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Review

Cephalalgia
An International Journal of Headache

International Headache Society

Current understanding of pineal gland structure and function in headache

Cephalalgia
2019, Vol. 39(13) 1700–1709
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DOI: 10.1177/0333102419868187
journals.sagepub.com/home/cep
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Abstract

Purpose: The pineal gland plays an important role in biological rhythms, circadian and circannual variations, which are key aspects in several headache disorders.

Overview: Melatonin, the main pineal secreting hormone, has been extensively studied in primary and secondary headache disorders. Altered melatonin secretion occurs in many headache syndromes. Experimental data show pineal gland and melatonin both interfere in headache animal models, decreasing trigeminal activation. Melatonin has been shown to regulate CGRP and control its release.

Discussion: Melatonin has been used successfully as a treatment for migraine, cluster headaches and other headaches. There is a rationale for including the pineal gland as a relevant brain structure in the mechanisms of headache pathophysiology, and melatonin as a treatment option in primary headache.

Keywords

Pineal gland, melatonin, headache disorders

Date received: 28 February 2019; revised: 9 June 2019; accepted: 17 July 2019

The pineal gland plays a pivotal role in biological rhythms, circadian and circannual variations, which are important aspects in several headache disorders (1). Melatonin, the main pineal secreting hormone, has been studied in primary and secondary headache disorders, and altered secretion has been found in the main primary headache disorders. Melatonin has been used successfully as a treatment for migraine, cluster headaches and other headaches (2). Therefore, there is a rationale for including the pineal gland as a relevant brain structure in the mechanisms of headache pathophysiology.

Pineal structure, connections and melatonin synthesis and action

The pineal gland is an unpaired epithalamic structure, originating as an evagination of the roof of the third ventricle and from the same embryological tissue from which the retinas originated (3). Its rich vascular supply is sustained by blood vessels branching from the posterior cerebral artery, and this gland is mainly innervated by the sympathetic nervous system originating from the superior cervical ganglia (4), in addition to sparse parasympathetic and central direct projections (Figure 1) (5).

In addition to glial cells, the pineal gland is rich in endocrine cells called pinealocytes, which derive from the photoreceptors' lineage and are responsible for synthesis of melatonin, the pineal hormone (6).

Melatonin is synthetized from tryptophan through four consecutive enzymatic steps. The intermediary product is serotonin, which is acetylated by the main enzyme, arylalkylamine- N- acetyltranferase (AANAT), whose activity is under circadian control mediated by the sympathetic innervation

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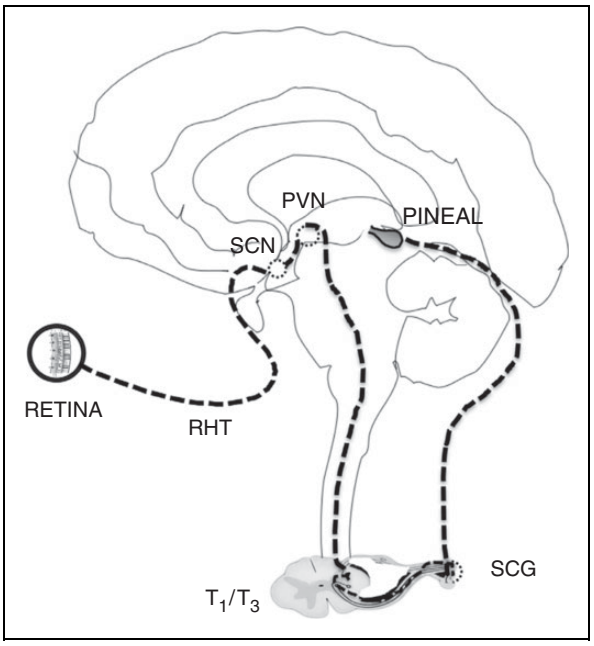

Figure 1. Neural control of pineal melatonin synthesis. Melatonin synthesis neural system control starts in the hypothalamic paraventricular nuclei, projecting to the preganglionic sympathetic neurons of the first thoracic segments of the spinal cord. After a projection of the postganglionary sympathetic neurons of the superior cervical ganglia, the conary nerve reaches the pineal gland (do Amaral and Cipolla-Neto, 2018 (7)). RHT: retinohypothalamic tract; SCN: suprachiasmatic nucleus; PVH: paraventricular nucleus; SCG: superior cervical ganglion.

(noradrenaline, beta and alpha adrenoreceptors, cAMP, PKA, CREB transduction pathway). N-acetylserotonin is then converted to melatonin by the action of the last enzyme, acetylserotonin- N- methyltransferase (ASMT).

Melatonin production is strictly circadian in nature and synchronized to the dark phase of the light-dark environmental cycle in all known mammalian species (both nocturnal and diurnal ones), including humans. In addition, melatonin is only synthesized during the night provided there is no light (mainly in the blue range) in the external environment. Blue light activates a complex neural system originating in intrinsically photosensitive retinal ganglion cells (photoreceptors containing melanopsin as the photopigment), which results in the inhibition of melatonin synthesis by the pineal gland (7). Moreover, this delicate and complex neural system is responsible for keeping melatonin's daily profile strictly following the duration of the night. In consequence, as the duration of the night regularly varies according to the season of the year (winter nights are longer than summer nights), melatonin's daily profile is the internal representative of the external photoperiod, synchronizing most of the behavioural and physiological circannual rhythms.

These characteristics of melatonin production determine the fundamental role it plays as a chronobiotic hormonal signal, controlling physiological and behavioural circadian and circannual rhythms that are fundamental to the adaptation of the organism to the environmental changes typical of the day and night and the seasons of the year.

In order to understand the role played by melatonin as a hormone, its functions and dysfunctions, it is necessary to describe its similarities to the other classical hormones, emphasizing what makes melatonin unique (8).

Melatonin, an ancient molecule, has many mechanisms of action that can be classified in two groups: Actions that are not mediated by receptors (or intracellular direct actions) and actions mediated by receptors. Due to its amphiphilic characteristic of diffusion, melatonin seems to lack a biological barrier, being found in all the compartments of the mammalian organism. Melatonin is able to diffuse through cell and organelle membranes so that it interacts directly with intracellular ligands, such as a number of proteins (e.g. Ca++/calmodulin-dependent protein kinase II, NO synthase, mitochondrial respiratory chain complexes I and IV, etc.) and oxygen and nitrogen free radicals. In this context, melatonin is one of the most powerful antioxidant molecules in nature, directly reacting with oxygen and nitrogen reactive species and destroying them. This antioxidant characteristics of melatonin justifies its putative use in ischemia-reperfusion clinical conditions such as hypoxic ischemic encephalopathy of the newborn, myocardial infarction, cerebrovascular ischemic accidents, and so on (8).

In addition to this intracellular direct action, melatonin is also able to interact with specific membrane receptors. Melatonin receptors are of two types: MTNR1A and MTNR1B. Both are G protein-coupled receptors mainly linked to G_i/G_o and Gq/G_{11} proteins (depending on the target organ and tissue), and their activation results in inhibition of adenylyl or guanylyl cyclase and activation of phospholipase C (in addition to other putative downstream messengers such as phospholipase A_2 and potassium channels).

It should be considered that the effects determined by melatonin's interaction with its molecular acceptors are expressed not only during the night, as would be expected. It should be considered that melatonin's actions are extended, through a specific prospective way of action (8), determining effects that will appear only the following day when melatonin is no longer present, and provided it is not circulating at all.

The role played by melatonin in human physiology and pathophysiology should take into consideration what was previously mentioned: Melatonin is the internal representative of the daily and seasonal

environmental light-dark cycle, so the daily profile of pineal melatonin is able to trigger not only day and night physiological adaptations but, in addition, different day and night adaptive mechanisms according to the annual season. This primordial physiological role of pineal melatonin necessarily implies that this hormone is able to control and regulate all the basic physiological functions such as the activity (wakefulness)-rest (sleep) cycle, eating-fasting, and all the subsidiary metabolic modifications, such as reproduction, cardiovascular and respiratory functions, the immune system, and so on (7–11). In order to do so, melatonin might act peripherally in several organs besides having the central nervous system as its main site of action.

Due to its particular anatomical epithalamic insertion, pineal melatonin is directly released in the cerebrospinal fluid of the third ventricle through the pineal recess, so its concentration is much higher in the ventricular system than in the peripheral blood.

Acting on the central nervous system, and due to the location of its receptors and its particularities of action, melatonin regulates basic, general neural functions such as neurotransmission (12), neuroprotection (antioxidant, anti-inflammatory, etc), and neuroplasticity, among others (8).

Moreover, melatonin is able to control specific functions, as mentioned above (metabolic and endocrine, cardiovascular, immunological, etc), acting in particular areas of the central nervous system such as the hypothalamus, brainstem, striatum, hippocampus, and so on. Among these, and one of the most integrative functions exerted by pineal melatonin, is the regulation of circadian rhythms in behaviour and physiology (8). Through its immediate and prospective effects, importantly melatonin contributes to the daily distribution of all the physiological and behavioural processes that are necessary to the adaptation of the organism to the light-dark cycle of the environment. The active phase of the daily cycle should be concomitant to high sympathetic and cardiorespiratory output, glucocorticoid secretion peak, high insulin sensitivity associated to the eating phase, stimulation of the immune system with the increased exposure of the organism through active interaction with the external environment, and so on. On the contrary, the daily rest phase is associated to sleep, fasting, gluconeogenesis metabolic shift, parasympathetic predominance, reduced cardiovascular output, and so on. Importantly, participating in this intricate and delicate daily distribution of behaviour and physiology integration, the absence or reduction of melatonin contributes to a pathological state called chronodisruption (13). Under this clinical condition, melatonin, adequately administered, is able to restore the circadian temporal organization, improving health (8).

Melatonin and pain

There is available evidence indicating that melatonin plays an important role in antinociception (14). Several experimental studies have shown antinociceptive action of melatonin in acute, neuropathic and inflammatory pain models (15). In a paw-withdrawal test of a neuropathic pain model, melatonin's analgesic effect lasted for a period of 1 hour (16). In electrically induced pain in rats, injecting melatonin intraperitoneally (ip) increased the antinociceptive effect for up to 3.5 hours (17). In a rodent tail-flick pain model, melatonin produced analgesia (18). In a mice hot-plate model of pain, melatonin had an analgesic action, which was more effective when administered in the evening (19). In rats with pain induced via a mechanical model of tail clamping, 2-bromomelatonin induced dose-dependent analgesia (20). In chemically induced pain in rats, which mimics acute pain in humans, melatonin also reduced pain (21). In all these different animal models of pain, administration of melatonin caused no adverse effects.

Mechanisms of action of melatonin's analgesic effects may involve multiple receptors and pathways. The most important are the MT1 and MT2 melatonin receptors, whose activation leads to reduction in cyclic AMP formation and reduced nociception (15). Melatonin is also able to activate opioid receptors indirectly via G(i) -coupled μ-receptors (22). In a neuropathic pain model in rats, the increase in pain threshold caused by administration of melatonin was blocked by an opioid, GABA(A), and a benzodiazepine antagonist (23). In patch-clamp recordings in rats induced with mechanical hyperalgesia, melatonin dose-dependently decreased NMDA-induced currents in spinal cord dorsal horn substantia gelatinosa neurons (24). The effect of melatonin in a nociceptive state induced by administration of formalin to the hind paw of rats was mediated through the alpha-1 adrenoceptor, alpha-2 adrenoceptor, muscarinic and nicotinic receptors in the spinal cord (25). The nitric oxide (NO)-arginine pathway has been documented to be involved in melatonin analgesia in an established mononeuropathy pain model in rats, looking at immunohistochemical detection of neuronal and inducible nitric oxide synthases in the dorsal root ganglia (26). Melatonin is also able to activate opioid receptors indirectly, to open several K+ channels, and to inhibit expression of 5-lipoxygenase and cyclooxygenase 2 (27). The melatonin antinociceptive action occurs at several levels, periphery as an anti-inflammatory agent (28), at the dorsal root ganglia nociceptive cells (29), the spinal cord and several supraspinal centers (30).

A number of chronic pain conditions other than headache disorders have been found to be improved with melatonin therapy, such as chronic back

pain (31), temporomandibular disorder (32), rheumatoid arthritis (33), fibromyalgia (34), irritable bowel syndrome (35,36). Melatonin has been tried during surgical operating conditions and has been shown to enhance both preoperative and post-operative analgesia (37). A meta-analysis looking at pain intensity as the endpoint after melatonin administration in 19 trials showed that melatonin significantly decreased the pain intensity, as evidenced by the pain scores, supporting the use of melatonin for antinociception (38).

Melatonin itself and its agonists have been primarily used in the treatment of primary sleep disorders, reducing sleep onset in primary insomnia, delayed sleep phase syndrome (39), and also secondary sleep disorders commonly found in psychiatric conditions and other chronic diseases (40). Restorative sleep is crucial for the homeostasis of virtually all body systems. Disorders known to be associated with pain, such as cancer, metabolic conditions, anxiety and depression, may all be accompanied by a decrease in sleep quality. In these scenarios, melatonin supplementation may be a potential candidate for sleep quality improvement, and may possibly improve secondary pain (41). Melatonin's effect on pain, however, has been shown to be independent of sleep changes (42).

Melatonin has also been studied for prevention and reversal of opioid-induced tolerance and hyperalgesia (43) as it reduces allodynia in experimental models (44). The variety of actions and the amount of melatonin studies in the pain field reinforces its putative importance in headache disorder pathophysiology and treatment, due to the common mechanisms shared between pain and headache disorders such as the opioid system, neurotransmitters (noradrenaline, acetylcholine), nitric oxide, GABA, NMDA and inflammation; and the pain conditions treated with melatonin are frequently associated with headaches, including temporomandibular disorders, irritable bowel syndrome, fibromyalgia, and chronic back pain.

Pineal gland role in headache pathophysiology

The pineal gland and its main secretory product, melatonin, have been implicated in mechanisms and treatment of primary and secondary headache disorders (1,45–49). The pineal gland plays a pivotal role in biological rhythms, responsible for the modulation of circadian and circannual variations of all physiological systems in the human body (50). Biological rhythms are important aspects in several headache disorders such as menstrual migraine, hypnic headache and cluster headache; all have been shown to have decreased melatonin levels during the headache state (1,51–53). Moreover, headache and sleep disturbances have been linked in several studies, in both clinical and pre-clinical *in vivo* studies in rodents (54).

Animal models have been extensively used in headache research, improving the understanding of mechanisms causing head pain (55). A study analysing c-fos expression within the trigeminal nucleus caudalis (TNC) of pinealectomized rats and controls receiving a capsaicin-induced activation found a significantly higher count of c-fos-positive cells in animals with pineal glands removed. Moreover, animals that received intraperitoneal melatonin showed a small number of c-fos-positive cells in the TNC (layer I/II) (56). In this same model, administration of melatonin was found to decrease CGRP levels (57). Melatonin has been shown to decrease CGRP in other studies. Melatonin injection *in vitro* decreased CGRP-mediated activity regulating cerebral arterial tone in the middle cerebral arteries of rats (58). In a neuropathic pain model in mice, melatonin inhibited the activation of peptidergic neurons and neuro-inflammation in the dorsal root ganglia neurons by down-regulating CGRP (59). In humans, melatonin treatment in 12 pure menstrual migraine patients and 12 control subjects showed significantly lower CGRP release (60). One may speculate on possible mechanisms behind the melatonin effect in CGRP, first by acting directly in CGRP receptors, or by regulating the withdrawal of sex steroids in the late luteal phase that are known to elevate CGRP levels (61,62). Melatonin is a potent antioxidant (63) and anti-inflammatory (64) compound that can affect CGRP by scavenging free radicals or inactivation of pro-inflammatory agents. In addition, in a study of the pineal gland innervation, substance P and CGRP were found in the nerve fibers supplying the pineal gland, suggesting these peptides may possibly regulate or modulate melatonin secretion (65).

Melatonin's effect in decreasing CGRP levels may have therapeutic implications; however, further research should be done to explore this topic.

Melatonin and the GABAergic system are also related. Melatonin has GABA-like effects (66), GABA is involved in the hypnotic action of melatonin (67), which increases the concentration of GABA in the hypothalamus (68) by augmenting GABA-induced chloride influx (69), potentiating GABAA receptors (70), and enhancing GABA binding (71).

For future studies, possible experimental approaches to clarify the role of the pineal gland and melatonin in the trigeminovascular system could be performed by removing the pineal gland, by treating animals with melatonin, or by stressing their day/night cycle.

Melatonin levels have been found to be decreased in episodic migraine (72), in acute migraine (45,51) menstrual migraine (51), chronic migraine (49), related light sensitivity in migraine (73) and migraine

comorbidity (74). Migraine patients with nausea and those with cheese- or chocolate-induced attacks, had significantly lower levels of melatonin (75). Other headache disorders such as tension-type headache (76) have shown altered melatonin levels, but the most extensively studied, cluster headache, has shown alteration in (77) and outside bouts (52,78), and in episodic and chronic cluster headache (76,79) throughout the year (48). Interestingly, one study measuring melatonin levels in hypnic headache did not show differences when comparing patients and controls (80). These studies show melatonin is possibly related in the mechanisms of all main headache disorders.

Melatonin and melatonin receptor agonists in headache treatment

Since the pineal gland and melatonin dysfunction have been implicated as a possible mechanism in the pathophysiology of headache disorders, melatonin supplementation, its agonists, and potentially other chronobiotic agents may be useful for the management of certain headache conditions. The most common chronobiotic therapy studied in headache disorders is melatonin supplementation (81). Melatonin has been largely used since the 1990s in the United States. Sold over the counter as a vitamin supplement, it has been ingested on a daily basis by thousands of individuals since then (82), and has been shown to be safe in humans (67) and animals (83). Other chronobiotic agents such as melatonin receptor agonists (agomelatine, ramelteon, tasimelteon) (84), or non-pharmacological options such as light therapy, should be further studied.

Melatonin in migraine treatment

Migraine is the headache disorder most studied in the field and the most disabling headache condition worldwide (85,86). Migraine treatment, as in other headache disorders, is divided into preventive and acute therapies. Although acute migraine care has been historically given more emphasis in drug design and specific pharmacological options (ergotamines and triptans) (87), recently migraine prevention has gained the deserved attention. New options are available, such as the specifically targeted anti CGRP monoclonal antibodies (88). Migraine prevention has pharmacological (89) and non-pharmacological options (90). Medications from different classes have been part of guidelines, such as antidepressants, antihypertensives, calcium-channel blockers, and antiepileptic drugs; all medications show similar efficacy (50% response rate in 50% of patients) but are not very well tolerated (91). Weight gain, cognitive dysfunction, fatigue, sleepiness, hair loss, digestive and other symptoms significantly limit patient adherence and treatment satisfaction (92). Therefore, better efficacy and tolerability in migraine treatments is very desirable.

Melatonin may fill this gap, it has been shown to be effective and very well tolerated in a well-designed clinical trial (46); in addition, melatonin's low cost makes it attractive for health care public policies in search of cost-effective management.

Melatonin has been studied in migraine prophylaxis, and very briefly for acute care. A systematic review (93) identified seven eligible articles, four randomized placebo-controlled studies and three open-label. It was concluded that melatonin might be effective for migraine prophylaxis. Immediate-release melatonin 3 mg was established as effective, and melatonin receptor agonist (agomelatine) 25 mg and prolonged-release melatonin 4 mg were effective in open-label studies. In a placebo-controlled trial, Melatonin 2 mg was equally effective when compared to placebo in a 2-month trial, with small sample size and several methodological issues such as a high placebo rate found (94). Another study comparing melatonin 3 mg delivered at bedtime, amitriptyline 25 mg and placebo, looking at migraine frequency during baseline versus 3 months of therapy as a primary endpoint, showed significant results in melatonin and amitriptyline takers when compared with placebo. Melatonin was as effective as amitriptyline in the primary endpoint, but in the secondary endpoint, 50% reduction, melatonin was superior to amitriptyline and placebo. Melatonin was better tolerated than amitriptyline, with a similar side effect profile to placebo, and a surprising and significant weight loss in the melatonin group (46).

Melatonin treatment was also studied in chronic migraine prophylaxis comparing with divalproate, showing similar efficacy and better tolerability in a double-blind study (95). Melatonin has been reported as effective for acute migraine therapy, intravenous infusion reducing an attack without side effects (96).

Melatonin treatment in the pediatric population

Melatonin has been used in the context of neurological and psychiatric pediatric treatments. On 4 October 2014, in Rome, the first European conference was held where a consensus and treatment guidelines for the use of melatonin in children was reached (97). The best evidence for efficacy is in sleep onset insomnia and delayed sleep phase syndrome. Children with autism spectrum disorder, attention-deficit/hyperactivity disorder and intellectual disability have sleep disturbance and can benefit from melatonin treatment. The consensus reinforced melatonin as a successful option in treating headache.

The excellent tolerability profile of melatonin makes it an easily accepted treatment concept for parents when deciding about the available migraine preventive options (80–83). Clinical evidence from randomized trials has been a challenge in pediatric headache. Triptans and preventive studies with good methodology have failed to meet primary endpoints observed in adult migraine trials (101–103). The Champ trial was a large randomized clinical trial comparing topiramate, amitriptyline and placebo for childhood and adolescent (between the ages of 8 and 17 years old) migraine prevention (102). The trial was terminated early due to futility after a planned interim analysis showed no differences in headache response observed in 52% of the amitriptyline group, 55% of the topiramate group, and 61% of the placebo group.

A pilot study in a pediatric population found improvement in 13 migraine patients taking melatonin compared to a further 13 taking placebo, without significant side effects (104). A trial open study of 60 children taking melatonin 0.3 mg/kg for 3 months showed significant reduction in migraine days, from 15.6 to 7.1 (105). Another open-label trial studied a total of 22 children taking melatonin 3 mg for the prevention of migraine ($n = 14$) and chronic tension-type headache ($n = 8$) during a 3-month period. The number of headache attacks significantly reduced in all headache types (106). A parallel, open-label study in 80 children showed amitriptyline 1 mg/kg was more effective ($p = 0.04$) than melatonin 0.3 mg/kg (107). In a survey of headache treatments used in tertiary Italian pediatric headache services, flunarizine was the most frequently used drug (18%), followed by melatonin (10%), antiepileptic drugs (7%) and pizotifen (6%) (108).

Melatonin in cluster headaches, other TACs and other primary headaches

Besides migraine, melatonin has been reported in the treatment of other headache disorders, cluster headaches, trigemino-autonomic cephalgias, hypnic headaches, primary stabbing headaches and tension-type headaches.

A double-blind, placebo-controlled trial in episodic cluster headache patients showed a decrease in headache frequency and analgesic consumption in the group treated with 10 mg melatonin compared with placebo (109), reports in chronic cluster headache patients also showed good response (110). Studying delayed sleep phase syndrome patients with primary headache disorders, including migraine, tension-type and also one cluster headache patient improved, with melatonin therapy adjusting the sleep rhythm (111).

Indomethacin-responsive headaches have been claimed to be good candidates for melatonin supplementation (112), since both share similar chemical structures (113). Case reports have been published showing melatonin efficacy in hemicrania continua (114,115), paroxysmal hemicranias (116), LASH syndrome (117) idiopathic stabbing headache (118,119), and hypnic headaches (53).

Pineal gland abnormalities and headache disorders: Pineal cysts, calcification and tumors

Headaches are associated with pineal lesions, cysts or tumors. Pineal cysts have been more often diagnosed with the increase and widespread use of high-resolution brain imaging in headache disorders (120). In autopsy series and during MRI evaluation, pineal cysts unrelated to headache have been reported in between 25–40% and 1.5–10.8% of cases, respectively (121).

Large pineal cysts may lead to hydrocephalus, resulting in a secondary headache, but case series and controlled studies have demonstrated the possible link between pineal cysts and headache mechanisms other than intracranial hypertension (47). Small cysts may, rarely, grow or present intracystic haemorrhage.

An initial report of five patients with pineal cysts and headache disorders hypothesized a melatonin secretion dysfunction as a possible cause in those cases (122). Pineal cysts are more common in middle-aged women; in this series, they were reported in four women and one man, mean age 37.6. The mean cyst diameter was 10.1 mm. Two patients had migraine without aura, one migraine with aura, one chronic migraine, and one hemicrania continua. Three patients had strictly unilateral headaches. In a man with pulsatile headache and a pineal cyst with a low nocturnal concentration of melatonin, the supplementation abolished the headaches, suggesting some role of melatonin in the headache mechanism (123).

A case control study of 51 patients with pineal cysts and healthy individuals (mean age 38) showed that headache disorders were twice as prevalent in patients with pineal cysts (52 vs. 26%). A high proportion of migraine with aura was found in pineal cyst patients (14 vs. 2%) (124).

Pineal calcification has also been related to migraine. In a study of 503 patients with migraine and 500 headache-free individuals, calcifications seen on computed tomography were significantly more common in migraine patients (80.6%) than in controls (55%) (125). Pineal calcification, however, has been a marker of pineal function and not a dysfunction or degeneration as found in other organs; this finding needs further replication.

Pineal gland tumors are rare, comprising nearly 1% of all brain tumors. Germ cell, parenchymal tumors,

gliomas, and papillary tumors are the main histological varieties (126). Headaches secondary to intracranial hypertension are reported, but limited information is available on headache features, as pinealectomized patients' follow-up regarding headache occurrence is an area for further investigation.

Conclusion

The pineal gland and its main secretory product, melatonin, may play a role in the pathophysiology of headache disorders. Melatonin treatment has been used in many headache disorders. Further studies are necessary for a better understanding of this research topic.

Article highlights

- Experimental and clinical evidence strongly suggest a role for melatonin in the pathophysiology of headache disorders.
- Melatonin decreases CGRP release.
- Melatonin supplementation is useful for headache treatment in certain scenarios; melatonin receptor agonists are potential candidates for future research.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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