

Cluster Headache: Evidence for a Disorder of Circadian Rhythm and Hypothalamic Function

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ABSTRACT: This article reviews the literature for evidence of a disorder of circadian rhythm and hypothalamic function in cluster headache. Cluster headache exhibits diurnal and seasonal rhythmicity. While cluster headache has traditionally been thought of as a vascular headache disorder, its periodicity suggests involvement of the suprachiasmatic nucleus of the hypothalamus, the biological clock. Normal circadian function and seasonal changes occurring in the suprachiasmatic nucleus and pineal gland are correlated to the clinical features and abnormalities of circadian rhythm seen in cluster headache. Abnormalities in the secretion of melatonin and cortisol in patients with cluster headache, neuroimaging of cluster headache attacks, and the use of melatonin as preventative therapy in cluster headache are discussed in this review. While the majority of studies exploring the relationship between circadian rhythms and cluster headache are not new, we have entered a new diagnostic and therapeutic era in primary headache disorders. The time has come to use the evidence for a disorder of circadian rhythm in cluster headache to further development of chronobiotics in the treatment of this disorder.

RÉSUMÉ: Céphalée vasculaire de Horton : données en faveur d'un désordre du rythme circadien et de la fonction hypothalamique. Cet article revoit la littérature sur les données en faveur d'un désordre du rythme circadien et de la fonction hypothalamique dans la céphalée vasculaire de Horton. Celle-ci a une rythmicité diurne et saisonnière. Bien qu'elle était traditionnellement considérée comme une céphalée vasculaire, sa périodicité suggère l'implication du noyau suprachiasmatique de l'hypothalamus, l'horloge biologique. La fonction circadienne normale et les changements saisonniers survenant dans le noyau suprachiasmatique et la glande pinéale sont corrélés aux manifestations cliniques et aux anomalies du rythme circadien observées dans les céphalées de Horton. Des anomalies de la sécrétion de la mélatonine et du cortisol chez ces patients, la neuroimagerie des accès de céphalée et l'utilisation de la mélatonine comme traitement préventif des céphalées sont discutées dans cette revue. Bien que la majorité des études sur la relation entre le rythme circadien et la céphalée de Horton ne soient pas récentes, nous sommes entrés dans une nouvelle ère diagnostique et thérapeutique dans le domaine des céphalées primaires. Il est temps d'utiliser les données en faveur d'un désordre du rythme circadien dans la céphalée de Horton pour promouvoir le développement de médicaments chronobiotiques dans le traitement de cette maladie.

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Cluster headache is a primary headache disorder, characterised by brief episodes of severe unilateral pain associated with autonomic signs and symptoms (Appendix 1). The signature feature of this fascinating headache disorder is its rhythmicity. Cluster headache is unique in that it displays both a circadian and circannual periodicity. Cluster headache periods tend to recur at the same time of year for a given patient and at the same time of day, with clock-like regularity. Though cluster headache has traditionally been thought of as a vascular headache disorder, the periodicity of cluster headache suggests involvement of the hypothalamus and, more specifically, the suprachiasmatic nucleus of the hypothalamus, the biological clock. This review will discuss the evidence for a disorder of circadian rhythm and hypothalamic function in cluster headache.

The normal biology of circadian rhythms and function will be summarized, followed by a discussion of the abnormalities of circadian function seen in cluster headache. While the majority of the seminal research done in this field occurred more than

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twenty years ago, the topic of circadian rhythms in cluster headache is worth revisiting. This review attempts to integrate the clinical features and abnormalities of circadian rhythm seen in cluster headache with functional knowledge of the circadian timing system.

MOLECULAR CIRCADIAN BIOLOGY

The circadian rhythm of behaviours and hormones arises from a rhythm at the level of expression of clock genes. The first clock gene was discovered in mutated *Drosophila melanogaster* fruit flies displaying unusual circadian rhythms and was mapped to the period (*per*) locus on the X chromosome.³ More recently, the timeless (*tim*) gene was identified.⁴

The protein products of *per* (PER) and *tim* (TIM) are believed to travel between the cytoplasm and nucleus of cells, and regulate their own expression, as well as that of target genes (Figure 1)⁵. PER and TIM bind together to function. Both genes are transcribed in the morning and their mRNAs accumulate in the daytime. The TIM protein is degraded by light, which causes a low level of TIM protein despite *tim* RNA transcription. PER cannot function without TIM, therefore, during the day the protein products are non-functional. After dusk, TIM levels are able to increase, and the two proteins can bind together and become functional. They enter the cell nucleus and inhibit their own genes and target genes. Subsequently, *per* and *tim* mRNA levels decrease and protein expression decreases. By morning, PER and TIM protein levels are low and transcription is no longer inhibited – the cycle begins again. It is believed that a

similar mechanism in mammals drives the circadian timing system.⁶ Clock genes provide the biological mechanism that generate circadian rhythms.

THE SUPRACHIASMATIC NUCLEUS OF THE HYPOTHALAMUS

The hypothalamus is the principle central regulator and integrator of the endocrine system. The synthesis and release of hormones from the anterior lobe of the pituitary gland is regulated by peptides secreted from the hypothalamus into the hypothalamo-hypophyseal portal system. The hypothalamus controls the output of hormones that have important effects on the modulation of sexual function and behaviour, thyroid secretion, cortisol secretion, stress responses, appetite, growth, temperature, water and salt balance, and lactation. The hypothalamus lies beneath the thalamus, and can be divided into three main areas with distinct groups of nuclei: the rostral supraoptic, middle tuberal and posterior mammillary areas. The suprachiasmatic nucleus of the hypothalamus is located in the rostral supraoptic area.

In mammals, the biological clock is located in the suprachiasmatic nucleus. Destruction of the suprachiasmatic nucleus induces the disappearance of circadian rhythmicity of hormone release⁷ and sleep-wakefulness cycles.⁸ Transplantation of neonatal rat suprachiasmatic nuclei into arrhythmic rats restores disrupted rhythmicity.⁹ The circadian rhythm is endogenously generated but entrained to daily light-dark cycles of the external environment by the retinohypothalamic tract. The circadian timing system consists of three major components:

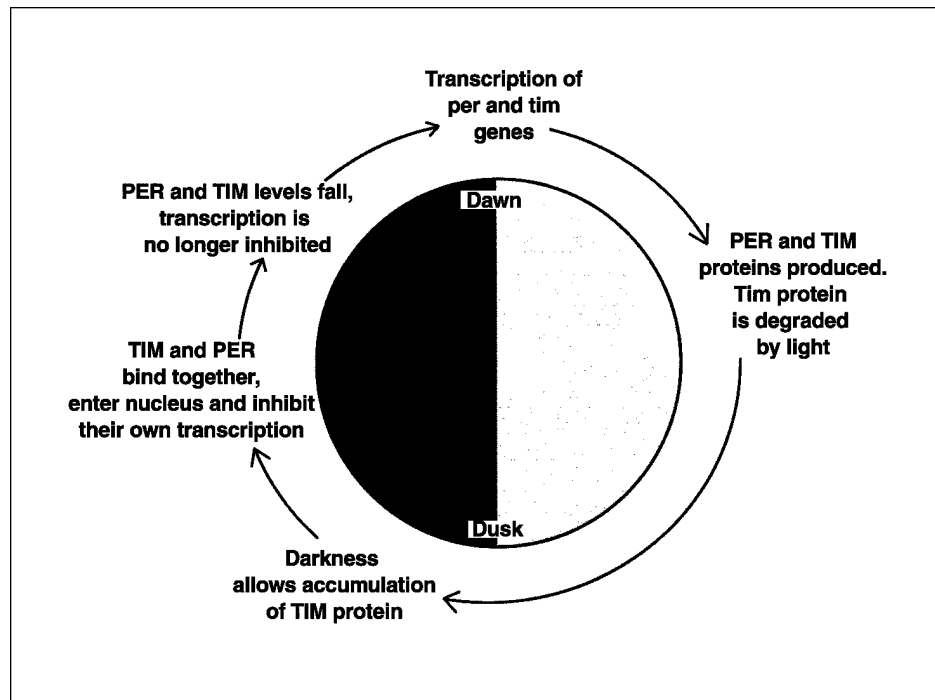


Figure 1: PER/TIM interaction.

photoreceptors from visual pathways mediating entrainment; a pacemaker of circadian rhythm – the suprachiasmatic nucleus itself; and output from the pacemaker that produces an entrained rhythm of several physiological behaviours, facilitating adaptation and survival.¹⁰

In humans, the suprachiasmatic nucleus is a paired group of cells lying dorsal to the optic chiasm and lateral to the third ventricle. The suprachiasmatic nucleus in humans is not as well differentiated as in other mammals, and there is variability in structure between subjects. The shape of the nucleus is sexually dimorphic, appearing elongated in women, and more spherical in men.¹¹ Distinct populations of vasopressin, vasoactive intestinal peptide (VIP), neuropeptide Y, and neurotensin neurons have been identified in the suprachiasmatic nucleus. The retinohypothalamic pathway terminates in a distinct subdivision of the suprachiasmatic nucleus, characterised by the presence of VIP neurons.¹⁰

A marked seasonal variation has been observed in the volume, total cell number and number of vasopressin cells of the human suprachiasmatic nucleus.¹² The volume of the suprachiasmatic nucleus is twice as large in the autumn as in the summer and contains almost twice as many cells. Similar seasonal variations occur in the number of vasopressin-containing neurons. The suprachiasmatic nucleus is smaller in summer than in any other season. In contrast to the annual variations in the human suprachiasmatic nucleus, no diurnal variations have been observed. However, in rats, neuronal inputs from retinal ganglion cells markedly reduce VIP immunoreactivity and VIP mRNA levels during the daytime.¹³ VIP and VIP mRNA reach a peak level at 02h00 and a trough at 14h00. It appears that the expression of VIP and its mRNA in the VIP neurons of the suprachiasmatic nucleus is light-dependent.

The annual variation in the total cell number of the human suprachiasmatic nucleus has been correlated to the photoperiodic cycle of the temperate zone. Peaks in the total cell number of the suprachiasmatic nucleus occur close to the spring and autumnal equinox. The annual minimum of total cell number was found to coincide with the summer solstice, with a second smaller minimum occurring at the winter solstice. These findings show that the suprachiasmatic nucleus undergoes its greatest increase in size when the photoperiod undergoes its largest rate of change. The shortening days of autumn, as well as the lengthening days of spring, appear to induce morphological changes in the suprachiasmatic nucleus.¹⁴ Circadian function and behaviour parallel dynamic changes within the suprachiasmatic nucleus.

MELATONIN AND THE PINEAL GLAND

The hormone melatonin is synthesised in the pineal gland. There is a daily rhythm of melatonin production, with peak levels occurring in the hours of darkness. The melatonin rhythm is endogenously generated by the suprachiasmatic nucleus. Environmental light entrains melatonin secretion to a 24-hour cycle.

Melatonin production and secretion are mediated by postganglionic retinal nerve fibres that pass through the retinohypothalamic tract to the suprachiasmatic nucleus, then to the superior cervical ganglion, and finally to the pineal gland. The release of norepinephrine to the pineal gland stimulates

melatonin production. During daylight hours, the retinal photoreceptor cells are hyperpolarized, which inhibits the release of norepinephrine.¹⁵ Further along the pathway, gamma-aminobutyric acid (GABA) release from the suprachiasmatic nucleus to the sympathetic system mediates the inhibitory effect of light on melatonin release by the pineal gland.¹⁶ With darkness, the photoreceptors release norepinephrine, and the system is activated.¹⁵

The pineal gland displays seasonal variations, being larger in winter than summer in volume and in the nuclear size of pinealocytes.¹⁷ The pattern of melatonin synthesis is also influenced by the photoperiod. During long photoperiods, such as the summer, the period of high melatonin synthesis is shortened, in contrast to the prolonged synthesis of melatonin during wintertime.¹⁸

Melatonin feeds back onto the suprachiasmatic nucleus. Melatonin receptors have been found on suprachiasmatic nucleus neurons, providing the link for a suprachiasmatic nucleus-pineal gland feedback loop. Sack et al¹⁹ propose that this feedback loop mediates circadian phase shifting and perhaps attenuates a suprachiasmatic nucleus dependent alerting mechanism in humans as well.

Melatonin shifts the circadian clock. Daily injections of melatonin produced phase advances sufficient to entrain a 24 hour cycle in rats that were previously free running with a circadian period greater than 24 hours, in constant dim light conditions.²⁰ The circadian phase shifting properties of melatonin have been applied to several disorders, such as jet lag, delayed sleep phase syndrome, and non-24-hour sleep-wake disorder.

The phase shifting effects of melatonin are dependent on the timing of melatonin administration and can occur with near physiologic doses. Administration of melatonin in the afternoon and early evening will advance (shift earlier) the phase of the circadian rhythms. Administration in the morning at 07h00 will delay (shift later) the phase.²¹ Knowledge of the patient's circadian phase prior to treatment will allow accurate timing of the melatonin dose in order to achieve the desired phase shift.

There is a correlation between circulating melatonin levels and sleep propensity. Evidence suggests that along with its chronobiotic properties, melatonin may have some sleep promoting activity. Daytime administration of melatonin when the endogenous levels of the hormone are low was shown to induce subjective feelings of sleepiness and fatigue, and improve sleep quality.²² The hypnotic effect of melatonin may be independent of its synchronising influence on the circadian rhythm and may be mediated by a lowering of core body temperature. The evening rise of melatonin is temporally related with the evening drop of core body temperature, and pharmacologic doses of melatonin can induce a decrease in body temperature.²¹ Melatonin functions as a chronobiotic, capable of modifying and adjusting the circadian timing system.

CORTISOL AND THE HYPOTHALAMIC PITUITARY AXIS

Cortisol release from the adrenal cortex also exhibits a daily rhythm. The anterior pituitary corticotroph cells synthesize adrenocorticotropic hormone (ACTH), which is released after stimulation of the cells by corticotropin-releasing hormone

(CRH). Corticotropin-releasing hormone release is controlled by several neurotransmitter systems, including acetylcholine and serotonin, which stimulate CRH release, and GABA and norepinephrine, which inhibit its release. Stress related stimuli will also affect CRH release. Release of both CRH and ACTH is modulated through a negative feedback effect of cortisol. Selective lesions of the suprachiasmatic nucleus in the rat lead to a loss of the rhythmic secretion of cortisol, with cortisol levels at all time points remaining in the range normally observed for morning values.⁷

Cortisol diffuses into its target cells, combines with receptor proteins in the cytoplasm, and is transported to the nucleus where it modifies gene expression and protein synthesis. Its many effects on metabolism include stimulation of hepatic glucose synthesis, breakdown of protein in muscle, skin and bone, an anti-inflammatory effect, and enhancement of lipid mobilisation. Cortisol protects against stress-induced hypotension, shock and death by mechanisms that are not well understood.²³ The cortisol rhythm is an example of how the circadian timing system controls physiology to enhance adaptation and survival.

ABNORMALITIES OF CIRCADIAN RHYTHM IN CLUSTER HEADACHE

It has long been observed that cluster headache periods tend to recur at the same time of year for patients. This led Kudrow²⁴ to a retrospective study in 404 patients with episodic cluster headache, noting the mean monthly frequency of cluster period onset, with consideration of the mean monthly duration of daylight. The frequency of cluster period onset increased with the gradual increase or decrease in daylight throughout the year, with peaks occurring seven to 10 days after the longest and shortest days of the year. Each peak lasted the months of January and July. The gradual rise of cluster period frequency was interrupted by a significant drop in cluster period onset beginning seven to 10 days after the resetting of clocks for Daylight Savings time in April and Standard time in October. The author hypothesised that the cluster period may somehow result from an inability to synchronise the internal circannual pacemaker to environmental light clues.²⁴

Cluster headache exhibits a relationship with the sleep-wake cycle and with the activity-relaxation cycle. Attacks may occur at the same hour every day.²⁵⁻²⁷ Cluster headaches are known to occur during sleep in up to two-thirds of patients.²⁸ Manzoni et al²⁹ found that when plotting the most common hours of onset for all patients, sharp peaks were found between 01h00 and 02h00, 13h00 and 15h00, and a final peak reached at around 21h00. This study was performed in Italy and the majority of the patients stopped working between 13h00 and 15h00. Russell³⁰ found that 71% of daytime attacks in his series occurred while patients were physically relaxed.

Nocturnal attacks usually begin one to two hours after falling asleep and, in patients with episodic cluster headache, are associated with rapid eye movement sleep.³¹ Almost 60% of recorded attacks in one series followed REM sleep, while REM comprised only 20% of total sleep time.³² Patients are able to have a transient remission of their cluster headache by skipping one night's sleep.³³

Abnormal sleep has also been reported in patients during the

cluster period. Subjective assessment of cluster patients in comparison to healthy controls has shown a reduced total duration of nocturnal sleep, increased time to fall asleep, a high frequency of nocturnal awakenings, and poor sleep quality. Objective polysomnographic findings were also significantly different in cluster patients than the control group, with cluster patients exhibiting a reduced total duration of sleep, increased time to fall asleep, increased latent periods of all sleep stages, increased percentage representation of superficial sleep stages (stages 1 and 2), reduced duration of REM stage, increased number of awakening episodes during sleep, and increased movement activity.³⁴ Sleep apnea is a common finding in patients with cluster headache and nocturnal attacks have been found in association with oxyhemoglobin desaturation.³² These studies indicate that not only do cluster attacks occur during sleep but sleep patterns themselves are altered in patients with this disorder.

ALTERATIONS IN THE SECRETION OF MELATONIN AND CORTISOL IN CLUSTER HEADACHE

Alterations in the circadian secretion of hormones has also provided evidence of deranged hypothalamic function in cluster headache. The first evidence of hypothalamic involvement in cluster headache came from the demonstration of lowered concentrations of plasma testosterone during the cluster headache period in men.³⁵ While this review will focus on the abnormalities observed in the secretion of melatonin and cortisol, alterations in the secretion of luteinizing hormone and prolactin, and altered responses of luteinizing hormone, follicle stimulating hormone, prolactin, growth hormone, and thyroid stimulating hormone to challenge tests have been demonstrated in patients with cluster headache.³⁶

One of the first studies of melatonin and cortisol secretion in episodic cluster headache was performed by Chazot et al.³⁷ Melatonin and cortisol secretion was studied over a 24-hour period, with blood collected every two hours during the day and at one hour intervals at night, in healthy controls and patients in their cluster bout. Most cluster patients had lowered nocturnal melatonin secretion, particularly in the early part of the night. Cluster patients displayed a significant phase advance in their melatonin rhythm, with the acrophase (time from midnight to peak hormone levels) occurring two hours earlier than control subjects. For cortisol, the rhythm appeared slightly blunted in the cluster headache group and was significantly phase advanced. The authors concluded that their data are compatible with a disturbance located in the suprachiasmatic nucleus of the hypothalamus, though the blunting of the cortisol rhythm could be due to a number of other causes as well. They emphasized the pathophysiological implication of the sympathetic superior cervical ganglion, which provides sympathetic innervation to the pineal gland, cranial blood vessels, choroid plexus, the eye, carotid body, and salivary and thyroid glands. The authors hypothesised that the unilaterality of cluster attacks and the associated autonomic features may be related to abnormal modulation from the superior cervical ganglion level, with impaired melatonin secretion as a consequence of this abnormality.³⁷

Waldenlind et al³⁸ studied 24-hour rhythms of serum cortisol

and melatonin in patients with cluster headache during and between cluster periods and in healthy controls. Compared to healthy controls, lower maximal nocturnal serum melatonin levels were found in cluster headache, both in the active period and in remission. Maximal cortisol levels and 24-hour means were significantly higher during the active cluster period but not during clinical remission, as compared to healthy controls. A delay of the cortisol minimum was found in the active cluster period as compared to the remission phase. The authors hypothesised that while the phase delay of cortisol may reflect an impaired chrono-organization of hormone secretion in patients with cluster headache, the higher 24-hour secretion of cortisol might represent an adaptive response to the pain of cluster attacks.³⁸

Leone et al³⁹ also studied the circadian secretion of melatonin and cortisol in patients with episodic cluster headache, during the cluster period, as compared to healthy controls. They found significantly lower plasma melatonin levels in cluster headache patients than controls, and no significant melatonin rhythm in one-third of their subjects. Cortisol 24-hour production was significantly higher in cluster headache patients than controls, while the amplitude and acrophase were similar. Almost half of their subjects with cluster headache had no cortisol rhythm. In addition, in healthy subjects, the timing of the melatonin acrophase correlated with that of cortisol. There was no correlation in the cluster headache patients. The authors concluded that the absence of any correlation between the pain parameters and the circadian production of these hormones suggested a primary derangement in the biological clock during the cluster period.³⁹ The reduction in night-time melatonin secretion and loss of the melatonin rhythm reported in these studies may reflect dysfunction within the synthetic pathway of melatonin production with consequent loss or alteration of its circadian phase shifting properties.

Further studies have assessed the cortisol and ACTH response to the insulin tolerance test and ovine CRH test. The insulin tolerance test produces hypoglycemia, induces a stress response, which increases CRH release and therefore ACTH and cortisol secretion. This test measures the integrity of the hypothalamic-pituitary-adrenal (HPA) axis and its ability to respond to stress. Ovine CRH stimulation assesses ACTH secretory dynamics. This test is used to diagnose primary and secondary adrenal insufficiency.⁴⁰ Leone et al⁴¹ found that both remission and cluster period patients had significantly higher basal cortisol levels than controls. A blunted cortisol response to ovine CRH was found in both active cluster and the remission phase, though the ACTH surge was normal. A reduced cortisol and ACTH response was found to the insulin tolerance test in both phases of the disorder.⁴¹ The authors repeated the study in a group of patients with low back pain due to disc herniation and did not find similar responses to these tests. They concluded that the altered HPA axis responsiveness in cluster headache patients is not a consequence of pain but rather due to hypothalamic derangement.⁴² The abnormal results of the insulin tolerance test point to dysfunction along the HPA axis in patients with cluster headache, while the results of the ovine-CRH test suggest an abnormal adrenal response. A normal ovine-CRH test would have more convincingly localized the problem in the hypothalamus. However, there is evidence that the

suprachiasmatic nucleus is involved in the setting of sensitivity of the adrenal cortex to ACTH, with experimental demonstration of a polysynaptic suprachiasmatic nucleus-adrenal cortex pathway.⁴³ Therefore, these findings could be consistent with hypothalamic dysfunction. A reduced response of the HPA axis to the insulin tolerance test has been reported in patients with brain tumours and multiple system atrophy involving the hypothalamus.⁴² One possible explanation for the changes observed in cortisol rhythm, secretion, and response to challenge tests may be failure of the circadian timing system in the entrained rhythm of physiologic processes.

MELATONIN AS PREVENTATIVE THERAPY IN CLUSTER HEADACHE

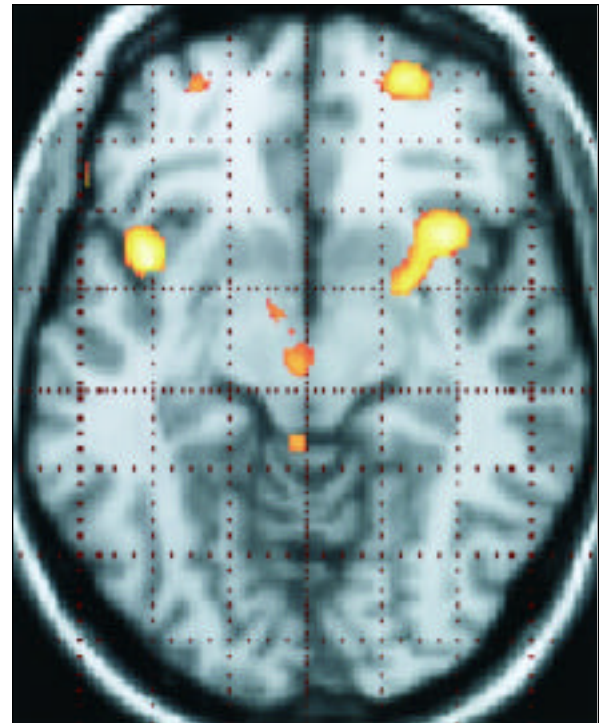
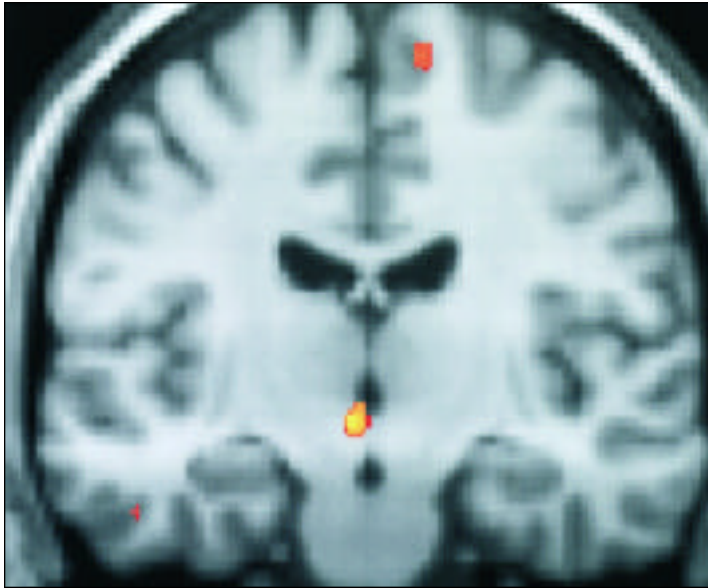
Leone et al⁴⁴ performed a double-blind pilot study of melatonin versus placebo in the prophylaxis of cluster headache. Twenty patients with cluster headache (18 episodic, two chronic) participated in the study. Patients with episodic cluster headache entered the study between the second and tenth day of their cluster bout. After a run-in period of one week without prophylactic treatment, patients were randomized to receive 10 mg melatonin or placebo for two weeks. The authors found that compared to the run-in period, there was a reduction in the mean number of daily attacks and a strong trend towards reduced analgesic consumption in the melatonin group but not in the placebo group. Five patients in the melatonin group responded to the treatment, with cessation of cluster headaches after five days of treatment.⁴⁴

NEUROIMAGING OF CLUSTER HEADACHE

More recently, positron emission tomography (PET) has been used to assess changes in regional cerebral blood flow as an index of synaptic activity during nitroglycerin-induced cluster attacks. May et al⁴⁵ found that in the acute pain state, activation was seen in the ipsilateral inferior hypothalamic grey matter, the contralateral ventroposterior thalamus, the anterior cingulate cortex and bilaterally in the insula, and in the cerebellar hemispheres (Figures 2 and 3). The area of hypothalamic activation occurred in the region of the circadian pacemaker neurons, further establishing the involvement of this area of the hypothalamus in the genesis of acute cluster attacks.⁴⁵ A PET study of patients in and out of their cluster bout demonstrated posterior hypothalamic grey activation only in patients with nitroglycerin-induced cluster headache attacks in the active cluster period. Hypothalamic grey activation was not seen in nitroglycerin-induced headaches out of the bout. Activation of the hypothalamus therefore appears to be specific to cluster headache.⁴⁶ In addition, voxel-based morphometry of T1-weighted MRI scans has revealed an increase in hypothalamic volume, located in the inferior posterior hypothalamus in cluster headache patients compared to normal controls.⁴⁷

DISCUSSION AND CONCLUDING REMARKS

Several correlations can be made between the biology of circadian rhythms and hypothalamic function and the clinical features of cluster headache. It is interesting to observe that both the suprachiasmatic nucleus and pineal gland undergo a change



Figures 2 and 3: Comparison of nitroglycerin - induced acute cluster headache attack and rest (no pain) in nine patients with active chronic cluster headache. Reprinted with permission from Elsevier Science (*The Lancet*, 1998; 352:275-78) Activations during the attack are shown as statistical parametric maps that show the areas of significant cerebral blood flow increases ($p < 0.001$) in colour superimposed on an anatomical reference derived from a T1 - weighted MRI. Significant activation was detected next to the third ventricle slightly lateralized to the left and rostral to the aqueduct. The activation is ipsilateral to the pain side and localized to the hypothalamic grey matter.

in size circannually, due to the lengthening and shortening of daylight hours. The suprachiasmatic nucleus undergoes its greatest change in size when the photoperiod undergoes its largest rate of change, just as the incidence of cluster bouts increases with the gradual increase or decrease in daylight throughout the year. One may hypothesise that perhaps a failure or dysfunction within the suprachiasmatic nucleus occurs and may be implicated in the pathogenesis of cluster headache.

A diurnal expression of VIP has been demonstrated in the rat, with peak levels occurring at 02h00 and a trough at 14h00. If this diurnal expression of VIP occurs in humans, the peak hours for cluster attacks (between 01h00 and 03h00) coincide with this peak of VIP secretion. VIP is a potent vasodilator, and elevation of VIP has been reported in a study of the external jugular venous blood of cluster headache patients during a spontaneous cluster attack.⁴⁸ The investigators of this study concluded that the elevation of VIP, a marker of parasympathetic activity, was due to activation of a brain stem reflex, the afferent arc of which is the trigeminal nerve and the efferent the cranial parasympathetic outflow from the seventh nerve. Perhaps a central derangement in the hypothalamic VIP synthesising neurons can be an additional explanation of these findings.

If cluster headache is due to a problem in the hypothalamic centre responsible for the synchrony of circadian rhythms, it is likely the phase resetting properties of melatonin that explain its efficacy as a preventative treatment in some patients with cluster

headache. Appropriately timed melatonin therapy can shift circadian rhythms. Kudrow²⁴ hypothesised that the circannual incidence of cluster bouts may result from an inability to synchronise the internal circannual pacemaker to environmental light cues. Melatonin feedback onto the suprachiasmatic nucleus through melatonin receptors mediates this phase shifting effect. Perhaps it is the chronobiotic effect of melatonin on cluster headache patients which is therapeutic. If this hypothesis is true, one would expect to see an effect of melatonin in cluster headache using appropriately timed, physiologic doses of the compound. Sack et al¹⁹ have advanced this theory in their analysis of the sleep-promoting effects of physiologic doses of melatonin, which they believe are due to its phase-shifting properties. As of yet, only a supraphysiologic dose of melatonin has been assessed as preventative therapy. If no response occurs at physiologic doses, it may be the other properties of melatonin-potentialiation of GABA inhibitory action,⁴⁹ inhibition of prostaglandin E2 synthesis,⁴⁴ vasoconstriction of cerebral arteries,⁵⁰ its mild hypnotic effect and ability to lower core body temperature, that explain its effect in cluster headache.

Nagtegaal et al⁵¹ reported a patient treated with melatonin for delayed sleep phase syndrome who also had cluster headache. Both disorders responded to melatonin therapy. One might expect to find an increased incidence of circadian sleep disorders in patients with cluster headache, if a circadian influence is implicated in its pathophysiology. While small series have

reported sleep dysfunction in patients with cluster headache, no studies have assessed the prevalence of specific sleep disorders in this patient population.

The effect of bright light therapy may be worth assessing in patients with cluster headache. Light, like melatonin, resets the circadian timing system according to a phase response curve. In the first half of the night, light exposure causes phase delays, and in the second half of the night, it causes phase advances.⁵² Light therapy has been used in the treatment of circadian sleep disorders, due to its ability to shift circadian rhythm, and in seasonal affective disorder, in which patients have a delay in the onset of melatonin secretion. If melatonin's effect is due to its phase shifting properties, light therapy may have a similar effect.

The majority of studies exploring the relationship between circadian rhythms and cluster headache are not new, in fact, the majority of articles discussing this relationship were published in the late 70s, 80s and early 90s. However, we have entered a new diagnostic and therapeutic era in primary headache disorders, with functional MRI and PET studies demonstrating abnormalities during both cluster⁴⁵⁻⁴⁷ and migraine^{53,54} attacks, and new, highly effective, specific headache medications. With the aid of these sophisticated imaging techniques and the ability to develop specific treatment for headache, the time has finally arrived to put all the research done by our predecessors to practical application and for further development in the area of chronobiotics in cluster headache.

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Appendix 1: The International Headache Society criteria for cluster headache¹ are as follows:

- A. At least five attacks fulfilling criteria B through D.
- B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes untreated.
- C. Headache is associated with at least one of the following signs that have to be present on the pain-side:
 1. Conjunctival injection.
 2. Lacrimation.
 3. Nasal congestion.
 4. Rhinorrhea.
 5. Forehead and facial sweating.
 6. Miosis.
 7. Ptosis.
 8. Eye lid oedema.
- D. Frequency of attacks: from one every other day to eight a day.

Cluster headache may be of an episodic or chronic form. Episodic cluster headache occurs in 85% of patients. In episodic cluster, attacks occur in periods lasting from seven days to one year separated by pain-free periods lasting 14 days or more. In chronic cluster headache, attacks occur for more than a year without remission or with remissions that last less than 14 days. Chronic cluster headache is unremitting in onset in 10%, and evolves from an episodic cluster headache pattern in 5%.²
