The Therapeutic Potential of Melatonin in Migraines and other Headache Types

Joel J. Gagnier, ND

Abstract

A large number of individuals suffer from migraine headaches. Several theories attempt to explain migraine etiology. One such theory holds that since environmental stimuli are well known to trigger migraine headaches, the pineal gland may be involved in migraine etiology. Specifically, a pineal gland irregularity may be the physical origin of migraine headaches, with subsequent physiological changes being secondary. Research has found the pineal hormone melatonin is low in migraine patients. Additionally, several studies found administering melatonin to migraine sufferers relieved pain and decreased headache recurrence in some cases. It has been suggested melatonin may play an important therapeutic role in the treatment of migraines and other types of headaches, particularly those related to delayed sleep phase syndrome. Current research supports the hypothesis that migraines are a response to a pineal circadian irregularity in which the administration of melatonin normalizes this circadian cycle; i.e., melatonin may play a role in resynchronizing biological rhythms to lifestyle and subsequently relieve migraines and other forms of headaches. In addition, research testing the administration of melatonin found it safe in migraine sufferers, with few or no side effects. However, a larger, randomized control trial is needed to definitively determine if administration of melatonin to migraine patients is effective.

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Introduction

In the United States, approximately 24 million individuals suffer from migraine headaches.[1] These occur more often in women than men, between the ages of 10 and 40, and often remit after age 50. In addition, there appears to be some familial origin. A migraine headache is defined as, "a benign recurring headache and/or neurologic dysfunction usually attended by pain-free interludes and often provoked by stereotyped stimuli. A migraine may be identified both by its activators (red wine, hunger, lack of sleep, glare, perfume, periods of letdown) and its deactivators (sleep, pregnancy, exhilaration, sumatriptan.")[2] A migraine headache can last 4-72 hours, is throbbing, moderate to severe in intensity, and unilateral; becomes worse with exertion; and is associated with nausea, vomiting, and sensitivity to light, sound, and smell.[1] Subcategories include common migraine, classic migraine, basilar migraine, and carotidynia.[2]

Joel J. Gagnier, BA (Hons), ND – Currently completing a M.Sc. in Clinical Epidemiology and Health-Care research at the University of Toronto under a Post-Graduate Fellowship from the Canadian Institute of Health Research and the Office of Natural Health Products. Correspondence address: 34 Blackwillow Way, North York, Ontario, Canada M2J 2A8. Email: j_gagnier@hotmail.com

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Theories of Migraine Pathophysiology

Several theories have attempted to explain migraine etiology.[2,3] Wolff[4] and Graham[2] postulated that the aura associated with a classic migraine was due to intracerebral vasoconstriction and the headache due to reflex vasodilation. This "vascular" hypothesis was deemed valid for many years;[2] although, as Sandyk[3] pointed out, "The theory was not supported by evidence from cerebral blood flow studies."[4-7]

Sicuteri[8] postulated that a decrease in serotonin was responsible for the pain associated with a migraine and that the dilation of vessels was nonessential. This theory is supported by the alleviation of symptoms with administration of serotonin precursors, the production of symptoms with 5-hydoxytryptophan (5-HTP) synthesis inhibitors, and the alleviation of symptoms with 5-HT1 receptor agonists such as sumatriptan.[2,9-11] Raskin[2] notes that the dorsal raphe, having the highest concentration of serotonin receptors in the brain parenchyma, may be the midbrain trigger for migraine.

In the 1940s, Lashley, Leao, and a host of other researchers thereafter, described a spreading neuronal depression across the occipital and cerebral cortex preceded by an excitatory wave-front.[2,12-15] More recent research describes a spreading wave of neuronal depression originating in the posterior cerebral regions.[16] Support for this theory abounds in cerebral blood flow (CBF), electroencephalogram (EEG), and magnetoencephalographic studies,[17-24] and suggests migraine etiology is due to a brain parenchymal disturbance leading to a spreading depolarization with vascular reactions being secondary.

Raskin outlines three mechanisms and anatomic regions that summarize the current understanding of the pathogenesis of migraine. "First, there is a vasomotor component mediated by constriction or dilation of arteries within and outside the brain. Second, there is a midbrain trigger, perhaps in serotonergic neurons of the dorsal raphe. Third, there is activation of a trigeminal vascular system, consisting of medullary neurons in the trigeminal nucleus caudalis that terminate on the walls of arteries and release neuroactive peptides."[2]

Some researchers have posited an environmental etiology since factors such as light, noise, smell, temperature, and humidity appear to contribute to migraine onset.[3] They suggest, in addition, that periodicity and seasonal fluctuations support an environmental etiology to migraine.[3,25-29] It has been hypothesized that the pineal gland is the connection between migraine headaches and environmental triggers, and that the causative neuroactive chemical is a hormone.[3,30-31]

The Pineal Gland, Melatonin, and the Migraine Connection

The pineal gland is considered a photoneuroendocrine transducer that translates environmental information into neuroendocrine molecules.[3,30-31] Brun et al[30] explain that melatonin, an indole compound, is the net result of this transduction. Melatonin is synthesized from serotonin via the enzyme N-acetyltransferase, which is emitted in a circadian cycle from the suprachiasmatic nucleus.[30] Also, the suprachiasmatic nucleus receives photic stimuli via the retinohypothalamic tract.[30] Of interest is Jacobsen's description of an oculocephalic sympathetic abnormality associated with migraine sufferers, the neural pathway of which regulates the secretion of melatonin by the pineal gland.[31]

Biochemical Studies of Melatonin and Migraines

A study to examine melatonin levels in migraine sufferers utilized 93 patients with headaches (75 women and 18 men; 38 with common migraine, 12 with ophthalmic migraine, 24 with either of the latter together with

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tension headache, and 19 with superimposed depression) and a control group consisting of 46 subjects (22 male and 24 female).[33] Groups were matched for sex and age and told to maintain the same light synchronization for two weeks before the study (lights off between 11 p.m. and 7 a.m.). Blood samples were drawn under low light at 11 p.m. and plasma melatonin measured in both groups. The entire migraine group had lower nocturnal plasma melatonin levels than the control group ($p<0.001$). More specifically, migraine sufferers without depression had lower nocturnal plasma melatonin levels than controls ($p<0.01$), and migraine patients with superimposed depression ($p<0.001$) exhibited the greatest deficiency of melatonin compared to the control group. Interestingly, this study found only females had significantly lower levels of nocturnal melatonin excretion (female patients: 0.29 ± 0.05 nmol/hr; male patients: 0.48 nmol/hr; $p<0.02$). The authors explain the lack of significance in the male group to be a result of the smaller sample size and conclude, "the abnormal melatonin level we report here could reflect a global sympathetic hypofunction – which has been demonstrated by hemodynamic and pharmacological tests in migraine – and/or a chronobiological abnormality." In light of this information the authors note melatonin could potentially act as a biochemical marker for migraine.

In another study, Brun and colleagues collected urine samples (between 7 p.m. and 7 a.m.) throughout an entire menstrual cycle, and measured melatonin levels in 10 female patients suffering menstrually associated migraines without aura. Controls consisted of nine females matched for age, body surface area, length of cycle, and fertility.[30] Compared to controls, the migraine patients had lower mean nocturnal melatonin throughout the entire menstrual cycle with no differences between luteal and follicular phases, whereas controls displayed only lower follicular phase melatonin. No correlation was found between time of headache or intensity of pain and nocturnal melatonin excretion. The highest levels of melatonin in migraine patients were during menses; the authors note this could reflect rhythmic changes due to pain and/or dyssomnia. However, since lower levels of melatonin were noted outside attacks, the authors speculated that decreases of melatonin might serve as a marker of impending migraine. The authors conclude that the abnormality of melatonin secretion in migraine patients over the entire cycle could be a sympathetic hypofunction and represent a "vulnerability of the rhythmic organization of the central nervous system."

Murialdo and colleagues looked at urinary excretion of melatonin in 12 female patients with menstrually-related migraines without aura and in eight controls who were headache-free healthy women.[34] Patients and controls were matched for body weight, body mass index, and daily activity, yet differed in mean age (controls: 28 ± 5.1 years; migraine patients: 36.7 ± 6.7 years). Menstrual cycles were similar among patients. The mean duration of illness in the migraine sufferers was 14.8 ± 6.4(SD) years, and patients did not take oral contraceptives or hormonal medication during the study or six months prior. They were, however, allowed small doses of nonsteroidal anti-inflammatories during severe migraine attacks. Nocturnal (20.00-08.00) and daytime (08.00-20.00) urine melatonin measurements were collected. Using a multiple criteria analysis of variance on the data, melatonin levels in patients (i.e., migraine sufferers) were found to be significantly lower than controls overall ($p = 0.0001$) and in all phases of the menstrual cycle. Also, mean urine melatonin levels measured during pain episodes ($n=51$) were significantly lower than during pain-free periods ($n=143$; 70.1 ± 12.8 vs 93.7 ± 10.7; $p = 0.033$, for pain vs pain-free periods, respectively). Overall, there was less melatonin in the migraine patients than controls and a further decrease in melatonin

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Table 1. Biochemical Studies of Melatonin and Migraines

Reference	Sample	Outcomes/Findings
33	Experimental: 75 female, 18 male (38 with common migraine) Control: 46 (22 male, 24 female)	1.) lower nocturnal plasma melatonin 2.) only women showed lower melatonin
30	Experimental: 10 females with migraines without aura. Control: 9 females	1.) lower nocturnal plasma melatonin through entire cycle 2.) highest melatonin in migraine patients was during menses
34	Experimental: 12 female patients with migraines without aura Control: 8 headache-free healthy women	1.) lower nocturnal and daytime melatonin in migraine patients 2.) melatonin during migraine attacks was lower

in the patients during attacks. The authors state that, "Sympathetic dysfunction in migraine, enhanced during the acute pain attack, could explain the decreased urinary levels of melatonin in our patients and the further fall in indole excretion during headache episodes."[34] Overall, these results are consistent with those presented above.

Although only three studies could be found that directly test melatonin in migraine patients, together they suggest female migraine sufferers have decreased nocturnal plasma melatonin levels both overall and during migraine attacks. More research is needed to clarify the results summarized in Table 1.

Melatonin Administration and Migraine

A small study by Claustrat et al looked at nocturnal plasma melatonin profile and melatonin kinetics during melatonin infusion in migraine patients.[35] The study consisted of 15 female patients: six current headache sufferers and nine healthy controls. The two groups were matched for age and fertility. In this open trial all 15 patients received a saline solution between 8 p.m. and 1 a.m. on the first night (N_0) and melatonin infusions of 20 ug at 4 ug per hour (9 p.m. to 1 a.m.) the next three nights (N_1,N_2,N_3). Blood was sampled between 8 p.m. and 8 a.m. at 20-minute intervals. Individual plasma profiles were disturbed in three migraine patients; two had a phase-delay (a late maximum plasma melatonin level) and one a phase-advance (an early maximum plasma melatonin level). Although four of the six headache patients had increased plasma melatonin, basal melatonin levels were relatively similar between groups. With infusion, two patients with previous phase delay demonstrated a phase advance in melatonin profile.

The authors suggest this finding, together with previous research, supports the

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hypothesis that melatonin may help in the resynchronization of biological rhythms. Four of the six patients reported headache relief the 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. The authors state such symptomatic improvement could be due to any number of the biochemical actions of melatonin: resetting the biological rhythm, relieving anxiety and insomnia, inhibiting prostaglandin synthesis, inhibiting nitric oxide synthesis, depressing calcium uptake, or directly affecting cerebral blood vessels via receptor sites. Although this study was neither blinded nor placebo controlled, melatonin profile changes and symptomatic relief following melatonin infusion support the hypothesis that migraines may be related to a melatonin profile abnormality, and that melatonin administration may be therapeutically indicated in such patients.

Another study investigated the effects of melatonin on varying headaches and their relation to delayed sleep phase syndrome (DSPS).[36] A control melatonin profile was taken in each patient prior to administration of exogenous melatonin. This double-blind, placebo-controlled, cross-over study randomly assigned 30 patients to a placebo group or a 5 mg melatonin group for 14 days, after which they were crossed-over for an additional 14 days. Patients received melatonin for at least three months following the initial 28-day period. Patients were questioned about their headaches at 2 weeks, and 3, 6, 9, and 12 months. A 54-year-old man with DSPS, who had migraine attacks without aura since childhood and twice per week the past five years, reported having only three migraines during the 12 months after beginning melatonin treatment. In addition, one patient with previous cluster headaches of two months duration twice per year for twenty years reported only one headache in the 12 months since beginning treatment. In three patients with chronic tension-type headaches complete disappearance of headaches occurred within two weeks of treatment.

In every DSPS patient the sleep-wake rhythm was advanced after melatonin treatment; i.e., their biological clock was synchronized to their lifestyle, allowing a normalization of sleeping pattern. Since headaches decreased dramatically in DSPS headache patients subsequent to melatonin administration, the authors suggest a causative relationship. However, nocturnal plasma melatonin in all 30 patients was similar and no differences during headache vs headache-free periods were noted. This precludes a melatonin deficiency and suggests melatonin may act to normalize the biological clock to lifestyle.

The authors suggest the decrease in psychological stress associated with lifestyle and biological rhythm synchronization could have decreased headache frequency. This hypothesis is supported by a separate intervention in which the 54-year-old migraine patient had similar decreases in migraine attacks when his lifestyle was adjusted to fit his sleep-wake cycle. This research suggests melatonin may allow relief of headaches associated with DSPS. The authors state, "The case histories described suggest that it may be worthwhile to ask patients with headache about their sleep-wake rhythm. When there is a combination of insomnia and trouble awaking at conventional times, DSPS should be suspected. In case it is impossible to adapt lifestyle to biological clock, it is worthwhile to try to adapt the biological clock to the lifestyle of the patient."[36] For example, melatonin treatment may be one way to resynchronize circadian rhythms to lifestyle and subsequently relieve headaches such as migraine. Studies are summarized in Table 2.

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Table 2. Melatonin Administration and Migraine

Reference	Sample	Melatonin Administration	Outcomes/Findings
35	Experimental: 6 female headache sufferers Control: 9 healthy females	Infusion of 20 ug at 4 ug per hour from 9 pm to 1 am for 3 nights	1.) 4 patients had headache relief after first infusion, 2 patients after 3rd infusion 2.) decreased pain during any migraine attacks
36	30 patients with delayed sleep phase syndrome in a double-blind placebo controlled crossover trial. Patients had varying headache types	5 mg oral for 14 days, then crossover	1.) decrease in migraine frequency in 1 patient 2.) decrease in cluster headache frequency in 1 patient 3.) remission of tension headache in 3 patients

Conclusion

Melatonin may play an important therapeutic role for the treatment of migraines and other types of headaches, particularly those related to delayed sleep phase syndrome. Additionally, this research found no adverse effects of melatonin during either IV infusion or oral administration. However, due to small sample sizes and lack of rigorous study design in the majority of the papers analyzed, no definitive conclusions can yet be made. A multi-centered, randomized, placebo-controlled, cross-over study considering DSPS is encouraged to clarify and further test melatonin's effectiveness in migraine patients. Other research may clarify the role of melatonin in other forms of headache.

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