Melatonin therapy in chronic pain syndrome

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Abstract:

Melatonin is a hormone secreted 80% by epiphysis and 20% by extrapineal structures. It performs several functions including chronobiotic, antioxidant, oncostatic, immune modulating, normothermal, and anxiolytic functions.There are numorouse studies demonstrating melatonin efficacy in relation to chronic pain syndromes. The present paper reviews the studies on melatonin use in various forms of headaches, and chronic back pain.The paper discusses the possible mechanisms of analgesia. Circadian rhythm normalization results in sleep improvement, which is disordered in chronic pain syndromes,hence there is evidence of melatonin-independent analgesic effect involving melatonin receptors.

Keywords:

Melatonin, Chronic pain, Headache, Migraine, Tension type headache, Cluster headache, Low back pain.

Sažetak:

Terapija melatoninom u sindromu kronične boli

Melatonin je hormon kojeg secernira epifiza, ali 20% dolazi iz eksprapienalnih struktura. Melatonin je kronobiotik, antioksidant, antitumoroski i imunomodulirajući agens, sudjeluje u održavanju tjelesne temperature te ima anksiolitička svojstva. Brojne studije pokazale su i njegov analgetski učinak u tretiranju kroničnih bolnih sindroma. To ostvaruje prije svega normalizacijom sna, koji je dereguliran u pacijenata sa kroničnim bolnim sindromima, ali isto tako, melatonin ima i direktno analgetsko svojstvo koje ostvaruje djelovanjem na melatoninske receptore.

Ključne riječi:

melatonin, kronična bol, glavobolja, migrena, tenzijska glavobolja, klaster glavobolja, bol u leđima

The presence of circadian rhythm in nature has been well known for a long time, introducing chronobiology in understanding of many processes in the human body. It was found that circadian rhythms are involved in each and every physiological proces, thus circadian rhythm disruption may result in several pathological conditions, while most diseases may cause circadian desynchronization. Good example is chronic pain syndrome which is always associated with various degrees of biological rhythm desynchronization.

The biological rhythms in mammals are controlled by the suprachiasmatic nuclei of the hypothalamus. 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, but there are also extrapineal sources of melatonin: cells of gastrointestinal tract , lungs and renal cortex, retina, lymphocytes, thrombocytes, mastocytes, etc. Some melatonin properties are well known; the others are still under study (1).

Melatonin and cortisol have chronobiological features, can regulate circadian rhythms, and normalize sleep and activity. 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 studies have revealed new melatonin properties such as anticancer and immune-modulating effects, the capability to improve mood and to decrease anxiety, to affect the cardiovascular and gastrointestinal system, 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. Contemporary therapy of chronic pain syndrome is in constant search for new molecules with analgesic capabilities. The goal 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.

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.

There are membrane melatonin receptors MT1/ MT2 and nuclear melatonin receptors RZRa/ RZRb. The membrane receptors involved in melatonin analgesic effect are indicated by MT1/ MT2 receptors localization in the thalamus, the hypothalamus, the dorsal horns of the spinal cord, the spinal trigeminal tract, and the trigeminal nerve nucleus.

The studies showed that melatonin has a complex analgesic effect, which is primarily based on the spinal nociception inhibition. It was suggested that melatonin can block calmodulin (CaM) interaction with specific enzymes (5). 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 MT2 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: dose-dependent and blocked by the selective MT2 receptor antagonist 4-phenyl-2-propionamidotetralin, superior to a high dose of melatonin (150 mg/kg) and comparable with Gabapentin (100 mg/kg) (6). Selective MT2 receptor partial agonists had analgesic properties through modulation of brainstem descending antinociceptive pathways, and MT2 receptors may represent a novel target in the treatment of neuropathic pain (6,7).

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 (8). The calcium channels play a role in the development and maintenance of central sensitization associated with inflammation and neuropathic pain. Ayar et al. (9) demonstrated that melatonin inhibits Ca2+ entry into the neurons of dorsal root ganglia. It results from Ca2+ channel blockade and a consequent decrease of intracellular free Ca2+ concentration.

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). Moreover, melatonin may modulate the functions of GABA receptors (10). The experiments revealed that melatonin increases GABA affinity to the receptors in a rat's brain . Melatonin and its analogues can bind to GABA receptors. Moreover, melatonin increases GABA concentration by 50% (11). 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.

Melatonin in Migraine

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. 3 mg of melatonin before sleep can decrease the frequency, intensity, and duration of pain in migraine patients (12). In a recent study, 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 (13).

Observational studies support a role for melatonin in the treatment of migraine. Adults with migraine have lower melatonin levels on migraine days compared to non-headache days and those with chronic migraine have lower melatonin levels than those with episodic migraine (14,15). Nocturnal melatonin levels are lower in women with migraine with aura whose attacks occur around menses compared to control women.

There is also experimental evidence supporting a therapeutic role for melatonin in migraine prevention, though with some conflicting data. In a double-blind, randomized, placebo-controlled, 3-arm trial with approximately 65 participants per arm, the efficacy of 3 mg of immediate release melatonin was superior to placebo and comparable to amitriptyline 25 mg nightly. The observed reduction in headache frequency at three months was: 2.7 in those treated with melatonin, 2.2 for amitriptyline (p=0.19), and 1.2 for placebo (p=0.009). The tolerability of melatonin was comparable to placebo and better than amitriptyline (16).

In a pilot study of adult patients with migraine or tension-type headache, melatonin 4 mg appeared to be an effective dose for migraine prevention(17).

Melatonin may be useful in the treatment of pediatric and adolescent migraine. In one study, 60 pediatric and adolescent participants were treated with up to 6 mg melatonin nightly . At three months, mean(SD) migraine attack frequency decreased from 15.6±7.6 to 7.1±4.4 per month (18). In a smaller pediatric study, 14 patients were treated with 3 mg melatonin nightly. Ten (71%) had a ≥50% improvement in headache frequency at 3 months (19). Melatonin was well tolerated in these pediatric studies: in the study where children received up to 6 mg of melatonin, 7(12%) had daytime sleepiness vs. 1(7%) in the smaller study where they received 3 mg (18,19).

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 (20). 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 (21).

In patients with episodic cluster headache, melatonin levels may have a reduced nocturnal peak during a cluster period, or even absent circadian rhythmicity (22). Cluster attacks often occur out of sleep (23). Hypothalamic dysfunction has been hypothesized to play a pathophysiological role in cluster headache (24) and melatonin supplementation may help replete low endogenous levels during a cluster period and help to phase shift sleep. In a randomized placebo-controlled trial consisting predominantly of episodic cluster headache patients (18/20 with episodic, 2/20 with chronic), melatonin 10 mg orally, when introduced early in a cluster period, i.e. 2nd to 10th day, was superior to placebo at decreasing cluster attack frequency. In the first week of treatment, mean (SD) attack frequency in the melatonin group vs. the placebo group was 1.9±1.5 vs. 2.7±0.9 (p<0.03), and in the second treatment week it was 1.5±1.7 vs. 2.5±0.9 (p=0.01). There were 10 patients per arm; five responded to melatonin and the other five did not. Improvement in the responders began within three days of treatment initiation and by five days none of the responders were still having cluster attacks. No significant side effects were noted (21). In recent study melatonin has been shown to be effective in acute treatment of migraine in children (25).

Melatonin in Tension Headaches

There is growing evidence that headaches are connected to melatonin secretion. The aim was to assess the potential effectiveness of melatonin for primary headache prevention. Forty-nine patients (37 with migraine and 12 with chronic tension-type headache, TTH) were prescribed oral melatonin, 4 mg, 30 minutes before bedtime for six months. Forty-one (83.6%) of the 49 patients completed the study. A statistically significant reduction in headache frequency was found between baseline and final follow-up after six months of treatment (p=0.033 for TTH patients and p<0.001 for migraineurs). The Headache Impact Test score was significantly reduced in both groups of headache patients (p=0.002 and p<0.001, respectively). At baseline, melatonin levels, measured both during a headache attack and a pain-free period, did not differ between patients with TTH and migraineurs (p=0.539 and p=0.693, respectively), and no statistically significant differences in Hamilton Depression Rating Scale scores were found between the two groups. This pilot study shows promising results, in terms of headache frequency reduction and daily quality of life improvement, in both groups (26).

Migraine attacks seem to begin in the morning hours pointing towards a possible role of the circadian clock in migraine. Seasonal and weekly distributions of migraine attacks are less clear,

possibly due to heterogeneity within the existing literature. Optimal melatonin dosing for treatment of each of these headache disorders may differ. Based on the range of doses reported to be effective for different disorders in this review, testing of broad dosing ranges may be needed to establish optimal dosing. Fortunately, even at very high doses melatonin appears to be remarkably safe and without serious side effects. In healthy volunteers, melatonin doses of 20–100 mg orally have been given without adverse effects other than mild transient drowsiness (27). Longer-term treatment trials have also supported melatonin's excellent safety profile—for example no serious adverse events occurred in the 8–12-week migraine preventive trials (28), and longer term treatment durations of six months or more for migraine, sleep, and other indications have also not raised safety issues (29).

For migraine, 3 mg appears to be the minimum effective dose in adults (16), and uncontrolled data suggest a slightly higher dose of 4 mg may also be helpful (17). Optimal dosing in pediatric migraine needs study in a randomized trial, but uncontrolled work suggests 3–6 mg may be an effective dosing range (18,19). For cluster headache, melatonin 10 mg (21) has been shown to be superior to placebo in treating cluster periods, however given that some patients needed doses up to 30 mg to get benefit (30), it is possible that higher doses in cluster headache could further optimize responder rate.

The optimal formulation of melatonin to use in each headache disorder also needs to be clarified. It is often not explicitly stated whether immediate release or prolonged release melatonin is being used in treatment trials, though when not specified it is probably more likely to be immediate release melatonin

It would also be worthwhile to establish the comparative efficacy of melatonin vs. melatonin receptor agonists, such as ramelteon, agomelatine and others. However, one of the potential advantages to a treatment like melatonin is that, if found to be effective, it can be easily accessed over the counter at relatively low cost. Melatonin receptor agonists would require a prescription and have potentially higher costs to the patient and the health care system. Thus accessibility and cost effectiveness argue for focusing research on immediate release melatonin as the first priority whenever it is medically appropriate to do so. Other strategies for improving circadian rhythms, could also be cost effective and merit study in primary headache disorders.

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Melatonin in Low Back Pain

Intervertebral disc degeneration (IDD) is the premise and pathological basis of a series of degenerative spinal diseases and the main cause of low back pain (LBP). Mechanistically, IDD is related to oxidative stress, insufficient autophagic flux, involvement of inflammatory mediators, activation of apoptosis pathways, and increased matrix metalloproteinases in the IVD. Melatonin is a natural molecule and can be a potential treatment for IDD by exerting multiple functions in disc cells, including antioxidant, anti-inflammatory, autophagy-promoting, and anti-apoptotic effects. Accumulated in vivo studies have shown that administration of melatonin can alleviate IDD caused by fibropuncture, inflammation or oxidative stress stimulation, as verified by histological and imaging assessments. Melatonin facilitates the survival of cells, promotes matrix anabolism; inhibits vascular invasion; mitigates calcification; and accelerates damage repair, thereby maintaining the structural integrity and orderliness of the IVD From the perspective of therapeutic strategies for IDD, the benefits of melatonin are comprehensive. The existing evidence supports melatonin as a potential therapy for the prevention and treatment of IDD (33).

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 (34, 35).

Conclusion

The effects of melatonin are still being researched. 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 rhythm,

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. There is a direct 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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