins involved in inflammation such as inducible nitric oxide synthase (iNOS) and caspase-3.¹⁰⁷ In addition, MT2 receptor agonists are considered to be effective in the treatment of neuropathic pain and have several advantages over melatonin.¹⁰⁸ MT receptors could transmit signals through the pertussis toxin-sensitive Gi/o protein and delivered to second messenger systems or through Gq/11-phospholipase C (PLC) and PKC-dependent mechanism to modulate Ca^{2+} signaling.^{109,110} Conversely, melatonin is considered to exert protective effects by suppressing PKC.⁶³ The potential mechanisms remain controversial and require further investigation.

Interestingly, melatonin induces a reduction in T-type Ca^{2+} channel currents via the MT2 receptor coupled to $G_{\beta\gamma}$ -mediated PKC η signal pathway. This subsequently reduces neuronal excitability and ameliorates CFA-induced mechanical hypersensitivity.¹¹¹ Melatonin is able to suppress the mitogen-activated protein kinase (MAPK) and calcium signaling pathways via the MT2 receptor, which suppresses mechanical allodynia and thermal hyperalgesia induced by cuff-implanted.¹⁷ The membrane receptors of melatonin are one of the most important mechanisms of its antinociception effect, especially MT2 receptor. Thus, it is more critical to make extensive efforts to explore the downstream pathways of melatonin membrane receptors. Interestingly, accumulated evidence shows that ROR2 is activated and upregulated after CCI, while inhibition of ROR2 reverses the nociceptive effect.¹⁶ Therefore, we speculate that melatonin may exert pain-promoting effects through activation of ROR instead of MT receptors, which needs further study.

Ion Channels and Membrane Potential

Abnormal ion channel expression and physiology have been demonstrated in a variety of pain models.^{112,113} Some groups show that melatonin inhibits abdominal pain caused by psychological stress via interacting with Ca^{2+} channels.¹¹⁴ Melatonin modulates against Ca^{2+} influx via desensitization of transient receptor potential vanilloid type

1 and melastatin type 2 (TRPV1 and TRPM2).¹¹⁵ Moreover, melatonin exerts anti-thermal hypersensitivity and anti-mechanical allodynia effect by inhibiting the activities of voltage-gated sodium channels Nav1.8 and Nav1.9. The thermal stimuli is transmitted by small unmyelinated C-fiber and thinly myelinated A- δ fiber, while the mechanical stimuli is transmitted by large myelinated A- β fiber.⁹⁷

In addition, melatonin reverses the inhibition activities of synaptosomal integral enzymes such as Na^+ , K^+ -ATPase, and acetylcholinesterase (AChE) in neuropathic pain induced by valproic acid.⁹⁹ However, in medial lateral habenula (MLHb) neurons, experiments shows that melatonin significantly augments the amplitude of glutamate-mediated evoked excitatory post-synaptic currents (EPSC), thus increasing glutamatergic synaptic transmission, which promotes the release of glutamate and increases neuronal excitability.¹¹⁶ In contrast, another study shows that melatonin inhibits excitatory synaptic transmission and reduces norepinephrine release in hippocampus.¹¹⁷ Therefore, melatonin may have a dual effect on neuronal excitability in the central nervous system. Thus, future molecular studies are required to determine the main effect of melatonin on neuronal excitability and neuropathic pain due to the complexity of central nervous network and duality of melatonin action.

NO/NOS System

NO is a physiological gas molecule, which is synthesized intracellularly directly by nitric oxide synthase (NOS) using L-arginine as substrate. NOS exists as a family of three distinct isoforms: neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS). NO/NOS system exerts a broad spectrum of physiological and pathophysiological activities in humans. Accumulating evidence demonstrates that the NO/NOS system plays an important role in the initiation and maintenance of nociceptive response in animal models.¹¹⁸ The enhanced levels of NO production and NOS expression are inhibited by melatonin administration in various nociceptive states.^{90,99} However, the protective effect is significantly reversed by L-arginine pretreatment.⁸⁸ Interestingly, the addition of luzindole does not distinctly influence the expression of nNOS, suggesting that the antinociceptive effect of melatonin in this pathway is not mediated by MT receptors.¹⁷ Moreover, another study reveals that NO propagates the hypersensitive potentiation induced by hind-paw ischemia possibly mediated by group II metabotropic glutamate receptors (mGluRs) as this effect was blocked by group II mGluRs agonist LY354740.¹¹⁹

Substantial evidence supports that melatonin partially but effectively reduces both cyclooxygenase-2 (COX-2) and iNOS expression, thus inhibiting the production of PGE2 and NO, respectively, which alleviates the hyperalgesia with inflammation.¹¹ Inhibition of NO production leads to decrease in PKC-dependent N-Methyl-D-aspartate (NMDA) receptor GluN1 subunit and ultimately contributes to improving the mechanical allodynia following peripheral nerve injury.^{120,121} In addition, another study suggests that reduction of NO production could mitigate allodynic and hypersensitive activities through NO-cGMP-PKG-K⁺-ATPase pathways.^{122,123}

Opiate System

Earlier studies revealed that melatonin exerts antinociception via the opiate system.^{124,125} In agreement with these results, the overexpression of opioid receptors is observed after hyperbaric oxygen treatment of neuropathic pain, suggesting that the opiate system participates in attenuation of allodynia.¹⁰⁶ Piromelatine is effective in treating neuropathic pain and sleep disturbance in PSL rats mediated by opioid receptors.⁹³ Melatonin not only increased the pain threshold of mechanical allodynia but also enhanced the threshold of thermal hypersensitivity.⁸⁹ Naloxone, an opioid receptor antagonist, reversed the anti-allodynic and anti-hypersensitive effect of melatonin suggesting that melatonin affects mechanical allodynia and thermal hypersensitivity through activation of opiate system.^{89,126,127} In addition, co-activation of δ -opioid and melatonin receptors could induce much longer analgesia than either receptor individually.¹²⁸ While, naltrindole, a selective δ -opioid receptor antagonist, can partly reverse melatonin-induced antinociception, suggesting the activation of δ -opioid receptors in the antinociceptive effect of melatonin in diabetic rats.¹²⁹

Adrenergic Receptors

Previous studies have shown that melatonin can accelerate norepinephrine transmission and activation of α_1 - and β -adrenoceptors.¹³⁰ Moreover, activation of the noradrenergic descending pathway inhibits the activities of the spinal cord nociceptive receptors, such as α_2 -adrenoceptors.^{131,132} It is documented that intrathecal melatonin alleviates mechanical allodynia response in the formalin test, which is mediated through α_1 -adrenoceptors, α_2 -adrenoceptors, muscarinic, and nicotinic receptors in the spinal cord.⁶⁰ In addition, agomelatine exhibits anti-allodynia through noradrenergic neurotransmission mediated by α_2 -adrenoceptors and β_2 -adrenoceptors.⁹¹

NMDA Receptors

Recent findings suggest that NMDA receptors pathways participate in the transmission of pain.¹³³ Melatonin is considered to attenuate morphine-induced hypersensitivity and tolerance by suppressing NMDA receptor subtype 1 (NR1) activities in the spinal cord.⁶¹ The up-regulation of NMDA receptor subtype 2B (NR2B), Ca²⁺/calmodulin-dependent protein kinase II (CaMKII), and cyclic adenosine monophosphate-response element-binding protein (CREB) is induced by nerve injury, which can be recovered by melatonin pretreatment.⁹⁸ Furthermore, melatonin administration attenuates the NR1 expression and reduces NMDA-induced currents in dorsal horn neurons in rodents with unilateral temporomandibular joint (TMJ) inflammation in a dose-dependent manner.¹³⁴ The treatment of neuropathic pain achieves more efficacy using a combination of melatonin and dextromethorphan (DM; a clinically available NMDA receptor antagonist).¹³⁵

Epigenetic Modifications

Epigenetic modifications alter gene expression without changing the primary DNA sequence. Epigenetic modifications primarily include DNA methylation, histone acetylation, and non-coding RNA interference. In the past decade, a growing number of studies have implicated epigenetic modifications in the induction and maintenance of neuropathic pain or inflammatory pain.^{136–139} Accumulating evidence suggests that spinal ten-eleven translocation methyl-cytosine dioxygenase 1 (Tet1)-dependent epigenetic demethylation is associated with nociception hypersensitivity development.¹⁴⁰ Melatonin has been reported to inhibit Tet1 expression, Tet1-metabolic glutamate receptor subtype 5 (mGluR5) promoter coupling, hence leading to mGluR5 promoter methylation enrichment and low expression of mGluR5 in dorsal horn neurons, subsequently mitigating neuropathic pain.¹⁰³ Melatonin has been reported to alleviate allodynia via histone acetylation modification. The experiment shows that the antinociceptive effect of melatonin is conducted by enhancing spinal serine-/threonine-specific phosphatase 2A (PP2A) expression that couples PP2A with histone deacetylase 4 (HDAC4) to dephosphorylate HDAC4 as well as prompts nuclear import of HDAC4, herein HDAC4 binds to histone of *hmgb1* gene and increases high-mobility group protein B1 (HMGB1) expression in neurons.^{101,141}

Other Mechanisms

Melatonin also is reported to show an inhibition of the Toll-like receptor 4 (TLR4)/NF- κ B pathway in the pulp of

acute pulpitis rats to exert a protective effect. Moreover, in LPS-stimulated human dental pulp cells, melatonin could also influence the TLR4/NF- κ B pathway.⁶² In the animal model of hyperalgesia associated with inflammation, the antinociceptive response of melatonin is mediated by inhibition of NF- κ B signaling and MAPK.¹¹ Conversely, in nerve injury-induced neuropathic pain, pinealectomy reverses the protective effect of melatonin due to phosphorylation of p38 MAPK, activation of microglia, and release of pro-inflammatory cytokines.⁹⁵ (Figures 2 and 3)

Furthermore, the current data suggest that short-term administration of melatonin after acute pain may be associated with the pain regulation and neuroprotective effects of BDNF levels.⁶¹ In addition, melatonin therapy has been found to partially reverse morphine-induced hypersensitivity and tolerance by inhibiting microglia activation via the heat shock protein 27 (HSP27)-related pathway.⁶⁵ Besides, it is reported that melatonin restored the antinociceptive effect of morphine through altering the expression of multiple genes.¹⁴² Thus, the molecular mechanism of melatonin exerting antinociceptive effect remains to be further studied.

Conclusion

Although melatonin and its analogs have been shown to attenuate hyperalgesia and allodynia in several animal models of acute, inflammatory, and neuropathic pain, conflicting evidence exists and the mechanisms are not fully understood. On the one hand, melatonin is a pleiotropic hormone with little side effects and has the potential to be used as an effective drug in antinociception activity. Therefore, an increasing number of clinical trials have been conducted to verify the analgesic effect of melatonin in humans. On the other hand, melatonin can travel throughout the body and act on a large number of targets due to its hydrophilicity and lipophilicity. At present, the main mechanism through which melatonin plays an antinociceptive role has not been determined. A comprehensive understanding of the underlying mechanisms for the observed effects of melatonin in nociception will be necessary before its use can be evaluated in clinical applications for the prevention and/or treatment of different pain states in humans. Thus, the exact mechanistic pathway by which melatonin exerts nociceptive effect remains to be elucidated.

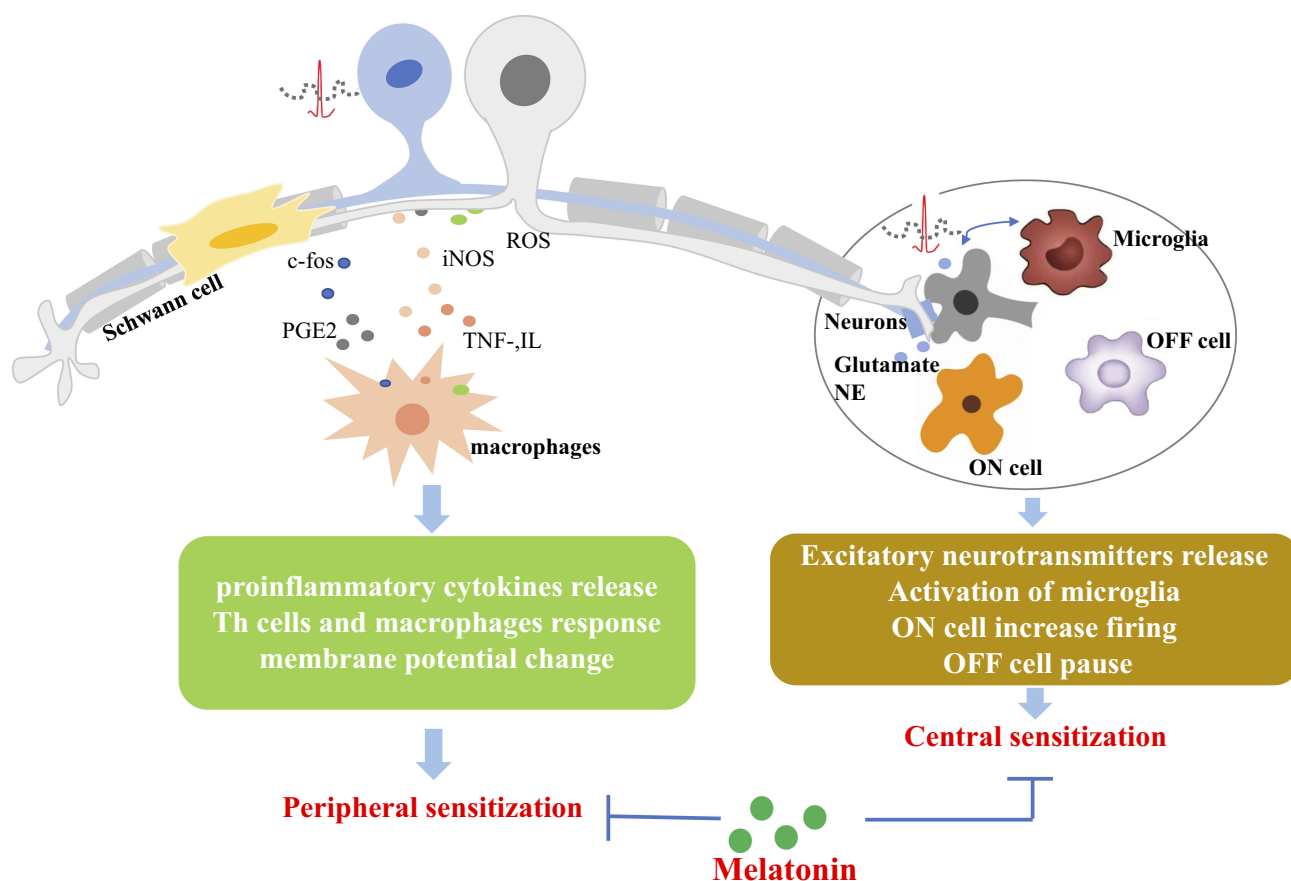


Figure 2 Schematic diagram of the primary mechanisms of melatonin and its analogs on neuropathic pain management.

Abbreviations: PGE2, prostaglandin E2; iNOS, inducible nitric oxide synthase; TNF, tumor necrosis factor; IL, interleukin; NE, norepinephrine.

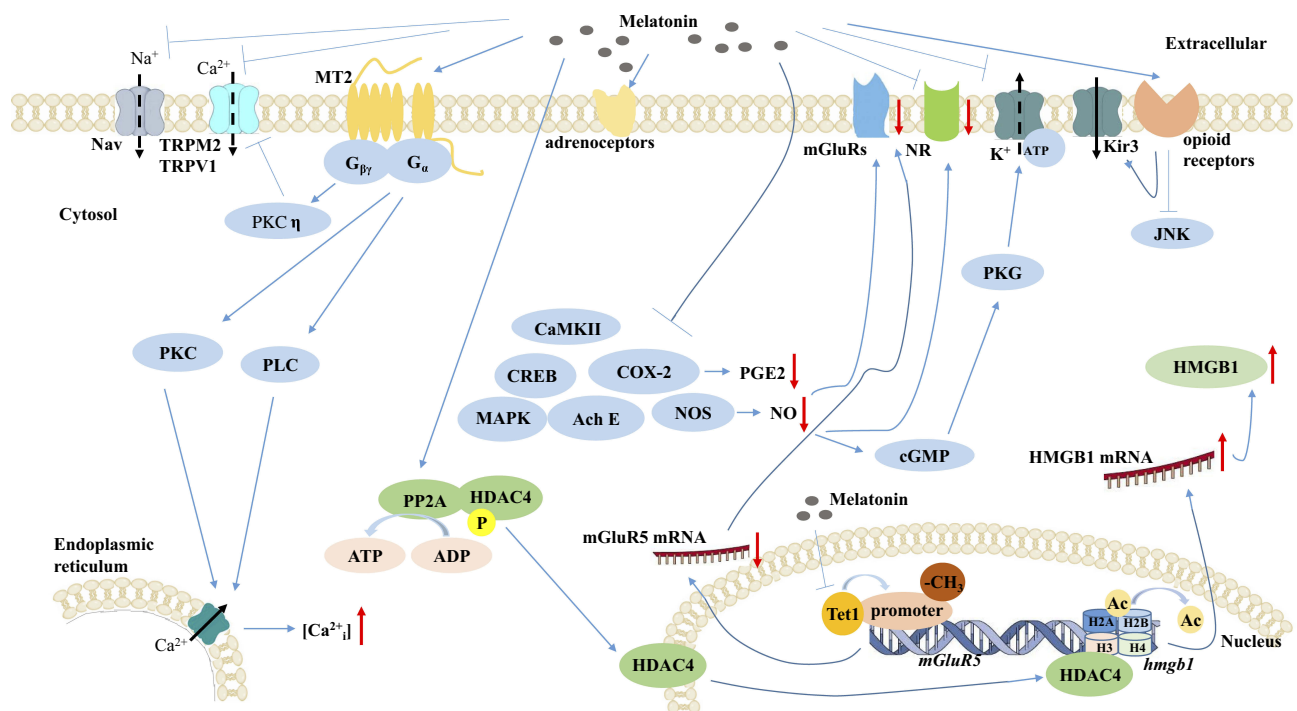


Figure 3 Schematic diagram of the primary mechanisms for regulatory effects of melatonin and its analogs on neurons in pain.

Abbreviations: MT2, melatonin membrane receptor 2; TRPM2, transient receptor potential melastatin type 2; TRPV1, transient receptor potential vanilloid type 1; PLC, phospholipase C; PKC, protein kinase C; Ca^{2+}_i , intracellular calcium; AchE, acetylcholinesterase; MAPK, mitogen-activated protein kinase; NOS, nitric oxide synthase; NO, nitric oxide; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; mGluRs, group II metabotropic glutamate receptors; NR, N-Methyl-D-aspartate receptor; JNK, c-Jun N-terminal kinase; CaMKII, Ca^{2+} /calmodulin-dependent protein kinase II; CREB, cyclic adenosine monophosphate-response element binding protein; Tet1, spinal ten-eleven translocation methyl-cytosine dioxygenase 1; HMGB1, high-mobility group protein B1; PP2A, spinal serine/threonine-specific phosphatase 2A; HDAC4, histone deacetylase 4; Ac, acetyl groups.

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Disclosure

The authors report no conflicts of interest in this work.

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