Plasma melatonin pattern in chronic and episodic headaches. Evaluation during sleep and waking

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On the basis of these different melatonin secretion patterns, it might be hypothesized that the involvement of the hypothalamus in chronic-type headaches differs from that displayed in episodic forms.

KEY WORDS: chronic migraine, chronic tension-type headache, cluster headache, melatonin, sleep stages.

Introduction

The relationship between headaches and sleep disorders is complex and difficult to analyze. Although clinical evidence and numerous studies indicate some sort of relationship, few studies have sought to clarify it (1,2). Headaches and sleep disturbances may show causal relations or mutual reinforcements in the individual patient (3). Changes in sleep duration and in sleep quality appear to be capable of producing headaches of different types (4,5). Cluster headache (CH) and migraine are frequently associated with sleep and sleep disorders (3). Early studies of the physiological effects of melatonin, a neurohormone produced by the pineal gland and regulated by the suprachiasmatic nucleus, typically reported hypnotic effects (6). It has been hypothesized that some headaches may be a response to a pineal circadian irregularity and following this line of thought it may be assumed that melatonin plays a role in the origin of several types of headache. Cluster headaches are characterized by unilateral paroxysmal attacks of severe pain with associated symptoms (6). Cluster periods or “bouts” tend to occur in the spring and autumn, seasons that coincide with marked changes in chronobiological rhythms related, in particular, to changes in the light-dark cycle, which regulates melatonin secretion. The periodicity of CH suggests involvement of the hypothalamic suprachiasmatic nucleus, the main biological pacemaker, or biological clock (7,8). The attacks occur during specific sleep stages, particularly the start of REM sleep, and are associated with other chronobiological factors (9).

Several sleep disorders have been associated with the occurrence of CH (3). Assessments of urinary melatonin levels in patients with CH give contradictory findings (10,11). Chronic migraine (CM) is a complex syndrome associated with many conditions including generalized anxiety disorder (70%) (12), insomnia (71%) (13), and major depression (80%) (12). The causes and mechanisms of CM are obscure: mechanisms allegedly responsible include central sensitization, defective central pain modulation, hypothalamic dysfunction, and a combination of all of these (14). Little is known about the role of pineal gland function in CM pathogenesis (14). The aim of this study was to explore pineal function in pa-
Patients with CH, CM and chronic tension-type headache (CTTH) during the different sleep stages. For this purpose we performed serial sampling of plasma melatonin during NREM sleep, REM sleep and waking in the first half of the night, using polysomnography for sleep staging.

Materials and methods

Thirty patients with primary benign headaches and ten controls, all men, aged 26 to 67 years, were enrolled in this study after they had given their written consent to it. The decision to include only males was made in order to avoid gender differences.

Three groups of patients were studied: CM without drug overuse (n=10; age 30 to 58 years, mean: 44±3), CTTH (n=10; age 36 to 67 years, mean: 46±2), and episodic CH (n=10; age 27 to 59 years, mean: 41±3). The CH patients were studied twice, during cluster and remission periods. The diagnoses were made according to The International Classification of Headache Disorders, 2nd edition (6). The age range of the control group was 26 to 64 years (mean: 44±3) (n=10). No statistically significant differences in age were found among the groups (p=0.2166).

The patients were studied after a drug washout period of at least five days for symptomatic medication and two months for preventive therapy. When the patients were asked about their sleep, none reported snoring, daytime sleepiness, or any other sleep or mood disorders.

No patient with CTTH had a history of nocturnal or waking headaches. Three CM patients had previously experienced headaches on waking, and four CH sufferers reported nocturnal attacks, nevertheless no patient presented an attack during the night of the study.

All the patients and controls underwent overnight (11 p.m.-7 a.m.) polysomnography (PSG) in order to disclose sleep disorders and establish the different sleep stages for blood sampling. The PSG studies were performed using a Stellate Harmonie Du computerized system, version 5.2 (Stellate Systems, Montreal, Quebec, Canada).

Surface electrodes were placed according to recognized international systems. The investigations included EEG (C3, C4, O1, O2), two-channel electro-oculography (with electrodes placed on the left outer canthus and right outer canthus), chin and shinbone electromyography, electrocardiography, and finger oximetry. A microphone, sensors and nasal and oral thermistors in the respiratory channels were used to assess air flow or to detect snoring; thoracic and abdominal belts were used to ascertain the degree of respiratory effort according to chest and abdominal movement, and the last two channels were used to detect body position and heart rate. All the PSG studies were evaluated by the same person (a neurophysiology expert).

Blood samples for melatonin measurements were collected, in the first half of the night, at the start of the NREM sleep stages 1, 2 and 4, at the beginning of the first REM sleep stage, upon waking, and after photostimulation.

The purpose of studying the different stages during the first half of the night was to exclude the biochemical changes that are linked to circadian physiology and to establish a relationship between the sleep stage and the type of headache independently of time of day. The blood samples were put into polypropylene tubes containing sodium heparin, kept on ice and stored at -70°C until assay.

Plasma melatonin was determined by RIA Kit DSL-BA-0800 (Labor Diagnostica Nord GmbH, Nordhom, Germany).

The significance of the differences within groups was analyzed by one-way analysis of variance followed by the Tuckey test for mean differences.

Results

The PSG studies were normal in all the patients and controls. Table I shows the mean plasma melatonin levels recorded in the headache groups and the controls in the different stages of slow sleep (NREM) and in REM during the period studied (the first half of the night). As expected, the control group displayed the normal pattern of melatonin plasma levels described in the literature: a nocturnal peak at 2 to 3 a.m. (p<0.05) and a decrease upon waking (Fig. 1). In this group, although the increase began to appear during stages 1 and 2 of NREM sleep, the highest concentration of the neurohormone was found during REM sleep.

Plasma melatonin levels did not show a normal curve either in the CM or in the CTTH patients. These two groups displayed a common pattern: a lack of melatonin plasma increase (peak) during the REM stage and also a lack of decreased values on waking. These patients never reached normal waking values (Fig. 1).

In the CM group, the levels were similar to those of controls in the NREM phases; this group recorded its lowest

<table>
<thead>
<tr>
<th>Sleep stage</th>
<th>Controls</th>
<th>CM</th>
<th>CTTH</th>
<th>CH bout</th>
<th>CH remission period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>44±7</td>
<td>44±13</td>
<td>86±7</td>
<td>9±2</td>
<td>40±3</td>
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<tr>
<td>Stage 2</td>
<td>46±9</td>
<td>49±9</td>
<td>64±13</td>
<td>15±3</td>
<td>50±5</td>
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<tr>
<td>REM</td>
<td>80±18</td>
<td>27±7</td>
<td>46±8</td>
<td>11±3</td>
<td>88±15</td>
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<tr>
<td>Stage 4</td>
<td>24±2</td>
<td>35±7</td>
<td>32±6</td>
<td>37±2</td>
<td>67±1</td>
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<tr>
<td>Waking</td>
<td>13±3</td>
<td>55±10</td>
<td>48±12</td>
<td>14±5</td>
<td>34±2</td>
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<tr>
<td>post-PS</td>
<td>37±10</td>
<td>50±13</td>
<td>45±8</td>
<td>12±3</td>
<td>30±3</td>
</tr>
</tbody>
</table>

Abbreviations: CM=chronic migraine; CTTH=chronic tension-type headache; CH=cluster headache; post-PS=after photostimulation.
levels in the REM stage and its highest levels on waking (p=NS). In the CTTH patients, although no significant differences were observed among samples, the highest levels were obtained during stage 1, decreasing progressively through to stage 4 (p=NS). The REM and waking melatonin concentrations were similar.

The plasma melatonin values of the CH patients (Fig. 2) studied during the “active cluster period” were low throughout the study, their values remaining within normal daytime range throughout the sampling, except for stage 4, in which a slight increase was observed (p=0.7478). Therefore, the plasma melatonin concentrations did not show the usual nocturnal increase and no peaks were observed. Rhythmicity was, instead, recovered during the remission period, when the CH patients showed similar values to those obtained in controls during NREM and REM, while the levels on waking remained slightly above those observed in the controls (p=0.0784). Photostimulation caused plasma melatonin concentrations to rise above waking values only in the control group (Fig. 1). In the different groups of patients (CM, CTTH, CH both in the active and in the pain-free period), photostimulation values were similar to those observed on waking. Consequently, it may be assumed that photostimulation did not exert any effect.

Discussion

Our control group displayed a normal plasma melatonin pattern: lower levels on waking and a nocturnal peak at 2 to 3 a.m., which we found to coincide with the REM stage. The suggestion that the pineal hormone melatonin is involved in different headache conditions is based on the important role played by the pineal gland in the maintenance of the homeostatic equilibrium in the presence of changing environmental conditions. In addition, hemi-cranial headache and unilateral orbital cephalalgia with or without sympathetic symptoms have been reported in pinealectomized subjects (15). To our knowledge, this is the first study that explores possible links between plasma melatonin, headaches (including both CH periods), and sleep stages. An altered pattern of melatonin secretion was observed in all three groups of patients with headache. The abnormal curve of plasma melatonin we found in our CM patients contrasted with the findings of Peres et al.
al. (14), whose CM patients without sleep disorders and controls presented similar nocturnal melatonin secretion levels and a delay in the nocturnal peak. Claustrat et al. (16) found significantly reduced nocturnal melatonin levels in “common migraine patients”, but did not test daytime values.

Little is known about the causes and mechanisms of CM. Mechanisms hypothesized to account for changes in the frequency and symptoms of this headache include chronic neurogenic inflammation, central sensitization, defective central pain modulation, hypothalamic dysfunction, and a combination of all of these (14).

Secretion of melatonin by the pineal gland is substantially suppressed by exposure to light (17,18). Salvesen et al. (19) found that migraine patients are more vulnerable to migraine attacks during the Arctic summer season, when bright daylight continues non-stop for months. The circadian rhythm of melatonin secretion is regulated by the suprachiasmatic nucleus in the hypothalamus (20). The suprachiasmatic nucleus may play a pivotal role in migraine (21) and the difference we found between our CM patients and controls supports the theory that CM is related to a hypothalamic involvement associated with a secondary chronobiological dysfunction.

On the basis of our findings in CTTH, a similar hypothalamic dysfunction could be assumed in these patients. In our CH patients, the absence of a nocturnal increase in melatonin during the cluster period and the trend to normal pattern of secretion during the remission period, indicate a specific plasma melatonin behaviour during each period.

A previous 24-hour study performed in patients during the active cluster period reported a significant decrease (vs controls) in melatonin concentrations at all time points studied, but with a nocturnal increase (22). Waldenlind et al. (23) found that the nocturnal melatonin peak was lower during cluster periods than remission periods, but in both cases they obtained a secretion curve.

Our patients had a plane curve during the active cluster period and we do not have an explanation for this discrepancy with the reports of other authors. The absence of a melatonin increase during REM sleep occurring between 2 and 3 a.m. (which has been considered a trigger) might render subjects susceptible to headache attacks. Pain-induced stress cannot explain the lack of increase because stress prompts a release of endogenous epinephrine, which increases melatonin production.

However, from a biochemical point of view, low melatonin levels may be due to reduced availability of serotonin, which is needed for the synthesis of the hormone. In CH, active cluster periods occur in the spring and autumn, when the light-dark cycle undergoes marked changes and one particular patient frequently experienced headache attacks at the same time of the day or night (24). Various indicators of a possible hypothalamic involvement in this headache have been suggested: the efficacy of lithium treatment, altered secretion of cortisol (25), and altered regulation of the hypothalamic-pituitary axis (26,27). If there were hypothalamic involvement in CH during the cluster period, melatonin secretion would be altered and this would affect pain in several ways. Melatonin receptors are present in the main cerebral arteries (28), and this hormone can modify the threshold of peripheral pain through its effect on prostaglandin synthesis (29). Furthermore, CNS melatonin strengthens the inhibitory action of GABA (30), thus a reduction in melatonin levels might reduce the pain threshold, as has been found in CH (31).

Reaffirming the role of the hypothalamus in CH pathogenesis, May et al. (32), using positron emission tomography, demonstrated marked activation of the hypothalamic ipsilateral ventral grey matter during nitroglycerin-induced CH attacks. In the light of previous clinical, biochemical and imaging evidence, our results support a central role of the hypothalamus in the pathogenesis of CH. On the other hand, it has been reported that melatonin may be effective in preventing CH attacks (33-35). In spite of the small number of patients studied, each one behaved in a consistent way within his group. All three groups of patients showed an altered pattern of melatonin secretion during the first half of the night. Although the presence of pain rather than a specific type of headache could be the cause of the altered pattern, our results allow us to hypothesize that the involvement of the hypothalamus in chronic pain behaviour headaches (CM and CTTH) differs from that present in episodic “paroxysmal” pain behaviour headache (CH), and that the hypothalamic involvement in this type of headache is strictly linked to the active period.

Acknowledgements

This project was supported by grants from CONICET (PEI #6338, PIP #2867 and PIP #5481), Argentina, and from the Italian Ministry of Health (RC2004 / Colombo 2000 Project).

References

10. Waldenlind E, Ekbom K, Wetterberg L et al. Lowered cir-
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cannual urinary melatonin concentrations in episodic cluster headache. Cephalalgia 1994;14:199-204
19. Salvesen R, Bekkelund SI. Migraine, as compared to other headaches, is worse during midnight-sun summer than during polar night. A questionnaire study in an Arctic population. Headache 2000;40:824-829
29. Leach CM, Thorburn GD. A comparison on the inhibitory effects of melatonin and indomethacin on platelet aggregation and thromboxane release. Prostaglandins 1980;20:51-56

Functional Neurology 2008; 23(2): 77-81