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Review Article

Melatonin and their analogs as a potential use in the management of Neuropathic pain

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Melatonin (N-acetyl-5-methoxytryptamine), secreted by the pineal gland is known to perform multiple functions including, antioxidant, anti-hypertensive, anti-cancerous, immunomodulatory, sedative and tranquilizing functions. Melatonin is also known to be involved in the regulation of body mass index, control the gastrointestinal system and play an important role in cardioprotection, thermoregulation, and reproduction. Recently, several studies have reported the efficacy of Melatonin in treating various pain syndromes. The current paper reviews the studies on Melatonin and its analogs, particularly in Neuropathic pain. Here, we first briefly summarized research in preclinical studies showing the possible mechanisms through which Melatonin and its analogs induce analgesia in Neuropathic pain. Second, we reviewed research indicating the role of Melatonin in attenuating analgesic tolerance. Finally, we discussed the recent studies that reported novel Melatonin agonists, which were proven to be effective in treating Neuropathic pain.

Introduction

Neuropathic pain (NP) results from the nerve damage and is very difficult to diagnose, with poor response to conventional medical interventions and remains a major health challenge across the world. NP can result in the induction of anxiety, depression, and fear, which can further aggravate the NP leading to a rise in health care expenditures and

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reduced productivity.[1] Moreover, there is a significant increase in the number of new cases mainly due to longer life expectations, change in behavior and environment.[2] Opioids have been in use from the ancient times to treat a variety of pain conditions. Though a number of drugs have been developed for the management of NP, yet there are no drugs that offer the same level of effectiveness as opioid analgesics, and they are commonly used for NP management.[3]

However, most of the opioid drugs are known to have several side effects including constipation, nausea, vomiting, drowsiness, and respiratory depression. Adverse reactions to opioid analgesics limit their use for prolonged periods. In one recent study, it is found that more than 80% of the patients that are under prolonged-opioid analgesics usage had at least one adverse reaction, while 24% stopped the therapy because of the adverse reactions.[3]

There is an increasing need for the development of new strategies for the effective management of NP with fewer side effects. Melatonin (MLT) and its analogs are gaining significant attention in the recent years due to their protective properties against various injuries to the nervous system.[4] Accumulating data indicate that MLT plays a key role in numerous physiological processes including circadian rhythm regulation,[5] body mass index maintenance,[6] reproduction,[7] immune responses,[8] neuroprotection,[9] and cardioprotection.[10] MLT is also known to have strong antitumor,[11] anti-inflammatory,[4] and anti-oxidant effects.[12]

The analgesic properties of MLT have garnered significant interest in the recent years. Given the fact that current therapeutics for NP were far from perfect, the constant search is necessary to identify new compounds with analgesic capabilities along with the search for existing drugs that are approved for treating other conditions. Further, the combination of two approved drugs with high efficacy and good safety profile to eliminate or minimize the undesirable side effects and tolerance can be considered as an ideal strategy to expand the therapeutic spectrum of the currently available drugs, which can result in faster clinical transition.

MLT is proven to be very efficient & safe in the management of NP in several studies on animal models which led to its use clinically in various pathological conditions and also in patients undergoing surgery.[13,14] Though the mechanism through which MLT modulates pain is not yet clearly understood, current research evidence suggests the chief involvement of β-endorphins, opioid, dopamine D_2, MT_2, and $GABA_A$ receptors and the nitric oxide (NO)-arginine pathway (Fig. 1).[15–17] In previous studies, it has been demonstrated that sleep deprivation can result in reduced pain thresholds and hyperalgesia.[18] Substantial sleep deprivation is reported in a majority of Neuropathic pain syndromes along with the signs of depression and anxiety, both of which can contribute to pain and sleep disturbance.[19] One recent report by *Melikoglu* et al. concluded that 80% of NP patients have sleep disturbances regardless of the cause for NP.[19] Other research evidence suggests that sleep disturbance can increase the risk of developing chronic pain resulting from an acute Injury.[20]

The relation between sleep and NP appears to be a complex process and the underlying Neurobiological mechanisms are yet to be known. Fortunately, there has been a substantial increase in research related to the interaction of pain and sleep. Recently, *Narita* et al. reported that NP can decrease the NREM (Non-rapid eye movement) sleep affecting the overall quality of sleep due to the suppression of γ-aminobutyric acid (GABAergic) transmission along with the upregulation of GABA transporters located on activated astrocytes in the cingulate cortex which are associated with sleep disturbances.[21] The circadian rhythm normalizing properties of MLT can result in improving the sleep disorders, which are inevitable in most of the chronic pain conditions.[22] These interpretations can explain the sleep disturbances in patients with NP, making MLT to be considered as a potential candidate for future adjuvant, in combination with opioid drugs for treating chronic pain conditions. In addition to MLT recently many MT2 agonists were approved to for the treatment of depression and insomnia.[23] On recent study reported that administration of MT2 agonist IIK7 results in the decrease of

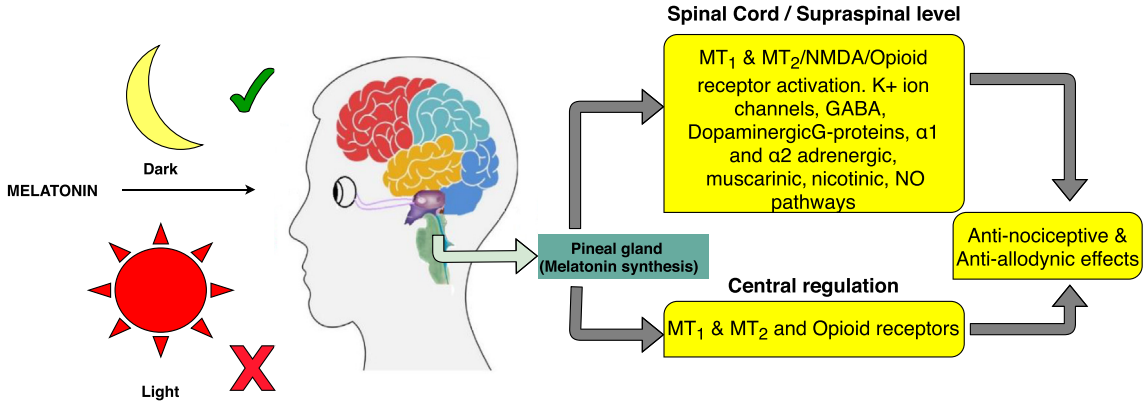

Figure 1 Regulation of melatonin synthesis by the pineal gland in the light-dark cycles and the mechanisms through with melatonin promotes anti-allodynic and anti-nociceptive effects. Melatonin seems to promote anti-nociceptive effects chiefly through the regulation of MT1/MT2 receptors in spinal cord and brain. Additionally, melatonin is shown to interact with other receptors such as GABAergic system, nitric oxide (NO)-arginine pathway, N-Methyl-D-aspartate (NMDA) and dopaminergic system to exert anti-nociceptive and anti-allodynic effects.

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NREM sleep onset latency,[24] which suggests that MT2 receptor subtype plays a key role in the sleep—stimulatory activity of MLT; additional drugs based on selective activation of MT2 receptors are expected to arrive the markets in the near future (See Table 1).

MLT use in preclinical Neuropathic pain syndromes

During the last fifty years, research evidence has been accumulating that MLT diminishes the nociceptive response to various noxious stimuli. However, very few studies have shed light on the ability of MLT to treat Neuropathic pain. The first report on MLT's analgesic efficacy dates back to 1969 when *Morris* et al. demonstrated that plasma levels of MLT are higher during the dark phase of circadian rhythm and mice were less susceptible to nociceptive stimulus during the dark phase.[25] Followed by this report many other groups reported the role of circadian rhythms in the perception of pain in various animal studies.[26—30] Indeed, surgical pinealectomy diminished the differential nociceptive thresholds reliant on the circadian phase.[31] However, pain perception depending on circadian rhythms & endogenous MLT concentration remains still unclear in Humans as one recent study showed no significant difference in thermal pain perception depending on the light/dark cycle in Humans unlike animals.[32]

Recently, *Huang* et al. reported that sleep deprivation can aggravate the chronic constriction injury (CCI) induced Neuropathic pain in rats through the activation of microglia along with a reduction in serum MLT levels.[33] In this study, it is important to note that MLT administration in a sleep-deprived CCI animal group diminished the activation of microglia and progression of Neuropathic pain, along with a significant reduction in the level of proinflammatory cytokines.[33] Neuropathic pain is often related to the desynchronization of circadian rhythms. Circadian rhythms play an important role in various physiological processes such as sleep-wake cycle, hormone secretion, temperature regulation and the functioning of the gastrointestinal tract.[34] Research evidence indicates that disturbance in circadian rhythms is the principal cause for various neurodegenerative disorders.[35] Recently, *Huang* et al. demonstrated that sleep deprivation can aggravate the nerve injury-induced Neuropathic pain with suppression of MLT secretion and enhanced activation of microglial cells in rats.[33] Circadian rhythms are associated with the suprachiasmatic nuclei (SCN) in the hypothalamus region, which harvest light-signals through the optic nerve of the retina. The pineal gland is located above the superior colliculus of the midbrain and secretes MLT. 80% of MLT production takes place in epiphysis and tissues including GI tract, lungs, and renal cortex, while eye retina secretes the remaining MLT.[36]

Though MLT has been widely reported to have analgesic effects in several studies, the anti-nociceptive effect of MLT in NP is still controversial and yet to be known. Hyperalgesia (increased sensitivity to pain) and allodynia (increased response of neurons that does not generally activate the nociceptive system) are two common symptoms found in Neuropathic pain.[37] Most investigations supported the anti-hyperalgesic and anti-analgesic effects of MLT in Neuropathic pain. However, the anti-allodynic effects of MLT still remain debatable. Sciatic nerve ligation (SNL) and chronic constriction injury (CCI) are the most commonly used procedures to induce hyperalgesia and allodynia in animal models. *Mocina* et al. demonstrated that intrathecal (3—100 μg) and oral (37.5—300 mg/kg) administration of MLT can significantly decrease tactile allodynia in SNL rats, whereas intrathecal/oral administration of MT2 and opioid receptors antagonist antagonized MLT's antiallodynic effects in a dose-dependent way.[38]

In contrary, *Ulugol* et al.'s studies revealed that I.P (intraperitoneal) & ICV (intracerebroventricular) administration of MLT in SNL mice can relieve hyperalgesia without any anti-allodynic effects.[39] *Zurowski* et al. have investigated the impact of MLT on Neuropathic pain model using CCI rat model. Surprisingly, their reports concluded that intraperitoneal administration (100 mg/kg) of exogenous MLT has anti-allodynic effects without any anti-hyperalgesic effects. Further, the anti-allodynic effects were blocked upon administration of non-selective opioid receptor antagonist naloxone and MT1/MT2 antagonist luzindole.[40] *Tu* et al. reported that intrathecal-administration of MLT can reduce the intensity and length of capsaicin-induced allodynia and hyperalgesia resultant from capsaicin injection.[41]

These contradictory results could be ascribed to the dosage, administration route and varying characteristic of the NP models used which might injure the DRG and primary afferents. The SNL model is susceptible to infections and frequently results in a motor deficit.[42] Whereas, the CCI models are subject to individual differences in pain perception depending on the snugness of the ligature used.[42] Additionally, there are some recent studies that have proven that CCI can result in the increase of macrophage levels demonstrating the involvement of immune system or inflammatory component due to the recognition of ligatures as foreign materials.[43] In comparison to SNL and CCI, NP induction by cuff implantation and partial sciatic nerve transection (PSNT) have more advantages since they promote allodynia and hyperalgesia without the involvement of inflammatory component and behavior injury.[43,44]

Some clinical studies investigated the relationship between MLT and Neuropathic pain. It is found that patients with chronic pain had diminished levels of MLT in blood and urine.[45] Furthermore, in patients with fibromyalgia, very low levels of MLT precursors (L-tryptophan and serotonin) are found which shows the importance of MLT in the management of chronic pain syndromes.[45]

Possible pathways of MLT's anti-nociceptive action

The physiologic mechanism by which MLT exerts analgesic actions is not yet fully understood. Accumulating evidence suggests the involvement of many systems including the MLT receptors (MT1 and MT2), opioid, GABAergic system, nitric oxide (NO)-arginine pathway, N-methyl-D-aspartate (NMDA) and dopaminergic system.[14—16] The lipophilic character of MLT aids in easier penetration across the BBB (blood brain barrier) gaining easier access to the central

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Table 1 Pre-clinical research examining analgesic effects of melatonin (MLT) & their analogs in neuropathic pain.

Animal & Behavior test used	Melatonin or its agonist dose and route of administration	Receptors involved	Antagonized by	Outcome	Reference
Ligation of the L5/L6 spinal nerves, Rats	Melatonin Intrathecal (3— 100 μg) and oral (37.5—300 mg/kg)	MT-2, Opioid	Luzindole, 4-P-PDOT, Naltrexone	Involvement of spinal MT2 and opioid receptors in the melatonin-induced antiallodynic effects.	Ambriz-Tututi et al.[38]
SNL, Mice	Melatonin 120 mg/kg, i.v. 0.1 nmol i.c.v.	Opioid peptides and L-arginine- NO-pathway	Naloxone, L-arginine	Alleviation of Hyperalgesia but not mechanical allodynia. L-arginine and naloxone administration reversed the anti-hyperalgesic effect of melatonin.	Ulugol et al.[39]
Capsaicin induced Hyperalgesia, Rats	Melatonin (2 μg) & 6-chloromelatonin (25 μg) Intrathecal	MT-2	4-P-PDOT	MLT can reduce the intensity and length of capsaicin-induced allodynia and hyperalgesia resultant from capsaicin injection.	Tu et al.[41]
Sciatic nerve cuffing, Mice	Melatonin (100 mg/kg), 8MPDOT (100 mg/kg) i.p	MT-2, NOS1	Luzindole	MLT exerts anti-allodynic effects through both MT2- dependent and independent pathways	Lin et al.[44]
Ligation of L5—L6 spinal nerves & spared nerve injury in Rats	UCM924 (20—40 mg/ kg, s.c)	MT-2	4-P-PDOT	Dose-dependent anti-allodynic effects, superior to MLT and comparable with Gabapentin without any noticeable motor coordination impairments.	Lopez-Canul et al.[49]
Formalin-induced nociception and tactile allodynia in diabetic rats	Melatonin oral administration (75—300 mg/kg)	MT-2	K-185	Melatonin dose-dependently reduced tactile allodynia in diabetic rats without the impairment of motor coordination.	Arreola-Espino et al.[55]
SNL, Rats	Melatonin (3, 10, and 30 μg), Intrathecal	MT-2	4-P-PDOT	MLT alleviates mechanical allodynia through spinal MT2- enhanced PP2Ac and downstream HDAC4 shuttling-dependent epigenetic modification of hmgb1 transcription.	Lin et al.[57]
Paclitaxel-induced painful peripheral neuropathy, Rats	Pretreatment with oral melatonin (5/10/50 mg/kg), given as a daily bolus dose	-	-	Melatonin significantly reduced the development of neuropathic pain from chemotherapy treatment.	Helen et al.[66]

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nervous system (CNS), exerting anti-nociceptive effects at a very lower dosage upon intrathecal administration in comparison to the systemic administration.[38,46,47]

Recently, a few groups have investigated the location of MT2 receptors using autoradiographic and immunohistochemical studies. Their findings suggest that MT2 receptors are situated in crucial regions of the brain that regulate the pain, such as the reticular and ventromedial (RVM) portion of the thalamus, the hypothalamus, the trigeminal tract, trigeminal nucleus, and the ventrolateral periaqueductal gray matter (VPAG).[48–50] Several groups have reported that MLT's analgesic properties are primarily mediated selectively by MT-2 sub-type but not the MT-1 type receptors.[51] *Wu* et al. were the first to demonstrate the MT-2 dependent analgesic action of MLT in nociceptive pain by using the animal model in which i.c.v injection of a non-selective agonist luzindole blocked the dose-dependent analgesic action of MLT.[52] Followed by this report many other groups reported that the analgesic action of MLT is linked to MT-2 receptors in animal models by using selective MT-2 agonists 4P-PDOT and K-185.[49,53,54] Recently, many groups have reported the efficacy of MLT in treating Neuropathic pain in which administration of MT-2 antagonists selectively blocked the analgesic effects. *Willis* et al. demonstrated that co-administration of MLT with MT-2 selective antagonist 4P-PDOT inhibited the anti-allodynic and anti-hyperalgesic effects of MLT in capsaicin-induced Neuropathic pain in a rat model.[41]

Monica et al. demonstrated that intrathecal/orally administered MLT have anti-allodynic effects in SNL rats which are selectively blocked by the pre-administration of non-selective MLT antagonist luzindole and selective MT2 antagonist 4P-PDOT.[38] In another study, *Espino* et al. reported that MLT is effective in reducing the formalin-evoked flinching in diabetic rats.[55] In this study, administration of selective MT-2 receptor antagonist K-185 completely blocked the anti-nociceptive effects of MLT.[55] Additionally, this study evaluated the effects of three other opioid antagonist's naltrexone (a non-selective opioid receptor antagonist), naltrindole (a selective delta opioid receptor antagonist) and 5′-guanidinonaltrindole (a selective kappa-opioid receptor antagonist). Interestingly, naltrexone and naltrindole partially decreased the anti-nociceptive effects of MLT whereas 5′-guanidinonaltrindole did not have any impact on the anti-nociception of MLT.[55] *Hsieh* et al. have recently reported that MLT/MT2-dependent analgesia involves spinal Tet1-dependent demethylation. This is the first report that is able to establish a link between MLT/MT2 signaling to Tet1-dependent epigenetic demethylation of nociceptive genes.[56] Though various reports have reported the analgesic effects of MLT very few reports have focused on the effect of MLT on epigenetic modifications. Recently, *Lin* et al. have reported that MLT relieves NP vis spinal MT2-enhanced PP2Ac and downstream HDAC4 shuttling-dependent epigenetic modification of hmgb1 transcription.[57] In another report, *Odo* et al. studied the effects of Neuropathic pain on circadian rhythms and MT receptor expression in the hypothalamus of SNL mice. Their results showed that Neuropathic pain can lead to sleep disturbance along with changes in circadian rhythm for mRNA expression of MT receptors.[58] These findings collectively support the chief involvement of MT-2 receptors in the anti-nociceptive effects of MLT.

Though MT-2 receptors play an important role in the modulation of NP by MLT, several reports suggest the close interaction of exogenous MLT with the opioid system and benzodiazepine-GABAergic pathway.[39,59] Some studies have shown that melatonin is capable of exerting anti-nociceptive effects by modulating the GABAA receptors located in the spinal cord region.[60,61] Others have shown that MLT is capable of modulating benzodiazepine binding site function on the GABAA receptor complex.[60] *Zurowski* et al. studied the interaction of MLT with MT, opioid and GABA receptor's using a CCI NP model by the administration of receptor-specific antagonist's naloxone (opioid antagonist), prazosin (MT3 antagonist), luzindole (MT1/MT2 receptor antagonist), picrotoxin (GABA(A) antagonist) and flumazenil (benzodiazepine antagonist).[40] It is interesting to note that naloxone pre-treatment completely blocked the anti-allodynic effects of MLT but not anti-thermal-hyperalgesic effects, whereas pazosin did not alter the effects of MLT, though luzidole significantly diminished the anti-nociceptive effects of MLT. However, administration of benzodiazepine antagonist flumazenil and $GABA_A$ antagonist picrotoxin blocked the anti-allodynic effects without affecting the anti-hyperalgesic action by the activation of the opioid and benzodiazepine-GABAergic pathway.[58] Wan et al. proposed than MLT might impart analgesia by the modulation of GABAA receptor functions though the direct interaction with MT2 type MLT receptors.[61] On the other hand, studies by *Dhanraj* et al. revealed that melatonin can prevent the development of U50 tolerance though the benzodiazepine—$GABA_A$ergic mechanisms.[62] Their studies revealed that inhibition of U50 tolerance by MLT was reversed by flumazenil and picrotoxin treatment, suggesting that benzodiazepine—$GABA_A$ergic mechanisms play an important role in the development of tolerance to U50 analgesia via MT-2 receptor independent mechanisms. Taken together these findings suggest that MLT imparts some effects though the direct interaction with GABAA receptors while others through MT-2 receptors.

Additionally, MLT is found to have free radical scavenging effects independent of the receptor. MLT is shown to be efficient in scavenging the free radicals such as nitric oxide (NO), singlet oxygen, hydroxyl radicals, peroxyl radicals, hydrogen peroxide and peroxynitrite anion.[63] Nitric oxide is believed to play key roles in the development of Neuropathic pain. For instance, NO may directly affect the peripheral injured axons or indirectly affect pain through *Wallerian* degeneration, resulting in sending signals to the dorsal horn of the spinal cord.[64]

In one recent report, *Lin* et al. assessed the Neuropathic pain behavior by studying the dorsal root ganglia (DRG) in a sciatic nerve cuffing model.[43] In this report, it was found that MLT administration has anti-allodynic and anti-hyperalgesic effects in cuff-implanted mice. Western blot revealed upregulation of MT2 expression in DRG, whereas the MT2 expression in the spinal cord and MT1 expression in the DRGs and spinal cord remained similar demonstrating that MT2 receptors of DRG are critical in arbitrating the sensory component of NP.[43] Further, microarray analysis and gene knockdown experiments in primary cultured neurons revealed that treatment with MT-2 agonist 8MPDOT or MLT resulted in MT2 activation resulting in the suppression of calcium signaling pathways via MAPK1.[43] Additionally, it is revealed that treatment with MLT or 8MPDOT inhibited the

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activation of peptidergic neurons and neuroinflammation in the DRG by the downregulation of c-fos, calcitonin gene-related peptide, and tumor necrosis factor-1α and interleukin-1β.[43] Interestingly, it is found that treatment with MLT resulted in the down-regulation of NOS1 (Nitric Oxide Synthase 1) gene whereas 8MPDOT treatment did not have any effect on NOS1. In this study, it is important to note that addition of MLT non-specific antagonist luzindole resulted in blocking the anti-allodynic effects of 8 MP but not those of MLT demonstrating that MLT suppresses Neuropathic pain via MT2-dependent (MAPK-calcium channels) and MT2-independent (NOS1) pathways.[43]

In another report, *Borsani* et al. evaluated the role of a low dose of MLT (5—10 mg/kg) in the modulation of nitroxidergic system in dorsal root ganglia and skin in a mononeuropathy established pain model using Sprague Dawley rats. DRG and skin are generally most affected by nervous impairment. It was reported that intrathecal administration of MLT has anti-hyperalgesic effects. Additionally, immunohistochemical analysis revealed that MLT modulates the nitroxidergic system at dorsal root ganglia and skin.[65]

Mitochondrial dysfunction resulting from the oxidative stress in the peripheral nerves is considered as a key factor in the generation of cancer-related Neuropathic pain. In one recent report, *Galley* et al. have described that MLT is effective in limiting the mitochondrial dysfunction *in vitro* and protects the rats from paclitaxel-induced Neuropathic pain.[66] *Wang* et al. demonstrated that MLT attenuates pain hypersensitivity and greatly reduces astrocyte-mediated spinal neuroinflammation in a rat model of oxaliplatin-induced Neuropathic pain.[67] In another report, *Areti* et al. demonstrated that MLT exerts protective effects by preventing neuronal apoptosis induced by oxaliplatin through the upregulation of autophagy pathway (via LC3A/3B) in peripheral nerves and DRG.[68] *Kumar* et al. studied the role of NO in MLT analgesic effects by using a CCI rat model. It was reported that pre-treatment of CCI mice with N(ω)-nitro-L-arginine methyl ester, followed by the treatment with sub-effective doses of MLT resulted in significant enhancement of anti-nociceptive action. In contrast, pre-treatment with L-arginine completely reversed the anti-nociceptive action, thereby suggesting the involvement of nitric oxide pathway in the protective effect induced by MLT in a Neuropathic pain model.[69] These studies demonstrate that MLT can be considered as a potential treatment option to limit the Neuropathic pain. From the current research evidence, it can be understood that oxidative stress is an important player in the cascade of events that lead to Neuropathic pain. However, it is necessary to completely know the role of oxidative stress in Neuropathic pain before suggesting therapeutic approaches that alter oxidative stress in Neuropathic pain.

Some recent evidence suggests that the interaction of MLT with NMDA receptor is another mechanism through which MLT modulates pain in peripheral and CNS. Some studies have shown that NMDA receptor regulates the spinal cord synaptic potentiation phenomenon which plays an important role in the progression and transmission of pain.[70]

Noseda et al. have revealed that MLT is effective in blocking the spinal cord synaptic potentiation phenomenon in a dose-dependent manner and could be mitigated upon the administration of MLT antagonist Luzindole.[71] In another study, *Escames* et al. reported that MLT inhibits NMDA-dependent excitation through the involvement of NOS inhibition and redox site modulation.[72] *Sutcu* et al. reported that MLT alters NMDA subunit concentrations in the hippocampus region in a dose-dependent pattern without initiating lipid peroxidation.[73]

MLT for prevention and reversal of opioid-induced tolerance and hyperalgesia

Opioids such as morphine are the most commonly prescribed drugs to treat both acute and Neuropathic pain.[74] Though a number of drugs have been developed for the management of NP, yet there are no drugs that offer the same level of effectiveness as opioid analgesics. However, the long-term use of opioids in conditions like Neuropathic pain can be challenging due to the progressive development of tolerance to the anti-nociception which necessitates the increase in drug dosage to reach adequate analgesic effect, resulting in aggravation of side effects.[75,76] The most common side effects include constipation, nausea, vomiting, drowsiness, and respiratory depression. Adverse reactions to opioid analgesics at high dosage limit their usage for prolonged periods. Thus, morphine-induced tolerance remains a major stumbling block limiting its clinical usage. Several studies have focused on the mechanisms and changes in Neuronal plasticity in the CNS that lead to tolerance development.[77]

Recent evidence suggests that protein kinase C (PKC) and NMDA play an important role in the desensitization of morphine receptors.[78,79] Co-administration of PKC inhibitors along with morphine is shown to be effective in attenuating the tolerance development in various animal models.[80—83] Similarly, co-administration of NMDA antagonists with morphine is shown to be effective in preventing tolerance development in nerve-injured animal models.[83—85] Thus, combinational therapy using therapeutics that suppress PKC and NMDA receptors along with opioids can be considered as an effective strategy to alleviate Neuropathic pain without the development of morphine tolerance. Other therapeutic benefits include greater efficacy, lower doses and minimal side effects as this procedure can target multiple underlying mechanisms. Previously, many research reports have concluded that MLT co-administration with morphine can prevent morphine-induced hyperalgesia and tolerance.[58,86—88] However, very less is known about the underlying cellular mechanisms through which MLT prevents morphine-induced hyperalgesia and tolerance. *Raghavendra* et al. demonstrated that co-administration of MLT (i.p) with morphine (s.c) during the induction phase (day1—9) of morphine tolerance successfully reversed morphine tolerance. However, co-administration of MLT during the expression phase (day 10) of morphine dependence, was not able to reverse morphine-induced tolerance. Additionally, it was demonstrated that administration of benzodiazepine receptor antagonist PK11195 reversed MLT-induced attenuation at both induction and expression phases suggesting the involvement of peripheral benzodiazepine receptors.[89] In the recent years, we have reported some drugs that can reverse, attenuate or inhibit morphine-induced tolerance such as baicalin,[90] naloxone,[91,92] resveratrol.[93] Followed by our reports new adjuvants to morphine have been reported, such as

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nalbuphine.[94,95] Very recently, we have reported that chronic infusion of morphine can elicit the morphine tolerance with the upregulation of heat shock protein HSP27 expression in the dorsal horn of spinal cord in rats. Further, we demonstrated that MLT-pretreatment can reverse morphine-induced tolerance in morphine-tolerant rats with the reversal of HSP27 expression induced by continuous infusion of morphine. Additionally, we found that continuous infusion of morphine can induce microglia activation which was antagonized by the treatment with MLT.[96] Our results are quite contradictory with *Raghavendra* et al.'s study in the reversal of tolerance in rats with pre-established tolerance, which might be resultant from the route of MLT administration as an intrathecal administration of MLT might be more efficient than s.c injection considering the short half-life of MLT.

Potential of MLT_2 agonists for Neuropathic pain

Though current research evidence suggests the involvement of various receptors in MLT mediated nociception, it is believed that most of the MLT's effects result from the activation of MT-1 and MT-2 type G protein-coupled receptors (GPCR). Though both of them belong to the GPCR family these receptors have contrasting and dissimilar physiological functions. For instance: MT-1 is involved in phospholipase C activation, decreases NREM sleep, modulates neuronal induction and mediates vasoconstriction and involved in tumor cell proliferation.

Whereas MT-2 mediates guanyl cyclase inhibition, phase shifts circadian rhythms of neuronal firing in the suprachiasmatic nuclei, inhibits dopamine release in the retina, induces vasodilation, inhibits leukocyte rolling in the arterial beds, and enhances the immune response.[97]

Current research suggests that MT-2 receptors play a more important role in mediating analgesic effects than the MT-1 receptors. Recently, *Comai* et al. have demonstrated that MT-2 receptor agonists are capable of producing strong analgesic effects with higher potency than MLT. Additionally, MT-2 agonists were known to produce prolonged antinociceptive effects at lower doses superior to that of a high dosage of MLT and similar analgesic effects like gabapentin without any motor coordination impairments in animal models.[98]

Thus, the side-effects associated with the current analgesics can be significantly reduced. Moreover, MLT has a very short half-life making MT-2 agonists as favorable alternatives. It is recently known that MT-2 receptors are located in brain regions crucial for the control of pain such as the reticular and the ventromedial nuclei of the thalamus (part of the ascending nociceptive pathway), ventrolateral periaqueductal grey matter (part of the descending antinociceptive pathway), trigeminal tract and trigeminal nucleus.[47–49] Numerous studies have demonstrated that analgesic properties of MLT are mediated specifically by MT-2 receptors by using a variety of MT-2 antagonists.[48]

Ramelteon was the first MLT agonist approved in the US for the treatment of insomnia (Both chronic and transient insomnia) in 2005. Ramelteon primarily targets sleep latency in insomniac patients. Followed by the approval of ramelteon, agomelatine (2009, EU) is approved for the treatment of depressive disorders, however, agomelatine was ceased in developmental stages in the US after some reports related to liver failure. Tasimelteon (2014, US) is approved for the treatment of non-24-hour sleep-wake disorder in totally blind individuals.[99] TIK-301 and piromelatine are other MLT agonists that entered phase II clinical trials in 2013. Though many MLT agonists are approved for the treatment of sleep and depressive disorders there are no clinical trials or approved MLT agonists for the treatment of Neuropathic pain. However, many promising pre-clinical findings suggest that MLT agonists have a strong potential for clinical transition.

8-Methoxy-2-propionamidotetralin (8MPDOT), N-{2-[(3-methoxyphenyl) phenylaminoethyl acetamide (UCM765), N-{2-([3-bromophenyl]-4-fluorophenylamino) ethyl acetamide (UCM924) and N-[(1-benzyl-1,2,3,4-tetrahydro-5-metho xyquinolin-2-yl) methyl]propionamide (UCM1014) and iik-7 N-Butanoyl 2-(9-methoxy-6H-iso-indolo[2,1-a]indol-11-yl)-ethan-amine are some of the recently developed MT-2 agonists. Some of the reported MT-2 agonists were known to be very effective in the management of Neuropathic pain with several benefits over MLT and comparative effects to that of clinically approved analgesics.

Recently *Canul* et al. evaluated the efficacy of MT-2 partial agonists UCM 765 and UCM 924 in acute, inflammatory and Neuropathic pain.[48] Their results showed that both the agonists were efficient in decreasing the sensitivity of hind-paws on a hot-plate with analgesic effects in a dose-dependent way similar to acetaminophen.[100]

Additionally, these two agonists were also effective in reducing the hind paw licking time upon formalin injection in a dose-dependent manner, which is comparable to ketorolac.[96] The MT-2 dependent anti-nociception was confirmed by the administration of MT-2 specific antagonist 4-P-PDOT which blocked the anti-nociceptive action of both the agonists. In SNL rat model, UCM 924 displayed a dose-dependent increase in paw with drawl pressure with 20 mg of dose producing comparable anti-nociceptive effects to that of gabapentin without impairment of motor coordination.[48] Additionally, they have investigated the distribution and location of MT-2 receptors in the brain and reported that MT-2 is expressed predominantly in the VPAG region of the brain, which modulates the brainstem descending antinociceptive pathways.[48] Further, by using the tail flick tests it is demonstrated that intra VPAG administration of UCM 924 can inhibit the activation of pronociceptive ON cells with the enhancement in the activation of anti-nociceptive OFF cells in the RVM region, which are blocked upon the administration of selective MT-2 antagonist 4P-PDOT.[48] However, additional studies are required to rule out the interaction of μ- and δ-opioid receptors in anti-nociception mediated by these two MT-2 agonists as VPAG is abundant in μ- and δ-opioid receptors in addition to MT-2 receptors.

Lin et al. studied the anti-nociceptive effects of MLT and MT-2 agonist 8M-PDOT in a cuff-implanted mouse model. Their studies revealed the upregulation of MT-2 expression in the DRG of cuff implanted mice. Both MLT and 8M-PDOT were found to have dose-dependent anti-allodynic and anti-hyperalgesic effects. However, in this report administration of luzindole resulted in blocking the anti-allodynic effects of 8M-PDOT but not those of MLT demonstrating that MLT suppresses Neuropathic pain via MT2-dependent (MAPK-calcium channels) and MT2-independent (NOS1) pathways.[43]

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Conclusions

Although the anti-nociceptive properties of MLT and MLT agonists remain unclear, and the preclinical studies have shown their efficacy in different pain paradigms, several questions related to the mechanism of action remain unanswered. For example, exogenous MLT is known to induce anti-nociception through the interaction of MLT receptors, opioid receptors, NO and NMDA systems. However, it is necessary to do additional research to know how endogenous MLT modulates the pain. The dosage, model used to induce Neuropathic pain, a method of drug administration and the phase of drug administration are some crucial factors that determine the efficacy of MLT.

In most of the pre-clinical studies, the dosage of MLT used is many thousand folds higher than the physiological dosage of MLT produced inside the body. There is some clinical evidence that MLT loses response at high doses due to a decrease in MLT metabolism.[101] Thus, there is a possibility that MLT exerts anti-nociception through different anti-nociceptive pathways depending on the dosage and might have a temporary loss of activity at a certain dosage. In addition, the model adopted for studying the Neuropathic pain might result in different outcomes even if the same dosage is used.

The expression of MT-2 receptors in the important regions of the brain such as the GABAergic neurons of the thalamus and the reticular thalamus validates their key role in modulating pain. There is strong preclinical evidence that suggests that MT-2 agonists are effective in Neuropathic pain modulation with benefits such as low toxicity with similar or superior activity to that of currently available analgesics with good pharmacological profile suggesting their potential for clinical transition.

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Conflict of interest

The authors have no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2018.09.017.

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