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Melatonin in Chronic Pain Syndromes

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ABSTRACT

Melatonin is a neurohormone secreted by epiphysis and extrapineal structures. It performs several functions including chronobiotic, antioxidant, oncostatic, immune modulating, normothermal, and anxiolytic functions. Melatonin affects the cardiovascular system and gastrointestinal tract, participates in reproduction and metabolism, and body mass regulation. Moreover, recent studies have demonstrated melatonin efficacy in relation to pain syndromes. The present paper reviews the studies on melatonin use in fibromyalgia, headaches, irritable bowel syndrome, chronic back pain, and rheumatoid arthritis. The paper discusses the possible mechanisms of melatonin analgesic properties. On one hand, circadian rhythms normalization results in sleep improvement, which is inevitably disordered in chronic pain syndromes, and activation of melatonin adaptive capabilities. On the other hand, there is evidence of melatonin-independent analgesic effect involving melatonin receptors and several neurotransmitter systems.

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INTRODUCTION

The role of the circadian rhythm in human life has been well known for a long time. The notion of the circadian rhythm introduced by Franz Halberg in 1959 overturned researchers' understanding of many processes in the human body. It was found that circadian rhythms are involved in several physiological processes, such as the sleep–wake cycle, body temperature regulation, hormone secretion, cell division and proliferation, gastro-intestinal tract function, etc. Circadian rhythm disorders may result in several pathological conditions, while most diseases may cause circadian

desynchronization. For example, chronic pain syndromes are always associated with various degrees of biological rhythm desynchronization. The biological rhythms in mammals are controlled by the suprachiasmatic nuclei of the hypothalamus. The suprachiasmatic nuclei that cannot receive light signals directly, receive them via an optic nerve passing the information from the retina [1]. Another important organ involved in biological rhythm regulation is the epiphysis or the pineal gland. The epiphysis is an endocrine gland in the diencephalon area above the superior colliculus of the midbrain. The epiphysis synthesizes and secrets neurohormone melatonin. It is noteworthy that though epiphysis secrets 80% of melatonin, there are extrapineal sources of melatonin: cells of gastrointestinal tract (GIT), lungs and renal cortex, eye retina, lymphocytes, thrombocytes, mastocytes, etc. Some melatonin properties are well known; the others are still under study. Melatonin has chronobiological features, can regulate circadian rhythms, and normalize sleep. Moreover, melatonin demonstrated antioxidant functions, which were laid into the foundation of its use in neurodegenerative diseases, e.g., Parkinson and Alzheimer's diseases [2]. Several experimental and clinical studies have revealed new melatonin properties such as oncostatic and immune-modulating effects, the capability to improve mood and to decrease anxiety, to affect the cardiovascular system and GIT, as well as the role of melatonin in reproductive functions and metabolism and body mass regulation [3]. The analgesic capabilities of melatonin have always attracted much interest. Given that the contemporary therapy of chronic pain syndrome is far from perfect, constant search is required for new molecules with analgesic capabilities as well as the research into the

existing substances used in the treatment of other conditions. The decisive factor is the combination of high efficacy and good safety profile of a drug [4]. Melatonin demonstrated efficacy and safety in nociceptive and neuropathic pain in several studies on animal models and clinical trials.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

MELATONIN IN EXPERIMENTAL RESEARCH (TABLE 1)

Yet in 1991, using a hot plate test in a nociceptive pain model, Golombek et al. [5] demonstrated that intraperitoneal injection of 20–40 mg/kg of melatonin produced the strongest analgesic effect if administered in the evening. The analgesic effect decreased after the administration of opiate antagonist naloxone or central benzodiazepine (BZD) antagonist Flumazenil suggesting the involvement of the central opioid and BZD receptors [5].

In a different study on a nociceptive pain model, Yu et al. [6] demonstrated the dose-dependent effect of melatonin using a group of rats that received intraperitoneal melatonin injections in various doses (30, 60, 120 mg/kg) combined with pain stimulation. The antinociceptive effect took place at 15 min after injection of 60–120 mg/kg of melatonin, peaked at 30 min, and continued for 100 min. The intravenous injection of naloxone neutralized the melatonin analgesic effect in 10 min [6]. Several other studies confirmed that

melatonin might be effective in relation to nociceptive pain. El-Shenawy in 2002 [7], Esposito in 2010 [8], and Mantovani in 2003 [9] demonstrated melatonin analgesic capabilities in relation to nociceptive pain in their experiments. Melatonin inhibited prostaglandins release and suppressed polymorphonuclear leukocytes integration at the inflammation site and suppressed inflammation inhibiting COX-2 and NO-synthase.

It is noteworthy that in the experiments, melatonin also demonstrated its efficacy in neuropathic pain. In 2004, Tu et al. [10] showed that melatonin administration decreased the intensity and duration of capsaicin-induced secondary mechanical allodynia and hyperalgesia, suggesting that melatonin effect on the CNS can hinder the onset and generalization of "central sensitization", resulting from capsaicin injection. In 2006, Ulugol et al. [11] demonstrated melatonin efficacy in relation to neuropathic pain. In the study on mice, sciatic nerve ligation causes pain associated with mechanical allodynia and thermal hyperalgesia. High-dose (120 mg/kg) melatonin intraperitoneal injections and 0.1 nmol intravenous infusion resulted in the increase of the pain threshold and a decrease of thermal hyperalgesia manifestation [11].

MELATONIN CLINICAL TRIAL EXPERIENCE (TABLE 2)

Melatonin in Migraine

There was much discussion recently that circadian rhythm disorders play an important role in the pathogenesis of headaches. In this situation, melatonin can decrease the frequency and intensity of pain syndromes through inherent analgesic mechanisms and circadian rhythm normalization. Melatonin receptors were found in the ganglia and nuclei of the trigeminal nerve, suggesting that melatonin decreases trigeminal vascular nociception. Several studies analyzed the association between night melatonin secretion and migraine. The study involving 146 migraine patients revealed a substantially lower urinary level of 6-sulphateoxymelatonin (basic melatonin metabolite) in migraine patients compared to a group of healthy volunteers [12].

Another study involving 34 patients assessed melatonin efficacy in migraine prevention. Peres et al. [13] demonstrated that 3 mg of melatonin before sleep can decrease the frequency, intensity, and duration of pain in migraine patients. In a recent study, the melatonin agonist agomelatine was successfully used in the treatment of migraine patients who took 25 mg/day of agomelatine for 3 months, leading to a decrease in migraine attack frequency and duration. Moreover, agomelatine treatment resulted in depression level decrease and sleep normalization in these patients [14].

Melatonin in Cluster Headaches

The pathophysiology of cluster headaches remains unclear, but modern concepts suggest the involvement of circadian rhythms in the pathogenesis of this disease; the studies revealed a decrease of night melatonin secretion in the cluster headache patients compared to the healthy controls as well as lower melatonin level during the cluster headache attacks compared to the remission period [15]. In a clinical study, cluster headache patients received 10 mg of melatonin or placebo before sleep for

14 days. The study revealed a significant decrease in the intensity and frequency of attacks in the study group compared to the control group. Moreover, the study group showed a tendency towards the decrease of analgesic intake compared to the control group though the difference was insignificant [16]. In a different study, the cluster headache patients took 2 mg of melatonin, however no significant difference in the pain syndrome compared to the control group was found; the findings can be explained by a low melatonin dose [17].

Melatonin in Tension Headaches

Melatonin demonstrated efficacy in tension headaches. Miano et al. [18] studied the possibility to prevent tension headaches in children. The study involved 21 participants who took 3 g of melatonin before sleep for 3 months. After the therapy, 14 of 21 patients reported a 50% or more decrease in the pain syndrome intensity, and four of them experienced no pain attacks at all [18].

Melatonin in Chronic Back Pain

The efficacy of melatonin in chronic back pain was then assessed in a study involving 178 patients (aged 40–65 years) with lower back pain over three points measured on a visual analogue scale for at least 12 months. The patients were stratified into six groups making three comparison pairs. The patients in study group 1 ($n = 31$) took one tablet of Artra® (Unipharm, Inc.; combination of 500 mg glucosamine hydrochloride and 500 mg chondroitin sulfate) twice a day for 1 month, then one tablet a day for 2 months and additionally Melaxen® (Unipharm, Inc.; 3 mg of melatonin 30–40 min before sleep), the patients from the comparison group ($n = 29$)

took Artra only. The patients in comparison group 2 ($n = 30$) took one tablet of Artra twice a day and 25 mg of diclofenac 2–3 times a day. The patients in study group 2 ($n = 30$) additionally took Melaxen (3 mg of melatonin 30–40 min before sleep). The patients in study group 3 ($n = 29$) took 25 mg of diclofenac three times a day and Melaxen (3 mg of melatonin 30–40 min before sleep). The patients in comparison group 3 ($n = 29$) did not take Melaxen. The results in group 1 were evaluated in 3 months, and in groups 2 and 3 in a month. The findings suggested significantly more expressed decrease in pain both in motion and at rest in the study groups compared to the comparison groups. Moreover, the patients demonstrated less influence of pain in daily activities, a decrease in anxiety and depression, and sleep normalization. That led to a conclusion that the addition of melatonin to the standard treatment scheme increases its efficacy in back pain [19].

Melatonin and Irritable Bowel Syndrome

Besides the epiphysis melatonin is synthesized by enterochromaffin cells in the GIT suggesting melatonin involvement in physiology and pathologies of the GIT. Melatonin synthesis and secretion in the GIT do not follow 24-h cycles. Melatonin stimulates macrophage inhibition and decreases the release of inflammatory mediators, preventing GIT mucosa ulceration and damage to the large intestines. Melatonin can decrease abdominal pains and facilitate defecation, not affecting anxiety and sleep in irritable bowel syndrome patients [20]. On the other hand, there is evidence suggesting the positive impact of melatonin on extra bowel symptoms in irritable bowel syndrome resulting from either anxiolytic or direct effect on the GIT [21].

Two randomized placebo-controlled clinical trials dealt with melatonin analgesic effects in irritable bowel syndrome patients. In both studies, the patients took 3 mg of melatonin. One study involved 40 patients who took either placebo or melatonin for 2 weeks [22]. The other study involved 17 patients who took either placebo or melatonin for 8 weeks with a 4-week "washout" period [23]. In both of the clinical studies, the patients reported a significant decrease in pain intensity compared to the control groups.

Chojnacki et al. [24] demonstrated that 6-month melatonin administration improves the bowel movement and abdominal pain decrease.

Melatonin in Fibromyalgia

Melatonin secretion disorder may be a part of fibromyalgia pathogenesis. However, the clinical evidence is controversial. Several studies analyzed the circadian rhythms and melatonin secretion in fibromyalgia patients. For example, one study revealed no significant differences in melatonin level in the fibromyalgia patients and in healthy people [25], while another study found significantly lower urine melatonin concentration in the fibromyalgia patients compared to the healthy controls [26].

A study was conducted in Russia to investigate the effect of 10-day evening administration of 1.5 mg of melatonin (Melaxen) on the subjective assessment and instrumental evaluation of night sleep quality in 11 fibromyalgia patients. Polysomnography confirmed night sleep disorders: difficulty in falling asleep, a longer latent period of surface and paradoxical sleep, deep sleep suppression, the decreased number of completed sleep cycles, an increased number of wake periods and sleep movements, etc. After the treatment, the patients reported subjective sleep improvement, confirmed by polygraphic registration: ease of falling asleep and shorter wake periods during sleep, etc. The patients also reported feeling better, a decrease in depression, and better fine motor function of the hands in the daytime. The findings suggest melatonin positive effect on the sleep quality in the patients with sleep disorders. These patients also reported a certain decrease of pain and depression levels [27].

In another open randomized study involving 21 female patients, 3 mg of melatonin was administered 30 min before sleep for 4 weeks. The patients reported significant sleep improvement and a decrease in the number of painful trigger points compared to the baseline level. The authors also reported good though insignificant results in relation to the therapy of pain, tiredness, and depressive symptoms [28].

Hussein et al. [29] did a double-blinded placebo-controlled study involving 101 fibromyalgia patients to assess the efficacy of various melatonin doses both separately and in combination with fluoxetine. The patients were stratified into four groups: group A patients took 20 mg/day of fluoxetine, group B patients took mg/day of melatonin, group C patients took 20 mg/day of fluoxetine in combination with 3 mg/day of melatonin, group D patients took 20 mg/day of fluoxetine in combination with 5 mg/day of melatonin. The treatment with fluoxetine only resulted in a decrease of tiredness, morning stiffness, anxiety, and depression. Melatonin treatment produced less effect on these symptoms though it was significant in relation to pain, depression, anxiety, and sleep disorders. The combined therapy with melatonin and fluoxetine decreased anxiety, tiredness, and significantly limited depressive symptoms [29].

In 2014, de Zanette et al. [30] reported the results of melatonin treatment of fibromyalgia patients. Sixty-three female patients (aged 18–65 years) were randomized into three groups: group 1 took 25 mg of amitriptyline before sleep, group 2 took 10 mg of melatonin before sleep, and group 3 took a combination of 25 mg of amitriptyline and 10 mg of melatonin. The treatment duration was 6 weeks. The study revealed that a combination of 25 mg of amitriptyline and 10 mg of melatonin and isolated administration of melatonin were more efficient than amitriptyline in relation to pain, morning stiffness, and sleep disorders in fibromyalgia patients [30].

The pathophysiological relations between circadian rhythm disorders remain unclear though the efficacy of melatonin in such patients is demonstrated in several clinical trials with a high level of evidence.

Melatonin and Rheumatoid Arthritis

How is melatonin involved in the pathogenesis of rheumatoid arthritis? Compared to healthy people, rheumatoid arthritis patients have a significantly higher level of melatonin secretion at night; in the morning, the blood serum melatonin level is higher in patients with shorter disease history [31, 32]. Inflammation cytokines such as interferon-gamma, interleukin-1, and interleukin-6 are secreted into the peripheral bloodstream in response to melatonin stimulation, moreover, melatonin is found in the synovial liquid in rheumatoid arthritis patients [33]. These findings suggest that melatonin produces an unfavorable influence on rheumatoid arthritis. On the other hand, melatonin inhibits the activity of matrix metalloproteinase (MMP), which is involved in the joint destruction in rheumatoid arthritis patients [34]. Thus, the role of melatonin in joint destruction calls for additional studies.

DISCUSSION OF POSSIBLE ACTION MECHANISMS

Melatonin demonstrated an analgesic effect in several experimental studies and clinical trials. What is the underlying mechanism of this effect? On one hand, the normalization of circadian rhythms, which are inevitably disordered in chronic pain syndromes, leads to the improvement of sleep and activation of melatonin inherent adaptive capabilities. On the other hand, there is evidence of melatonin-inherent analgesic effect realized through receptors and several neurotransmitter systems.

Melatonin Receptors

There are membrane melatonin receptors MT_1/MT_2 and nuclear melatonin receptors $RZR\alpha$/$RZR\beta$. The membrane receptors involved in melatonin analgesic effect are indicated by MT_1/MT_2 receptors localization in the thalamus, the hypothalamus, the dorsal horns of the spinal cord, the spinal trigeminal tract, and the trigeminal nerve nucleus. Moreover, the experimental studies demonstrated that administration of luzindole, to MT_1/MT_2 melatonin receptors antagonist, or 4-P-PODT/ Ḱ-185 substances, MT_2 receptors selective antagonists, decreases the antinociceptive effect. The studies showed that melatonin has a complex analgesic effect, which, however, is primarily based on the spinal nociception inhibition.

Melatonin receptor activation decreases the intracellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine

monophosphate (cGMP) [35]. Melatonin inhibits such mediators as Ca^{2+}, diaglycerol, inositol phosphate, and arachidonic acid, at least, in the anterior pituitary in rats [36]. Electrophysiological study demonstrated that melatonin activates calcium-dependent ion C1-channels through phospholipase and this effect can be inhibited by specific melatonin MT_1/MT_2 receptor antagonists [37]. It was suggested that melatonin can block calmodulin (CaM) interaction with specific enzymes [38]. This evidence is of great importance since CaM kinase plays a crucial role in central sensitization.

A recent experimental study evaluated the efficacy of a novel selective melatonin MT_2 receptor partial agonist N-{2-([3-bromo phenyl]-4-fluorophenylamino)ethyl}acetamide (UCM924) in two neuropathic pain models in rats and examined its supraspinal mechanism of action. In rat L5–L6 spinal nerve ligation and spared nerve injury models, UCM924 (20–40 mg/kg, subcutaneously) produced a prolonged antinociceptive effect that is: (1) dose-dependent and blocked by the selective MT_2 receptor antagonist 4-phenyl-2-propionamidotetralin, (2) superior to a high dose of melatonin (150 mg/kg) and comparable with Gabapentin (100 mg/kg), but (3) without noticeable motor coordination impairments in the rotarod test. Double-staining immunohistochemistry revealed that MT_2 receptors were expressed by glutamatergic neurons in the rostral ventrolateral periaqueductal gray. In vivo electrophysiology combined with tail flick showed that microinjection of UCM924 into the ventrolateral periaqueductal gray decreased tail flick responses, depressed the firing activity of ON cells, and activated the firing of OFF cells; all effects were MT_2 receptor-dependent [39]. In a different study, López-Canul et al. [40] studied

antiallodynic effects of MT_2 receptor agonists on animal neuropathic pain models by ON- and OFF-cells activation. The study involved N-{2-[(3-metoxiphenyl) phenylamino]ethyl} acetamide (UCM765) and N-{2-([3-bromo-phenyl]-4-fluorophenylamino)ethyl}acetamide (UCM924) as partial MT_2 receptor agonists. The animal models of acute and inflammation pain included hot-plate and formalin tests. The maximum antinociceptive effect was produced by 20 mg/kg of UCM765 and UCM924 and was comparable to 200 mg/kg of acetaminophen and 3 mg/kg of ketorolacum [40]. Altogether, these data demonstrated that selective MT_2 receptor partial agonists had analgesic properties through modulation of brainstem descending antinociceptive pathways, and MT_2 receptors may represent a novel target in the treatment of neuropathic pain [39, 40].

Interestingly, the MT_1 and MT_2 receptor localization differs. MT_1 receptors are found in the spleen, hippocampus dentate gyrus, the islands of Calleja (in the striatum), suprachiasmatic nuclei, the superior colliculi of the corpora quadrigemina, the black substance, etc. MT_2 receptors are predominantly found in the hippocampus CA3 subfield, thalamic reticular nucleus, supraoptic nucleus, the inferior colliculus of the corpora quadrigemina, and ventrolateral parts of the periaqueductal gray [41]. The different localization of MT_1 and MT_2 receptors indicates that they play different roles and perform different functions, which should be kept in mind when selective MT_1 and MT_2 agonists are used [42].

As for nuclear receptors, on one hand, RZRβ plays a specific role of a transcription factor in the sensory system, and on the other hand, RZRα melatonin receptors are involved in inflammatory reactions. Steinhilber et al. [43] reported that melatonin can decrease the

Table 1 Melatonin's antinociceptive effect: studies on animal models

Melatonin or its agonist dose and route	Animal model used	Blocked by	Type of receptors involved	Effect of melatonin	References
Melatonin 20–40 mg/kg i.p.	Hot plate	Naloxone and flumazenil	Opioid and BZD	Antinociception, the strongest analgesic effect if administered in the evening	Golombek et al. [5]
Melatonin 30, 60, or 120 mg/kg i.p.	Hot water tail flick test	Naloxone	Opioid	Antinociception, the dose-dependent effect	Yu et al. [6]
Melatonin 0.5 or 1.0 mg i.p.	Electrical tail stimulation	–	–	Antinociception	El-Shenawy et al. [7]
Melatonin 25–100 mg/kg i.p.	Inflammatory type of pain	–	–	Antinociception	Esposito et al. [8]
Melatonin 0.1–30 mg/kg i.p. or 0.001–0.1 nmol/site intracerebroventricular	Tail suspension test	Guanosine 5′-monophosphate, ascorbic acid, L-arginine or S-nitroso-N-acetyl-penicillamine	NMDA receptors and NO-pathway	Antinociception	Mantovani et al. [9]
Melatonin 6-chloromelatonin	Capsaicin-induced hyperalgesia	4-P-PDOT	MT2 melatonin receptors	Antinociception, the efficacy in neuropathic pain, decreased intensity and duration of secondary mechanical allodynia and hyperalgesia	Tu et al. [10]
Melatonin 120 mg/kg i.v. 0.1 nmol i.c.v.	Ligation of sciatic nerve (neuropathic pain)	Naloxone	Opioid peptides and L-arginine-NO-pathway	Antinociception, decreased mechanical allodynia, and thermal hyperalgesia	Ulugol et al. [11]

Table 1 continued

Melatonin or its agonist dose and route	Animal model used	Blocked by	Type of receptors involved	Effect of melatonin	References
UCM924 (20–40 mg/kg, subcutaneously)	L5–L6 spinal nerve ligation and spared nerve injury models	Selective MT2 receptor antagonist 4-phenyl-2-propionamidotetralin	MT2 receptors	Dose-dependent effect, blocked by the selective MT2 receptor antagonist, superior to a high dose of MLT (150 mg/kg) and comparable with gabapentin (100 mg/kg), but without noticeable motor coordination impairments in the rotarod test	Lopez-Canul et al. [39]
MT2 melatonin receptor partial agonists UCM765 and UCM924 (5–40 mg/kg, s.c.)	Hot plate and formalin tests	MT2 antagonist 4-phenyl-2-propionamidotetralin (4P-PDOT, 10 mg/kg)	MT2 melatonin receptors	Antinociception	Lopez-Canul et al. [40]

Table 2 Melatonin's antinociceptive effect: clinical studies

Chronic pain syndrome	Drug and dose	Total n	Total groups	Duration of treatment	Results	Reference
Migraine	–	146	2 (the migraine patients and the group of healthy volunteers)	–	Lower urinary level of 6-sulphateoxymelatonin (basic melatonin metabolite) in migraine patients compared to the group of healthy volunteers	Masruha et al. [12]
Migraine	Melatonin 3 mg	34	1	1-month baseline period and 3-month therapy phase	Decreased frequency, intensity, and duration of pain in migraine patients	Peres et al. [13]
Migraine	Agomelatine 25 mg	20	1	3 months	A decrease in the frequency and duration of migraine attacks, a decrease in the depression level, and sleep normalization	Tabeeva et al. [14]
Cluster headaches	–	–	2 (cluster headache patients and healthy controls)	–	A decrease in night melatonin secretion in cluster headache patients compared to the healthy controls; lower melatonin level during the cluster headache attacks compared to the remission period	Peres et al. [15]
Cluster headaches	Melatonin 10 mg or placebo	20	2 (the study and control groups)	14 days	A significant decrease in the intensity and frequency of attacks in the study group compared to the control group	Leone et al. [16]
Cluster headaches	Melatonin 2 mg or placebo	9	1	2 month (1 month for placebo and 1 month for melatonin)	No significant difference in the pain syndrome compared to the control group was found; the findings can be explained by a low melatonin dose	Pringsheim et al. [17]

Table 2 continued

Chronic pain syndrome	Drug and dose	Total n	Total groups	Duration of treatment	Results	Reference
Tension headaches	Melatonin 3 mg	21	1	3 months	A decrease in the pain syndrome intensity	Miano et al. [18]
Chronic back pain	I a—Artra (combination of 500 mg glucosamine hydrochloride and 500 mg chondroitin sulfate) twice a day for 1 month, then one tablet a day for 2 months and melatonin 3 mg I b—Artra twice a day for 1 month, then one tablet a day for 2 months II a—Artra twice a day, diclofenac 25 mg 2–3 times a day and melatonin 3 mg II b—Artra twice a day, diclofenac 25 mg 2–3 times a day III a—Diclofenac 25 mg 3 times a day and melatonin 3 mg III b—Diclofenac 25 mg 3 times a day	178	6	Ia, Ib: 3 months IIa, IIb, IIIa, IIIb: 1 month	A significantly more expressed decrease in pain both in motion and at rest in the study groups compared to the comparison groups. The patients demonstrated less influence of pain on daily activities, the decrease in anxiety and depression, and sleep normalization	Kurganova et al. [19]
Irritable bowel syndrome	Melatonin 3 mg or placebo	17	2 (the study and control groups)	8 weeks with a 4 week washout period	A significant decrease in pain intensity compared to the control groups	Lu et al. [23]
Irritable bowel syndrome	Systematic review	–	–	–	Decreased abdominal pains and the facilitation of defecation not affecting anxiety and sleep	Mozaffari et al. [20]
Irritable bowel syndrome	Melatonin 3 mg or placebo	18	2 (the study and control groups)	8 weeks	The positive impact of melatonin on extra bowel symptoms	Saha et al. [21]

Table 2 continued

Chronic pain syndrome	Drug and dose	Total *n*	Total groups	Duration of treatment	Results	Reference
Irritable bowel syndrome	Melatonin 3 mg or placebo	40	2 (the study and control groups)	2 weeks	A significant decrease in pain intensity compared to the control groups	Song et al. [22]
Irritable bowel syndrome	Melatonin 3 mg or melatonin 5 mg or placebo	80	3	6 months	Decreased abdominal pain	Chojnacki et al. [24]
Fibromyalgia	–	22	2 (the fibromyalgia patients and healthy people)	–	No significant differences in melatonin levels in fibromyalgia patients and in healthy controls	Klerman et al. [25]
Fibromyalgia	–	16	2 (the fibromyalgia patients and healthy people)	–	Significantly lower urine melatonin concentration in fibromyalgia patients compared to healthy controls	Wikner et al. [26]
Fibromyalgia	Melatonin 1.5 mg	11	1	10 days	Sleep improvement, better feeling, decrease of depression, and better hand fine motor function in the daytime	Levin et al. [27]
Fibromyalgia	Melatonin 3 mg	21	1	4 weeks	Significant sleep improvement, a decrease in the number of painful trigger points	Citera et al. [28]
Fibromyalgia	Group A: Fluoxetine 20 mg Group B: Melatonin 5 mg Group C: Fluoxetine 20 mg and melatonin 3 mg Group D: Fluoxetine 20 mg and melatonin 5 mg	101	4	8 weeks	The combined therapy with melatonin and fluoxetine decreased anxiety, tiredness, and significantly limited depressive symptoms	Hussain et al. [29]

Table 2 continued

Chronic pain syndrome	Drug and dose	Total *n*	Total groups	Duration of treatment	Results	Reference
Fibromyalgia	Group 1: Amitriptyline 25 mg Group 2: Melatonin 10 mg Group 3: Amitriptyline 25 mg and melatonin 10 mg	63	3	6 weeks	Combination of 25 mg of amitriptyline and 10 mg of melatonin was more efficient than amitriptyline in relation to pain, morning stiffness, and sleep disorders in fibromyalgia patients	de Zanette et al. [30]
Rheumatoid arthritis	–	–	–	–	Melatonin inhibits the activity of matrix metalloproteinase, which is involved in the joint destruction in rheumatoid arthritis patients	Rudra et al. [34]
Rheumatoid arthritis	–	–	–	–	Inflammation cytokines are secreted into the peripheral bloodstream in response to melatonin stimulation; melatonin is found in the synovial liquid in rheumatoid arthritis patients	Cutolo et al. [33]

expression of 5-lipooxygenase (5-LOX), an important inflammatory mediator, in B-lymphocytes through RZRα receptors.

The Influence on Ion Channels

The experiments demonstrated that the antinociceptive effects of melatonin at least partially involve the activation of calcium channels. At the cell level, melatonin activates G-protein coupled Kir3 channels that in turn inhibit a series of action potentials in neurons. Moreover, melatonin activates K+ ion release in the cerebellum cells, suprachiasmatic nucleus, and other areas of the nerve system [44].

The calcium channels play a decisive role in the development and maintenance of central sensitization associated with inflammation and neuropathic pain—it is the very effect that mediates the effect of Gabapentin which widely used for neuropathic pain treatment. Ayar et al. [45] demonstrated that melatonin inhibits Ca^{2+} entry into the neurons of dorsal root ganglia. It results from Ca^{2+} channel blockade and a consequent decrease of intracellular free Ca^{2+} concentration.

Melatonin and GABA

There is evidence suggesting that the central effects of melatonin involve the facilitation of GABAergic transmission by GABA receptor modulation. The epiphysis is connected via afferent fibers with the suprachiasmatic nucleus, which in turn is connected with the subparaventricular area and the dorsomedial nucleus. The neurons in the suprachiasmatic nucleus can provide both excitation and inhibition of the subparaventricular nucleus and the ventrolateral preoptic nucleus (these mechanisms are mediated by glutamate and GABA, respectively). It was mentioned before that melatonin inhibits a series of action potentials in the neurons of the suprachiasmatic nucleus that may cause the loss of inhibition (and the consequent excitement of the structures innerved from the suprachiasmatic nucleus) or the loss of excitation (leading to increase in inhibition). Moreover, melatonin may modulate the functions of GABA receptors [46]. The experiments revealed that melatonin increases GABA affinity to the receptors in a rat's brain [64]. Melatonin and its analogues can bind to GABA receptors. Moreover, melatonin increases GABA concentration by 50% [47]. Thus, the data suggest a significant interconnection between melatonin and GABAergic systems, and some of the melatonin neuropharmacologic effects (including hypnotic activity) are evidently mediated through GABA receptors and may be blocked by GABA antagonists.

CONCLUSIONS

The effects of melatonin are still being researched. Some of these effects remain debatable, while others are doubtless. The analgesic effect of melatonin is among the latter. Its effects in relation to pain were demonstrated in several experimental studies on animal models and clinical trials with patients with various pain syndromes. That leads to understanding that melatonin antinociceptive mechanisms have a complex structure. On one hand, being a chronobiotic melatonin restores circadian rhythms, increasing the adaptive capabilities of the body. On the other hand, the anxiolytic effect of melatonin leads to a decrease in pain through the decrease of anxiety and vegetative reactions.

Finally, there is a separate analgesic effect of melatonin on the melatonin receptors in the areas of the brain responsible for pain perception and control and on several neurotransmitter systems (GABA, opioid system, L-arginine/NO pathway, etc.). It is noteworthy that melatonin has a very high safety profile. The literature describes the potential adverse effects of melatonin, including day sleepiness, headaches, vertigo, abdominal discomfort, irritability, and confusion. However, in practice, clinical trials in various pain syndromes revealed an extremely low level of adverse effects.

It is no doubt that it is too early to consider melatonin as an analgesic. Nevertheless, given melatonin's potential in relation to both neuropathic and nociceptive pain, melatonin deserves special attention and may become an efficient addition to the existing drugs for pain syndrome treatment.

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