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Melatonin and its Receptors

Review Article

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Abstract

Background: Melatonin (5-methoxy-N-acetyltryptamine) is a hormone that has numerous physiological functions. Synthesized and released during nighttime, melatonin exerts its physiological effects in a circadian manner. Melatonin acts by binding to its different types of receptors. The purpose of this systematic review is to summarize recent findings about melatonin, its receptors, and the differential functionalities of the most characterized melatonin receptors MT1 and MT2.

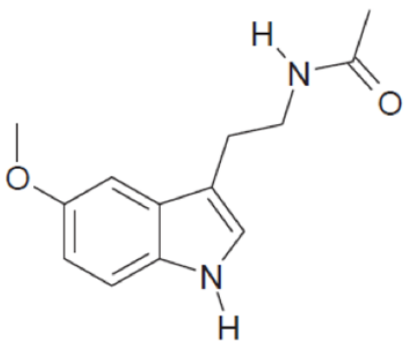
Methods: We searched PubMed and Google Scholar for studies that reported melatonin receptor subtypes, their differential functionalities, biochemical structures, signal transductions, and various functions of melatonin such as pain, sleep, temperature, and antioxidative effects. We chose seventy articles for this systematic review.

Summary: These studies highlight melatonin's range of physiological functions and the differential functionalities of the melatonin receptors MT1 and MT2; they characterize the receptors' signal transduction cascades and their biochemical structures. More studies assessing melatonin receptors' functions would help patients with disorders in sleep, pain, and circadian rhythm.

Introduction

"Think in the morning. Act in the noon. Eat in the evening. Sleep in the night." (William Blake, The Marriage of Heaven and Hell). (1)
Long before our investigation into chronobiology, the daily light/dark cycle dictated our lives. The human physiological system has synchronized to when the sun rises and sets and to when the sky is clear blue or pitch black. The neurohormone melatonin plays a pivotal role in this process.
Melatonin (5-methoxy-N-acetyltryptamine) (Fig. 1) is a hormone that regulates a wide range of physiological functions including circadian rhythms, (2) mood regulation, (3) anxiety, (4) sleep, (4) pain, (3) immune responses, (2) and cell cycle. (2)

Enzymes drive the synthesis of melatonin. Tryptophan hydroxylase (TPH) converts tryptophan, a precursor to melatonin, into 5-hydroxytryptophan. (5) Subsequently, aromatic amino acid decarboxylase (AAD) converts 5-hydroxytryptophan into serotonin. Arylalkylamine-N-acetyl transferase (AANAT) then converts the serotonin into N-acetylserotonin. Finally, hydroxyindole-O-methyltransferase (HIOMT) converts N-acetylserotonin into melatonin (Fig. 2). (6) Melatonin travels through the circulatory system to the capillaries and affects various organs. (6) Its amphiphilic biochemical structure facilitates its transportation throughout the body. (7) where it exerts different physiological effects on different organs.



Melatonin (5-methoxy-N-acetyltryptamine)

Fig. 1: Chemical Structure of Melatonin

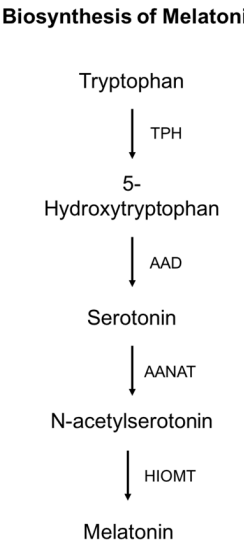


Figure 2. Biosynthesis of Melatonin. (2) Tryptophan hydroxylase (TPH) converts tryptophan, a precursor to melatonin, into 5-hydroxytrytophan. Subsequently, aromatic amino acid decarboxylase (AAD) converts 5-hydroxytrptophan into serotonin. Arylalkylamine-N-acetyl transferase (AANAT) then converts the serotonin into N-acetylserotonin. Finally, hydroxyindole-O-methyltransferase (HIOMT) converts N-acetylserotonin into melatonin.

Melatonin has a short half-life. It shows a biexponential decay with a first distribution half-life of 2 minutes and a second metabolic half-life of 20 minutes. (8) Therefore, melatonin's clearance is rapid upon its release in the bloodstream. Hence, the physiological concentration of circulating melatonin delivers the message of environmental darkness throughout the body; for this reason melatonin is known as the "chemical expression of darkness". (9) The concentration of melatonin peaks during nighttime

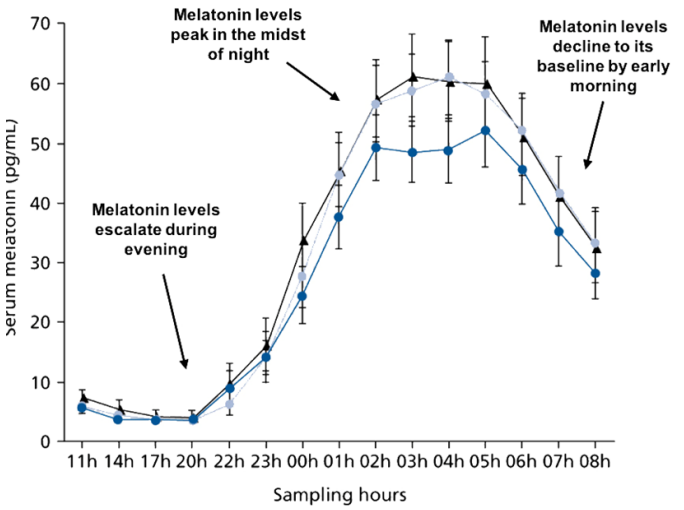


Figure 3. Concentration of melatonin during night and day phase in three different 24-h sessions. The concentration varies depending on the time block due to the circadian regulation of suprachiasmatic nucleus affecting the synthesis and release of melatonin. (13) Its concentration is maximal at 2-4 AM and minimal throughout the daytime. (13) Reproduced from (14) Selmaoui B, Touitou Y. Reproducibility of the circadian rhythms of serum cortisol and melatonin in healthy subjects. A study of three different 24-h cycles over six weeks. Life Sci. 2003;73:3339-49.

(between 2:00 AM and 4:00 AM) and declines during daytime. (10, 11) Melatonin is mostly synthesized by the pineal gland and is secreted during the nighttime. (8) Light exposure suppresses the release and synthesis of melatonin in a dose-response manner. The intensity of environmental light determines the amplitude of the synthesis and the release of melatonin (Fig. 3).

Melatonin also regulates a wide range of physiological functions including circadian rhythmicity. It interacts with a brain region in the hypothalamus known as the suprachiasmatic nucleus (SCN), the so called "master clock." The SCN regulates the synthesis and secretion of melatonin in a circadian pattern that corresponds to the environmental daily light/dark cycle (Fig. 3). Although melatonin has diverse physiological functions, its primary role is to provide photoperiod information about the environmental light/dark phase so that the organism can adjust its physiology to the 24-hour cycle.

If the SCN is lesioned, the rhythm of melatonin release is abolished; (12) this experiment shows the importance of the SCN in generating a circadian pattern of melatonin release. However, melatonin can also send feedback to the SCN. (13) Therefore, melatonin performs a dual role as (a) a possible feedback signal to the SCN by binding to melatonin receptors MT1 and MT2 within the SCN and (b) as an SCN-dependent output signal that influences cells in the central and peripheral nervous system. (2) Communications between the SCN and the pineal gland proceed via a multi-synaptic pathway that allows for the synthesis and the release of melatonin according to the environmental light/dark phase. (14) A limited subset of retinal ganglion cells in the eyes detect the intensity of environmental light. (15) This information from the retina is then transferred to the SCN via the retinohypothalamic tract. (16) This tract enables not only the information to be transmitted from the retina to the SCN, but also allows the SCN to entrain the physiological rhythm to the 24-hour cycle. Pinealectomy (the removal of the pineal gland) abolishes most of the nocturnal rhythm in mammals, (17) demonstrating the importance of the pineal gland and melatonin in the maintenance of biological rhythms.

Though the versatility of melatonin in its physiological functions has been well-elucidated, this review will focus more on the known melatonin receptor subtypes. The purpose of this review is to describe recent findings on melatonin receptor subtypes such as MT1, MT2, GPR50, MT3, and nuclear receptors and to report recent findings about signal transduction and the differential functionalities of the two most characterized melatonin receptor subtypes, MT1 and MT2, with respect to pain sleep and circadian rhythms.

The Melatonin Receptors

Melatonin receptors were first cloned using *Xenopus laevis* melanophore (18) using a method to unbiasedly isolate proteins known as expression cloning strategy. (19) This sparked interest in melatonin and led to research that characterized mammalian high-affinity melatonin receptors. (20)

The melatonin receptors were later characterized in the early-1990s using the high-affinity radioligand 2-[125I] iodomelatonin. (21) This radioligand served as a visual tracer to localize melatonin receptors that are expressed in native tissues. Visualization of 2-[125I] iodomelatonin has been made possible by autoradiography, thus enabling anatomical localization of melatonin receptors.

Initially, melatonin receptors were classified based on their affinity for the 2-[125I]iodomelatonin radioligand as the high-affinity ML1 (dissociation constant Kd <300 pM) and the low-affinity ML2 (Kd 0.9-10 nM). (22) Later, two subtypes of ML1 receptor were cloned (20, 23) and they were initially referred to as Mel1a and Mel1b. Moreover, the nomenclature of ML2 was later modified, and the receptor is now named MT3, a third subtype of the melatonin receptor which, unlike MT1 and MT2, displays low affinity to melatonin. (23) Before, another cloned melatonin receptor from Xenopus laevis melanophores was identified and named Mel1c, but this subtype has only been found in non-mammals. (18) Development of diverse partial agonists and antagonists that show differential affinity to one of the melatonin receptor subtypes (24) has enabled investigators to characterize the differential functionalities of the melatonin receptors. (25)

MT1 and MT2

The human MT1 (formerly named Mel1a) receptor spans 350 amino acids whereas the human MT2 (formerly named Mel1b) receptor spans 362 amino acids. (26) Their molecular weights are 39-40 kDa and they display homology in 55% of their amino acids overall and 70% within the transmembrane domain. (26) Melatonin receptors MT1 and MT2 are both membrane-bound G-protein coupled receptors (GCPRs) with 7 transmembrane alpha-helical domains. (27) The amino terminus is on the extracellular side and the carboxyl terminus is on the intracellular side. (13) Features unique to melatonin receptors among the GCPRs are (a) a NRY motif downstream from the third transmembrane domain and (b) a NAXIY motif in the seventh transmembrane domain. (13, 20, 23, 28)

Two melatonin receptors display different chromosomal localizations. The MT1 melatonin receptor gene was localized in human chromosome 4q35.1 and mouse chromosome 8. (29) Conversely, the MT2 melatonin receptor was localized in human chromosome 11a21-22 and mouse chromosome 9. (23)

Melatonin MT1 and MT2 receptors have been localized through several laboratory techniques including *in situ* hybridization and immunohistochemistry. (13) The peripheral tissues where MT1 is expressed include the cardiovascular system, immune cells, testes, ovaries, skin, liver, kidneys, adrenal cortex, placenta, breasts, retina, pancreas, and spleen. (5) MT2 is distributed in the immune cells, retina, pituitary gland, blood vessels, testes, kidneys, gastrointestinal tract, mammary glands, adipose tissue, and skin. (5)

A recent study examined the distribution of MT1 and MT2 in an adult rat's brain using polyclonal anti-MT1 and anti-MT2 antibodies (30) visualized under light, confocal, and electron microscopes. (31) This study thoroughly mapped the anatomical localization of MT1, finding abundant MT1 receptors in the retrosplenial cerebral cortex, basal forebrain, hippocampus, medial habenula, anterodorsal nucleus of thalamus, dorsal mesencephalon, substantia nigra (pars compacta), and pars tuberalis of the pineal

gland. (31) On the other hand, MT2 receptors were widely expressed in the reticular thalamus, substantia nigra (pars reticulata), supraoptic nucleus, red nucleus, CA2 and CA3 areas of the hippocampus, (31, 32) and on the glutamatergic neurons in the ventral lateral periaqueductal grey matter (vlPAG), which is involved in the descending pain-control pathway (vlPAG-rostral ventral medulla). (33) As opposed to radioligand studies that crudely determined the anatomical localizations of melatonin receptors, this study attempted for the first time to use antibodies to specifically localize different subtypes of melatonin receptors.

Signal Transduction via MT1 and MT2

Since both MT1 and MT2 melatonin receptors are G-protein coupled receptors, this review will briefly touch upon the G-proteins.

G-proteins:

Signal transduction is pivotal to an organism's survival. For an organism to adapt to an ever-changing environment, it must immediately respond to changes in the environment. This detection of changes happens through signal transductions (signal processes), many of which are mediated by G-proteins. Ligands such as hormones, neurotransmitters, and chemokines exert their effects on their target cells by binding to heptahelical transmembrane receptors (G-protein coupled receptors) coupled to heterotrimeric G-proteins. (34) After a ligand binds to a receptor, it induces a conformational change that activates a heterotrimeric G-protein.

Heterotrimeric G-proteins are composed of alpha, beta and gamma subunits; they are located on the intracellular surface of a cell. (35) G-proteins are classically divided into four different families based on their alpha subunits: $G_{i/o}$, G_s, $G_{q/11}$, $G_{12/13}$. If the G-protein is in an inactive state, guanosine diphosphate (GDP) is bound to the alpha-subunit of the G-protein. Once the G-protein is activated, GDP gets released from the alpha subunit and guanosine triphosphate (GTP) associates with the alpha subunit. This association causes a dissociation between the G-beta-gamma and the G-alpha-GTP subunits. The G-beta-gamma and the G-alpha-GTP subunits can activate many intracellular effectors to mediate further signalling. To study the cellular signaling mediated by G-proteins, researchers have used Pertussis Toxin (PTX; a virulence factor synthesized by *B. pertussis*) as a reagent in mammalian cells in signaling studies. PTX has an inhibitory effect on G-protein coupled receptor (36) and PTX sensitivity also displays an involvement of G-proteins in the $G_{i/o}$ family. (37)

Melatonin receptors are seven transmembrane-spanning proteins belonging to the GPCR superfamily. In mammals, two melatonin receptor subtypes have been cloned, the MT1 and MT2 which are encoded by the MTNR1A and MTNR1B genes respectively.

MT1:

The MT1 melatonin receptor is coupled to both PTX-sensitive (G_{i2} and G_{i3}) and insensitive ($G_{q/11}$) G-proteins. (38) Activation of the MT1 melatonin receptor inhibits forskolin-stimulated cyclic adenosine monophosphate (cAMP), (39, 20) protein kinase A signaling, and cAMP-responsive element binding protein (CREB) phosphorylation. (40) The inhibitory effect on forskolin-stimulated cAMP formation was abolished when the non-selective MT1/MT2 antagonist luzindole is pre-administered. (41) Moreover, activation of the MT1 melatonin receptor increases the phosphorylation of mitogen-activated protein kinase 1 and 2 (MEK1 and MEK2), extracellular signal-regulated kinases 1 and 2 (ERK1 and ERK2), (42) and potassium conductance through K_{ir} inwardly rectifying channels. (43)

MT2:

The MT2 melatonin receptor is also coupled to the inhibition of forskolin-stimulated cAMP formation. (23) Petit and colleagues (44) also examined a potential modulation of cyclic guanosine 3'-5'-monophosphate (cGMP) by expressing them in human embryonic kidney cells. While MT2 modulated cGMP level in a dose-dependent level, MT1 did not show any modulation of the cGMP level. (44) MT2 signaling also increases the level of protein kinase C (PKC) activity in the SCN; this effect is blocked by an administration of the MT2 selective antagonist 4P-PDOT. (41) Like with MT1, MT2's inhibitory effect on forskolin-stimulated cAMP formation is also abolished when luzindole is pre-administered. (41) Moreover, MT2 activation reduces calcium-dependent release from the rabbit retina. (26, 45)

GPR50:

Besides MT1 and MT2, another mammalian melatonin receptor-related receptor known as GPR50 has been isolated. (27) However, unlike MT1 and MT2, melatonin is unable to bind to GPR50 as a ligand. This receptor remains an orphan because its natural ligand is unknown. (46) GPR50 also belongs to the GPCR family. GPR50 is now believed to be a mammalian orthologue of Mel1c melatonin receptor subtype based on an in silico approach and an examination of the synteny between the two genes. (47)

MT3:

As mentioned above, melatonin displays a low affinity for MT3. Originally, it was widely believed that MT3 belonged to the GPCR family. However, MT3 turned out to be a human homologue of cytosolic enzyme quinone reductase II. (48) The existence of MT3 was initially hypothesized after researchers observed its different binding and kinetics profile from those of MT1 and MT2. (48) The existence of MT3 was confirmed when it was purified via affinity chromatography; purified MT3 showed a 95% homology to quinone reductase II, which has detoxifying properties. The pharmacological profile of MT1 and MT2 is 2-iodomelatonin>melatonin>>N-acetylserotonin, whereas that of MT3 is 2-iodomelatonin>melatonin=N-acetylserotonin. (13) More studies should explore the relationship between melatonin's antioxidative effects and the functionality of the MT3 receptor.

Nuclear Receptors:

Melatonin also mediates its physiological actions by binding to nuclear receptors. Nuclear receptors are ligand-inducible transcription factors that can affect gene expression and thereby regulate development, the maintenance of homeostasis, cellular proliferation and differentiation, and apoptosis. (49) There are about 200 members of the nuclear receptor superfamily, a vast number of which are orphans. (50) Melatonin is a natural ligand of nuclear receptors that belong to the subfamily of retinoid Z receptors or retinoid orphan receptors (RZR/ROR). (51) There are three members of the RZR/ROR subfamily: RZR/ROR(alpha), RZR(beta) and ROR(gamma). (52) It has been reported that melatonergic signalling via nuclear receptors mediates aspects of the immune system. Indeed, RZR/ROR(alpha) activation by melatonin increases the level of interleukin (IL) 2 and IL-6 production by human mononuclear immune cells. (53) The RZR(alpha) nuclear receptor is also able to repress the expression of the gene 5-lipoxygenase, an enzyme responsible for the biosynthesis of allergic and inflammatory mediators, in human B lymphocytes. (54) On the other hand, RZR(beta) melatonin receptor mRNA has been found using *in situ* hybridization in sensory regions such as the cortical areas of the somatosensory, visual and auditory systems, the thalamic nuclei for each of the sensory pathway, and the dorsal horn of the spinal cord. (55) These results suggest that RZR(beta) plays a selective role as a transcription factor in the sensory system. (55) After the initial identification of the nuclear receptor subfamily, research in this area has become dormant. More studies are needed to unravel the selective roles of RZR/ROR(alpha), RZR(beta) and ROR(gamma).

To recapitulate, melatonin exerts its physiological effects by binding to the membrane-bound proteins MT1 and MT2 (Kd=10–200 pM) and, with lower affinity, to MT3 (Kd=3–9 nM). (48) It also likely exerts its effects by binding to the nuclear receptors subfamily ROR/RZR.

Functions of MT1 and MT2

Selective Ligands:

Due to a paucity of available selective partial agonists for melatonin receptor subtypes, the functional characterization of MT1 and MT2 melatonin receptors remains incomplete. Pharmacological studies have been carried out using antagonists such as luzindole (MT1/MT2 nonselective)

and 4-phenyl-2-propionamidotetralin (4P-PDOT) (MT2 selective). Recently, there were also studies published that used selective partial agonists including N-{2-([3-bromophenyl]-4-fluorophenylamino)ethyl}acetamide UCM924 (MT2 selective). (24, 25, 33, 32) Characterization of MT1 and MT2 function has also been carried out via genetic deletion of either the MT1 and/or the MT2 receptor. (4)

Complementarity of MT1 and MT2:

MT1 and MT2 fulfill complementary or opposing roles (4) as demonstrated by several studies. For example, melatonin binds to two receptor subtypes in vascular smooth muscle: MT1 mediates vasoconstriction, whereas MT2 mediates vasodilation. (56) Moreover, it has been reported that MT1 and MT2 melatonin receptor subtypes mediate opposing modulations of the type-A gamma-aminobutyric acid (GABAA) receptor. (57) Potentiation of the GABA receptor-mediated current occurred via MT1 in the rat SCN. However, repression of the current occurred via MT2 binding in the hippocampus. GABA is the primary neurotransmitter responsible for synaptic inhibition in the central nervous system. (57) Moreover, MT1 and MT2 melatonin receptor subtypes mediate the regulation of temperature in an opposing manner, contributing to the circadian rhythm of body temperature. (*Gobbi et al.*, unpublished) These results suggest the selective roles of the MT1 and MT2 melatonin receptor subtypes.

Regulation of Sleep and Circadian System:
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The SCN plays a pivotal role in regulating the wake/sleep cycle. Therefore, this review will first discuss the role of melatonin receptors MT1 and MT2 in the SCN, and then discuss their respective contributions to sleep.

There have been conflicting results on the differential functionalities of the melatonin MT1 and MT2 receptors in the SCN between *in vitro* and in vivo studies. Activation of the MT1 receptor in vitro in rodent SCN slices inhibits the neuronal firing of the SCN in a concentration dependent manner. (58, 59) While in vivo, the inhibition of neuronal firing in the SCN was not observed in mice with disrupted MT1 but was demonstrated in mice with disrupted MT2. (59,60) Activation of MT2 receptor in vitro shifts the phases in the SCN's electrical activity. (59) The melatonin-mediated phase shifts were abolished when the rat SCN slice was incubated with the selective MT2 antagonist 4P-PDOT. (58) However, these studies have never been applied in in vivo models and studies in MT2 knockout (KO) mice and with the selective MT2 agonists have not observed any phase shift. (32, 61) Furthermore, MT2 receptors are scarcely present in the SCN. (31) Dubocovich and her colleagues (62) used wheel running activity as a measure of assessing circadian behaviour (63) and measured the effects of melatonin administration on circadian phase shifts and on re-entrainment after a change in the timing of dark onset on wild type (WT) and MT1 KO mice. Melatonin was given to both groups 2 hours before the onset of the circadian phase shift. MT1 KO mice did not display the phase shifting that was observed in WT mice after the administration of melatonin. This study demonstrates that the MT1 receptor is responsible for mediating phase shifts in vivo.

Altogether, these results suggest that the MT1 receptor, and not the MT2 receptor, is primarily involved in phase shifting. However, it will be crucial to perform further in vivo studies with selective full and/or partial agonists and antagonists to further elucidate the differential functionalities of MT1 and MT2 melatonin receptors.

The architecture of normal sleep involves a progression from wakefulness to non-rapid eye movement sleep (NREMS) and then to rapid eye movement sleep (REMS). The state of wakefulness, REMS, and NREMS show different electrical signatures in electroencephalogram testing (EEG). EEG is paired with electromyogram (EMG) and is the gold standard technique for sleep research at both preclinical and clinical levels. (39)

Melatonin plays an important role in generating the sleep architecture. Recently, Ochoa-Sanchez et al. examined the effects of the partial MT2 receptor agonist UCM765 on the sleep–wake cycle of rats and that of mice lacking MT1 or MT2 receptors. (32) The administration of the novel MT2 receptor partial agonist UCM765 promoted NREMS in WT mice, whereas this administration did not result in these effects in MT2 KO mice. (32) MT2 KO mice showed a reduction in NREMS compared to the WT mice, but the MT1 KO mice did not show reduction in NREMS (Fig. 4). (32) This study demonstrates that the MT2 melatonin receptor is responsible for mediating NREMS. (25, 32) In another study, the same group showed that MT1 KO mice displayed a 37.3% decrease in REMS duration, whereas MT2 KO mice showed only a 17.3% decrease in NREMS duration in a different study. (61). Altogether, these findings illustrate that MT1 and MT2 play selective roles in sleep: MT1 is responsible for mediating the effects of melatonin on REMS whereas MT2 is responsible for mediating the effects of melatonin on NREMS.

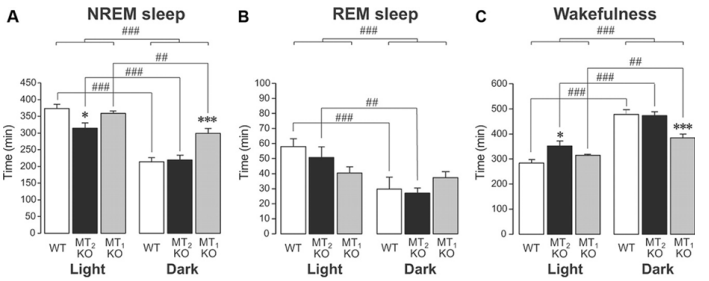

Fig. 5. The distribution of cosmic string loop radii. Note that there is a large drop-off after R_{c1}.

In summary, the melatonin receptors MT1 and MT2 exhibit opposing roles in sleep. The MT1 receptor activation increases REMS whereas the activation of MT2 receptor in reticular thalamus induces NREMS. Since melatonin has similar affinities to both MT1 (pKi=9.85) and MT2 (pKi=9.62), (64) this lack of selectivity can explain why a non-selective agonist such as melatonin is a less valid hypnotic promoter (65). However, a selective MT2 receptor agonist could cause potent hypnotic effects (Fig. 4).

Pain:

Several studies have analyzed the potential role of melatonin to modulate pain. (3, 66) Melatonin reduces nociception to different levels of pain-inducing stimuli. (3) For example, intraperitoneal (i.p.) administration of melatonin demonstrated analgesic effects in mice. (67) Golombek et al evaluated the pain threshold by measuring the latency of the response to the stimulus through the hot plate test. The hot plate evokes spinally processed pain-related behaviors and thus measuring nociception in rodents. (68) Since the synthesis of melatonin occurs in a circadian pattern, (10) a time-dependent melatonin-induced analgesia was observed. (67) The maximal melatonin-induced analgesic effect has always been expected to be at nighttime as melatonin synthesis peaks during the dark phase. (10) The mice displayed a maximal analgesic effect (longest latency in the hot plate test) at 8:00 PM, which supports the claim that melatonin mediates analgesic effects. Moreover, melatonin-induced analgesic mechanisms seem to involve the opioid receptors as melatonin-induced analgesia is blocked by naloxone, a non-selective antagonist of opioid receptors. (3)

Yu and colleagues (69) suggested that the MT2 melatonin receptor subtype is responsible for melatonin-induced antinociception in a study employing the antagonist luzindole, which has a 25-fold greater affinity for MT2 compared to MT1. (70) By using the novel MT2 selective partial agonist UCM924 at the doses of 20-40 mg/kg, Lopez-Canul and colleagues found that UCM924 mediates a superior antinociceptive effect than a larger dose (150mg/kg) of melatonin does. (33) This analgesia was nullified when the rat was pre-injected with MT2 receptor selective antagonist 4P-PDOT, a finding which further supports that MT2 receptors mediate melatonin-induced analgesia (Fig. 5). (33) The authors also demonstrated that this analgesic effect occurs by deactivating pronociceptive (ON) cells and activating antinociceptive (OFF) cells in the descending pain-control pathway (vlPAG-rostral ventral medulla) (Fig. 6). (33) A recent study suggests a novel epigenetic mechanism through which melatonin decreases neuropathic allodynia (pain that occurs from harmless stimuli) via its activity at the MT2 receptor; this mechanism involves a decrease in the expres-

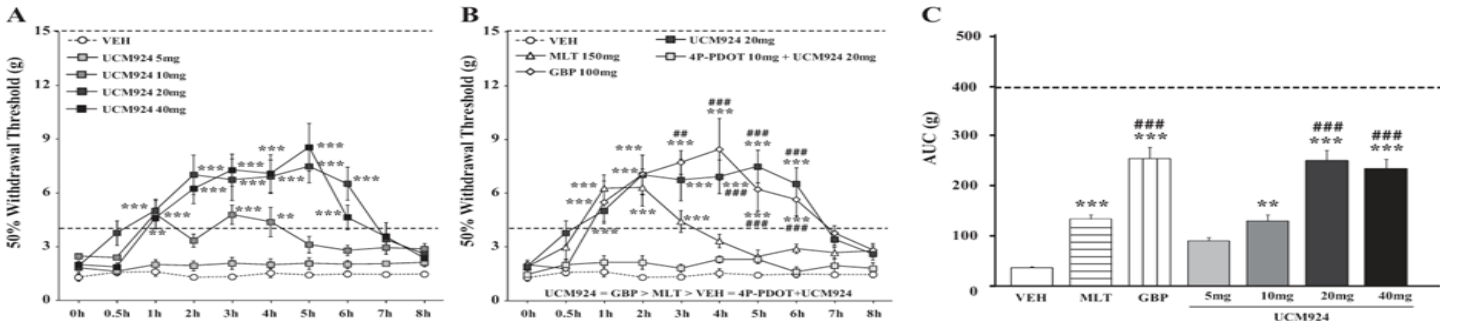

Figure 5. UCM924 reduces tactile allodynia in neuropathic rat model. Time course and dose-response (A). Comparison amongst UCM924, Melatonin and Gabapentin (analgesic drug) effects (B). Area under the curve (AUC) of antiallodynic effect of UCM924, Melatonin and Gabapentin (C). Reprinted from Lopez-Canul et al. Selective melatonin MT2 receptor ligands relieve neuropathic pain through modulation of brainstem descending antinociceptive pathways. Pain. 2015;156(2):305-17. Reprinted with permission.

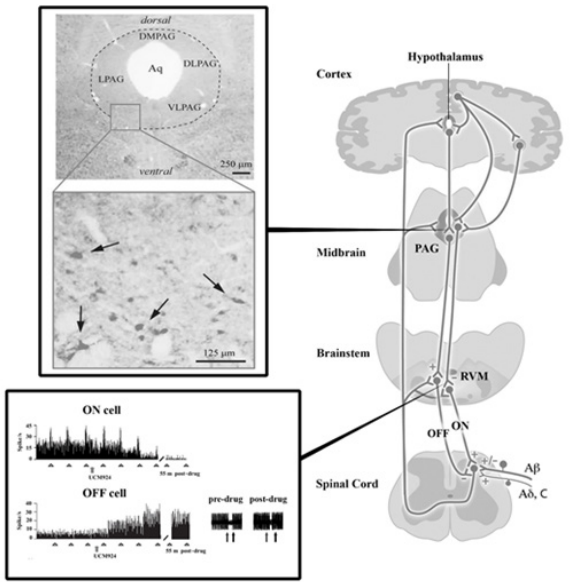

Fig 6. Descending pain-control pathway (vlPAG-rostral ventral medulla) mechanism. MT2 receptors localized in vlPAG activate antinociceptive OFF cells and deactivate pronociceptive ON cell projection in rostral ventral medulla. Reprinted from Posa et al. Targeting melatonin MT2 receptors: A novel pharmacological avenue for inflammatory and neuropathic pain. Curr Med Chem. 2017 Feb 8. doi: 10.2174/0929867324666170209104926.

sion of phosphatase 2A's catalytic subunit. (71) The decrease in allodynia was blocked by the selective MT2 antagonist 4P-PDOT. (71) Additional studies are required to better characterize the biochemical mechanisms of melatonin-mediated pain modulation.

Conclusion

This review summarizes some recent findings about melatonin, its receptor subtypes MT1 and MT2, their differential physiological roles, and their differential molecular pathways. Studies of the melatonin receptors have been made possible by the use of selective partial agonists and antagonists for specific melatonin receptor subtypes, and genetic deletion of each subtype.

Melatonin is a pleiotropic hormone that mediates various physiological functions in different organs of the body. Due to its implication in so many health-related issues, further studies are required to fully characterize the functionalities of each melatonin receptor subtype. Such characterization could help countless patients who suffer from circadian rhythm-, pain-, and sleep-related health issues.

Acknowledgements

I would like to express my gratitude to Tobias Atkin for revising this article. I would also like to thank Danilo de Gregorio for helping me with my poster and abstract.

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