

REVIEW

Melatonin, the pineal gland and their implications for headache disorders

MFP Peres

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There is now evidence that melatonin may have a role in the biological regulation of circadian rhythms, sleep, mood, and ageing. Altered melatonin levels in cluster headache and migraine have been documented. Melatonin mechanisms are related to headache pathophysiology in many ways, including its anti-inflammatory effect, toxic free radical scavenging, reduction of proinflammatory cytokine up-regulation, nitric oxide synthase activity and dopamine release inhibition, membrane stabilization, GABA and opioid analgesia potentiation, glutamate neurotoxicity protection, neurovascular regulation, serotonin modulation, and the similarity of chemical structure to that of indomethacin. Treatment of headache disorders with melatonin and other chronobiotic agents is promising. A double-blind, placebo-controlled trial shows melatonin is effective in cluster headache prevention, other studies also show benefit in other disorders. Melatonin plays an important role in headache disorders, offering new avenues for studying their pathophysiology and treatment. □*melatonin, pineal gland, migraine, cluster headaches, pathophysiology, treatment*

Mario Fernando Prieto Peres, Av. Albert Einstein 627, 05651-901 São Paulo, SP Brazil. Tel. + 55 11 9606 6184, fax + 55 11 3285 5726, e-mail marioperes@yahoo.com Received 4 May 2004, accepted 27 August 2004

Introduction

Life on the planet Earth is under 24-h rhythmicity, the day–night cycle, due to the rotation of the Earth on its axis. It is also under the circannual rhythm, due to the translation movement, generating a different day–night ratio according to the place's latitude, and the seasons of the year (1). The nervous system evolved over the milenia to meet the demands of environmental conditions, including the light–dark cycle, in order to assure survival and reproduction of living organisms. It has been demonstrated in past decades that the circadian biological rhythm is not only the response to the 24-h day–night environment but is also due to a system in the brain (2). A synchronization system to adapt the internal to the external environment is one of the key elements of the central nervous system to maintain life.

Three centuries ago, the French philosopher Rene Descartes described the pineal gland as 'the seat of

the soul', but it was not until the late 1950s that melatonin, the principal substance secreted by the pineal gland, was identified (3). It was no longer accepted as a vestigial organ.

The pineal gland and its main secretory product, melatonin, are the main elements in the synchronization of internal biological events to the environment. Melatonin is absent during the day in men and its nocturnal secretion is the main biological event signalling to the organism when it is night.

There is increasing evidence that headache disorders have many connections with melatonin secretion and pineal function. In this paper we overview the putative role of melatonin in the pathophysiology and treatment of headache disorders.

Pineal gland and melatonin

In humans, the pineal gland lies in the centre of the brain, behind the third ventricle. Because of its pine

shape format the organ was called the 'pineal' gland. The gland is usually 8 mm in diameter, weighting 1 g (4). It consists of two types of cells: pinealocytes, which predominate and produce both indolamines (melatonin) and peptides (such as arginine vasotocin), and neuroglial cells (5). The gland is highly vascular. Melatonin is a derivative of the essential amino acid tryptophan. The pinealocytes are the principal location for melatonin biosynthesis, after its uptake into cells. Tryptophan is first hydroxylated and then decarboxylated, resulting in the formation of 5-hydroxytryptamine (serotonin) (6). Serotonin is N-acetylated, with the resulting formation of N-acetylserotonin which is subsequently O-methylated to form melatonin (6). Melatonin is present in the earliest life forms and is found in all organisms including bacteria, algae, fungi, plants, insects, and vertebrates including humans. In all species melatonin synthesis exhibits a circadian rhythm (7).

Once melatonin is synthesized in the pineal gland, it is quickly released, generating a blood melatonin rhythm reminiscent of that seen in the gland. Being an amphiphilic molecule, melatonin is capable of entering every cell in the organism; additionally, it readily crosses all morphophysiological barriers, including, the blood-brain barrier and the placenta (8). Melatonin is enzymatically degraded in the liver to 6-hydroxymelatonin (5) and finally excreted in the urine as 6-sulphatoxymelatonin. Urine analysis is widely used as a measure of melatonin secretion, since it is correlated with the nocturnal profile of plasma melatonin secretion (9).

Melatonin was first identified in bovine pineal tissue (10) and has been subsequently portrayed exclusively as a hormone. Recently accumulated evidence has challenged this concept. Several characteristics of melatonin distinguish it from a classic hormone, such as its direct, non-receptor-mediated free radical scavenging activity (11). As melatonin is also ingested in vegetables, fruits, rice, wheat and herbal medicines, from the nutritional point of view melatonin can also be classified as a vitamin. It seems likely that melatonin initially evolved as an antioxidant, becoming a vitamin in the food chain, and in multicellular organisms, where it is produced, it has acquired autocoid, paracoid and hormonal properties (12).

A family of receptors for melatonin on cell membranes has recently been cloned (13). The distribution of the receptors seems to be broad, species-specific, and G-protein-coupled. Principally, there are three high-affinity melatonin receptors, MEL1a, MEL1b, and MEL1c, of which the first two are found in humans. The gene for MEL1a receptor is localized

into human chromosome 4q35.1 (14) and is present in both kidney and intestine. MEL1b receptor is mapped to human chromosome 11q21-22 (15).

At present, indications for melatonin therapeutic applications include sleeping disorders, circadian rhythm disorders, insomnia in blind people, insomnia in elderly patients, ageing, Alzheimer disease and as an adjuvant in cancer therapy (16).

Relevance of melatonin and chronobiology in neurology

Chronobiological disorders occurring in men can be divided in two types: (i) the environmental or external variety, due to life style or environment, as in shift workers, individuals crossing time zones in jet lag syndrome, and in maladaptation to daylight savings; (ii) the endogenous or internal type, including the delayed and advanced sleep phase syndromes, and the non-24-h sleep-wake disorder with free-running circadian rhythm (2). It has been proposed the endogenous type may underlie many conditions including depression, chronic fatigue, fibromyalgia, and migraine (17).

Sleep is well known to play an important role as a restorative function. In human beings, it has a circadian rhythm, normally occurring at night, usually together with nocturnal melatonin secretion (18). This has led to the idea that melatonin is an internal sleep facilitator in humans, and therefore useful in the treatment of insomnia and the readjustment of circadian rhythms. There is evidence that administration of melatonin is able to induce sleep when the drive to sleep is insufficient; to inhibit the drive for wakefulness from the suprachiasmatic nuclei (SCN); and induce phase shifts in the circadian clock such that the circadian phase of increased sleep propensity occurs at a new, desired time (19).

Many neurological disorders occur with a marked rhythmicity, dependent either on the 24-h or on the seasonal cycle. Thus maladaptation is probably linked to pineal function and melatonin secretion, including stroke, multiple sclerosis, facial paralysis, and seasonal affective disorder (2, 20).

The pineal gland is a fotoneuroendocrine organ, converting external luminous stimuli into a hormone secretion, being responsible for the synchronization between internal homeostasis and the environment. Consequently, an altered synchronization system may interfere with all neurological diseases. Sleep and circadian rhythms are often disrupted in people with neurological disorders (21). The symptoms associated with neurological disease may be due in part to disruption of the sleep-wake

cycle. Alternatively, various neurological disorders may themselves disrupt the sleep–wake cycle, resulting in a positive feedback loop whereby disrupted sleep and wake exacerbate the neurological disorders while the disease itself has a negative effect on the sleep–wake states (22).

Symptoms associated with those disorders may fluctuate according to a specific rhythm (circannual, circamensual, circadian) and are often related to either sleep or wake periods. Epilepsy, dementia, movement disorders, multiple sclerosis, cerebrovascular disorders, neuromuscular disorders and brain tumours have all been linked to an altered chronobiology, melatonin dysfunction, or benefited from melatonin treatment (21). Primary headaches also follow this rule. Migraines, cluster headaches, indomethacin-responsive headaches and hypnic headaches have all been related to melatonin dysfunction.

Melatonin and migraine

Melatonin and migraine are linked in several ways. Clinical symptoms may fluctuate, some patients reporting their headaches predominantly or specifically at a certain period of the day. Both episodic (55%) and chronic (62.5%) migraineurs reported waking up in the morning with headaches or being woken up at night by the headache (23). In addition,

headaches occurring in the morning period have been attributed to sleep disorders (24). A distribution of migraine attacks according to the oestrous cycle is evident in migraine. True menstrual migraine occurs in 14% of migraineurs (25). Menstrually associated migraine can occur in up to 55% of cases (26). A circannual variation can be observed in cyclic migraine (27) or in the cluster–migraine association (28).

Peres et al. (29) studied chronobiological features in 200 chronic or episodic migraine patients; 93 (46.5%) reported headaches after changing the sleep schedule. A significant delay was presented in 54% of patients, ranging from –2.5 to +5.0 h. Most patients (69%) delayed the sleeping phase, as opposed to those (31%) who advanced it. Individuals shifts above 2 h represented 12.5% of patients. There is much evidence for the relevance and impact of changes in biological rhythm in migraine patients, and also the possible opposite effect of migraine in the sleeping schedule of patients.

Melatonin was first studied in migraine patients by Claustrat et al. (30), in 1989, showing lower plasma levels in samples from patients drawn at 23.00 h compared with controls (studies are summarized in Table 1). Migraine patients without depression had lower levels than controls, but migraineurs with superimposed depression exhibited the greatest melatonin deficiency. Murialdo

Table 1 Clinical studies performed with melatonin in headache disorders

Author	Year (reference)	Disorder	Dosage type	Dose administered	Results
Claustrat et al.	1989 (30)	Migraine	Plasma	–	Lower levels in patients vs. controls
Murialdo et al.	1994 (31)	Migraine	Urinary	–	Lower levels during attacks
Brun et al.	1995 (32)	Migraine	Urinary	–	Lower levels
Peres et al.	2001 (33)	Chronic migraine	Plasma	–	Peak delayed, lower levels in insomnia
Claustrat et al.	1997 (34)	Status migrainous	Plasma	I.v. infusion	Disrupted rhythm, headache relief
Nagtegaal et al.	1998 (35)	DSPS	–	5 mg PO	Improvement in CTTH, migraine and cluster
Chazot et al.	1984 (38)	Cluster headache	Plasma	–	Decrease in nocturnal levels
Waldenlind et al.	1987 (39)	Cluster headache	Plasma	–	Lower levels during bouts vs. remission
Waldenlind et al.	1994 (40)	Cluster headache	Urinary	–	Lower levels in smokers
Leone et al.	1995 (41)	Cluster headache	Plasma	–	Rhythm disruption in patients
Leone et al.	1996 (44)	Cluster headache	–	10 mg PO	Effective in double-blind placebo-controlled trial
Peres & Rozen	2001 (45)	Chronic cluster	–	9 mg PO	Effective in two refractory patients
Capo & Esposito	2001 (49)	Hypnic headache	–	3 mg PO	Good response
Rozen	2003 (52)	Hemicrania continua	–	9 mg PO	Complete response
Rozen	2003 (53)	Idiopathic stabbing headache	–	9 mg PO	Complete response

DSPS, Delayed sleep phase syndrome; CTTH, chronic tension-type headache.

et al. (31) also found nocturnal urinary melatonin to be significantly decreased throughout the ovarian cycle of migraine patients without aura compared with controls. During the luteal phase, when melatonin levels should normally increase, migraine patients showed a less pronounced change when compared with controls. Melatonin excretion was further decreased when patients suffered a migraine attack.

Brun et al. (32) studied urinary melatonin in women with migraine without aura attacks associated with menses and controls. Melatonin levels throughout the cycle were significantly lower in the migraine patients than in controls. In the control group, melatonin excretion increased significantly from the follicular to the luteal phase, whereas no difference was observed in the migraine group. Melatonin may be implicated in the pathogenesis of menstrual migraine.

Peres et al. (33) studied the plasma melatonin nocturnal profile. Thirteen sets of samples were collected hourly from 19.00 h to 7.00 h in chronic migraine patients and controls. Lowered melatonin levels in patients with insomnia were observed compared with those without insomnia, and a phase delay in the melatonin peak in patients vs. controls, suggesting a chronobiological dysfunction in chronic migraineurs.

Only small studies showed a benefit in migraine patients treated with melatonin. Claustrat et al. (34) studied the nocturnal plasma melatonin profile and melatonin kinetics during melatonin infusion in six patients with status migrainous. Individual plasma profiles were disturbed in three migraine patients; two had a phase delay and one a phase advance. Four of the six patients reported headache relief the next morning after melatonin infusion began and the remaining two patients did so after the third night of infusion. In addition, three patients described that during migraines there was a decrease in the pulsatility of pain.

Another study (35) investigated the effects of melatonin on varying headaches and their relation to delayed sleep phase syndrome (DSPS). Thirty DSPS patients were treated; in one patient with migraine, attacks dramatically decreased after beginning melatonin treatment. One patient was successfully treated during a migraine attack by means of external (pico Tesla) magnetic fields (36).

Melatonin may be implicated in the pathogenesis of migraine, menstrual migraine, cyclic migraine and chronic migraine. It might also play a role in migraine comorbid disorders, particularly depression and insomnia.

Melatonin and cluster headaches

It has been suspected that melatonin may be involved in cluster headache genesis, primarily because melatonin is a sensitive marker of endogenous rhythms, which are disrupted in cluster headache (37).

In 1984, Chazot et al. (38) detected a decrease in nocturnal melatonin secretion and abolished melatonin rhythm in cluster headache patients. Waldenlind et al. (39) also showed lowered nocturnal melatonin levels during cluster periods than remissions. Determining urinary levels of 6-sulphatoxymelatonin throughout the year, Waldenlind et al. (40) found higher melatonin levels in women than in men. Swedes had higher melatonin levels than Italians, and smokers lower levels than non-smoking cluster headache patients. Leone et al. (41) observed melatonin and cortisol peaks significantly correlated in controls but not in cluster headache patients, indicating a chronobiological disorder in these patients.

Blau and Engel (42) found that increases in body temperature from exercise, a hot bath or elevated environmental temperature triggered cluster headaches in 75 of 200 cluster headache patients. This finding can be explained by a decrease in melatonin secretion caused by temperature increase (43). Melatonin for cluster headache prevention was then studied in a double-blind, placebo-controlled trial by Leone et al. (44), with a significant decrease in cluster headache attacks in the melatonin-treated group compared with placebo. Two patients with chronic cluster headache in the trial did not respond to melatonin therapy, but Peres and Rozen (45) described two chronic cluster headache patients who responded to melatonin 9 mg at bedtime. Melatonin prevented not only nocturnal cluster attacks but also daytime attacks. Nagtegaal et al. (46) studying melatonin treatment in delayed sleep phase syndrome identified a patient with episodic cluster headache in whom both disorders improved after melatonin treatment. Melatonin plays an important role in the pathophysiology and treatment of cluster headaches.

Melatonin and other headaches disorders

Hypnic headache is a benign, recurrent headache disorder that occurs only during diurnal and nocturnal sleep. Headaches are often frequent, usually occurring every night, with striking consistency the same time every night (47). Hypnic headache is typical in the elderly. Since melatonin secretion significantly declines with ageing, one may speculate that melatonin deficiency is a possible cause of hypnic headache (48). Few reports have shown

improvement with melatonin treatment. Good response was detected in three patients, although no controlled trial has been conducted so far (49). Martins and Gouveia (50) reported a case of hypnic headache associated with traveling across time zones: a 68-year-old woman flew from Portugal to Brazil, shifting 3 h in her sleep phase. The time zone shift was considered the trigger for the hypnic headaches. Melatonin was not given to the patient.

Peres et al. (51) described a patient with hemicrania continua with seasonal variation, proposing that the similarity of melatonin's chemical structure to that of indomethacin could be one of the possible mechanisms of action involved in indomethacin-responsive headaches. Rozen (52) reported the case of a hemicrania continua patient who responded to melatonin 9 mg, and described three idiopathic stabbing headache patients treated with melatonin with excellent clinical response and side-effect profile (53). Future studies will clarify the role of melatonin in indomethacin-responsive headaches and hypnic headaches.

Headaches, pineal cysts, and other chronobiological disorders

Pineal cysts are common findings in neuroimaging studies, found in 1.3–2.6% of brain magnetic resonance imaging (MRIs). Sawamura et al. (54) examined brain MRIs of 6023 consecutive patients finding pineal cysts (>5 mm) in 1.3% of patients imaged. The cysts predominantly occurred in females; 29 cysts in 3008 males (0.96%) and 50 cysts in 3015 females (1.65%). Young women between the ages of 21 and 30 years (the decade of life migraine increases its prevalence three-fold) had the highest frequency (5.82%). All the studies showing high prevalence of pineal cysts in brain MRI are biased by the recruitment criteria, usually not controlling for the reason (neurological signs or symptoms) the examination was ordered. Only one study (55) showed what should be the right incidence of pineal cysts analysing 1000 asymptomatic volunteers. Incidental pineal cysts were found in brain MRI of only two patients (0.2%).

Pineal region lesions (benign, malignant tumours or cysts) can be clearly symptomatic, when the lesion size (usually >15 mm) compromises other brain structures, causing hydrocephalus. Headache is the most common symptom. Unilateral headaches has been reported in pinealectomized subjects (56).

Mandera et al. (57) analysed 24 paediatric patients (17 girls, mean age 9 years, and seven boys, mean age 14 years) with pineal cysts and found an abnor-

mal melatonin secretion profile. Wober-Bingol et al. (58) found two pineal cysts (2.1%), 7–8 mm, in 96 headache patients with MRI incidental findings. One patient had migraine without aura, another chronic tension-type headache. Follow-up of 16 months in both patients revealed no change in headache frequency and pattern, suggesting the benign nature of the lesion.

Peres et al. (59) reported five headache patients with pineal cysts, four women and one man, whose cysts ranged from 8 to 13.5 mm. Two patients had migraine without aura, one had migraine with aura, one chronic migraine, and one hemicrania continua. Three patients had strictly unilateral headaches. Pineal cysts may be not incidental in headache patients; abnormal melatonin secretion might hypothetically be involved in the mechanism of those patients; however, this has yet to be determined.

Jet lag is a travel-induced circadian rhythm phenomenon that afflicts healthy individuals following long-distance flights through several time zones. Typical symptoms are daytime sleepiness, fatigue, impaired alertness, headaches, irritability, loss of appetite, decrease in physical performance and difficulty in initiating and maintaining sleep. It is attributed to transient desynchronization in the circadian rhythm until the internal biological clock is rephased to the new environmental conditions (60). Headache features, diagnosis and impact have never been properly studied in patients with jet lag syndrome. Peres et al. (29) studied migraine patients reporting frequent travelling across time zones, most of whom (79%) reported worse headaches after such journeys.

Shift work involves a substantial employed population worldwide. Pucci et al. (61) studied 157 employees, finding primary headaches in 26.7%, shift work being a major risk factor. Ho & Ong (62) studying 2096 individuals in a randomized survey in Singapore found that individuals who performed shift work had more frequent headaches. Peres et al. (29) found 86% of migraineurs had their headaches made worse after shift work.

Delayed and advanced sleep phase syndromes (DSPS, ASPS) are chronic, long-term circadian schedule disorders. Various primary headaches were found in DSPS patients (46): three women had chronic tension-type headache, one patient migraine with aura, one cluster headache. Their headaches decreased dramatically after melatonin 5 mg therapy.

Mechanisms

Melatonin may play a role in headache pathophysiology by several mechanisms (Table 2).

Table 2 Melatonin mechanisms potentially related to headache disorders

Anti-inflammatory effect
Toxic free radical scavenging
Nitric oxide synthase activity inhibition
Dopamine release inhibition
Membrane stabilization
Similar chemical structure to indomethacin
GABA potentiation
Opioid analgesia
Glutamate neurotoxicity protection
Neurovascular regulation
Serotonin modulation

Melatonin has been shown to possess anti-inflammatory effects, among many others actions. By virtue of its ability to directly scavenge toxic free radicals (6), it reduces macromolecular damage in all organs. The free radicals and reactive oxygen and nitrogen species known to be scavenged by melatonin include the highly toxic hydroxyl radical ($\cdot\text{OH}$), peroxyxynitrite anion (ONOO^-), and hypochlorous acid (HOCl), among others. Melatonin also prevents the translocation of nuclear factor-kappa B ($\text{NF-}\kappa\text{B}$) to the nucleus and its binding to DNA, thereby reducing the up-regulation of a variety of proinflammatory cytokines, interleukins and tumour necrosis factor-alpha (63). Melatonin inhibits the production of adhesion molecules that promote the adhesion of leucocytes to endothelial cells, attenuating transendothelial cell migration and oedema (64).

Melatonin inhibits the activity of nitric oxide synthase (65), besides playing a role in membrane stabilization (66).

Inhibition of dopamine release by melatonin has been demonstrated in specific areas of the mammalian central nervous system (hypothalamus, hippocampus, medulla-pons, and retina) (67). A growing body of biological, pharmacological, and genetic data supports a role for dopamine in the pathophysiology of migraine (68).

Melatonin has been related to GABA and glutamate neurotransmission, and both to headache pathophysiology (69). It is thought that the hypnotic activity of melatonin is mediated by the GABAergic system (70). Melatonin rapidly and reversibly potentiated the GABA-A receptor-mediated response (71). Neuroprotection by melatonin from glutamate-induced cytotoxicity during development of the brain (72), and the antagonistic effects of melatonin on glutamate release and neurotoxicity in the cerebral cortex (73) have been reported.

Melatonin induces activated T lymphocytes to release opioid peptides with immunoenhancing and antistress properties. A melatonin-immuno-opioid network has been proposed. Cytokines named melatonin-induced-opioid (MIO) have been found to act on an opioid-binding site. Since melatonin may behave as a mixed opioid receptor agonist-antagonist, it is possible to potentiate the opioid analgesic efficacy (74). Melatonin is also involved in cerebrovascular regulation (75), and modulation of serotonin neurotransmission (spontaneous efflux and evoked release) (76).

In light of recent discoveries in headache mechanisms, we hypothesize that melatonin may interfere in cortical spreading depression, probably via its effect on the nitric oxide (NO), GABA and glutamatergic systems. Second, the mechanisms involved in the pathophysiology of migraine and psychiatric comorbid disorders may be linked to the serotonergic and dopaminergic systems.

Perspectives

Further studies are necessary for a better understanding of the role of melatonin in the pathophysiology and treatment of headache disorders. A more careful clinical examination of circadian and circannual variation in primary and secondary headaches in different latitudes is needed, as is the study of headache diagnosis, impact, and treatment response in chronobiological disorders. Animal models of cephalic pain and the genetics involved in chronobiological rhythms are important tools for further research.

Treatment of headache disorders with melatonin is promising, particularly in cluster headaches, hypnic headaches, indomethacin-responsive headaches, and migraine. Melatonin may also be important in migraine comorbidity. Insomnia in headache patients is the most likely associated condition in migraine to respond to melatonin therapy. Decreased melatonin levels may predict response to melatonin treatment, as occurs in insomnia associated with other diseases (77). Other chronobiotic agents, such as melatonin receptor agonists, light therapy, and magnetic fields can also be tested.

Melatonin has the potential to interfere in many biological processes and illnesses, not only in the brain. Given that melatonin has this potential, the question arises, how specific is the role of melatonin in headache disorders? Knowledge of melatonin has increased recently and at this stage it is vital to address this issue of specificity.

Melatonin is a molecule responsible for synchronization between the organism and the environment. Its mechanisms are in general modulatory. The melatonergic system is then not likely to be more specific than any of the other systems (serotonergic, dopaminergic, glutamatergic, GABAergic or NO) in the brain for headache disorders. One pathway for a more specific role is the discovery of new receptors for the melatonergic system, and more research linking melatonin and headache mechanisms.

Melatonin plays an important role in headache disorders, offering new avenues for studying their pathophysiology and treatment.

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