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MIGRAINE (R COWAN, SECTION EDITOR)

Why Does Sleep Stop Migraine?

Marcelo E. Bigal · Richard J. Hargreaves

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Abstract The relationship between sleep and migraine headaches is complex. Changes in sleep patterns can trigger migraine attacks, and sleep disorders may be associated with increased migraine frequency. Furthermore, migraine patients and their doctors very consistently report that sleep relieves already established migraine attacks. Herein we will try to answer the question, "Why does sleep stop migraine?" Since evidence for this relationship is largely based on empirical clinical observation, we will not provide a clinical review of the association. Instead, we will focus on the pathophysiology of migraine attacks and its intersections with sleep biology.

Keywords Migraine · Sleep · Trigger factors · Migraine cessation

Introduction

Migraine is a chronic neurological disorder characterized by episodic attacks of headache and associated symptoms [1]. In Western countries, the condition affects 12 % of the adult population [2]. Migraine is a heterogeneous condition that results in a range of symptom profiles and various degrees of disability both within and among different individuals. The disability of migraine can be severe, imposing a considerable burden to the suffer and society [3] (Fig. 1).

Since migraine attacks occur episodically, it is important to consider potential risk factors for the onset of attacks, as well as strategies to relieve established attacks [4•]. Risk factors for migraine attacks are often called migraine triggers [5, 6]. Relieving strategies include pharmacological and non-pharmacological treatment of attacks that serve to decrease the severity and duration of pain and associated symptoms [1].

Sleep is vital. It is regulated by homeostatic and circadian processes, and it is highly organized and dynamic. Many environmental factors can reduce or disrupt sleep and sleep abnormalities are a hallmark of many neurological and psychiatric diseases. Sleep dysfunction can have profound consequences on physiology, behavior and the ability to function in the waking state [7].

The relationship between sleep and migraine headaches is complex. In early childhood, certain sleep disorders (e.g., bruxism and nocturnal terror) are considered to be childhood periodic disorders, predicting migraine onset later in life [8]. After migraine onset, changes in sleep patterns are recognized as important migraine triggers [9, 10]. Interestingly, most studies suggest that it is the change in the pattern (sleeping less or more than usual), not a specific sleep feature (insomnia or hypersomia) that triggers migraine attacks. As an aside, poor ability to cope with internal and external changes may be one characteristic of the migraine brain, since a similar pattern has been reported for other triggers. For example, weather changes, but not specific weather parameters, have been reported as migraine triggers [11].

Specific sleep disorders seem to be, in turn, risk factors for migraine chronification among individuals with episodic migraine [12]. In a large, cross-sectional study of 3,323 Danish men, snoring was associated with headaches overall. The authors reported that this association was independent of weight, age, gender, hypertension and other sleep disturbances, including secondary to caffeine consumption [13]. In a separate population-based case-control study, individuals with frequent headaches were more likely to be habitual or daily snorers than controls [14].

Although changes in sleep patterns can trigger migraine attacks, and sleep disorders may be associated with increased migraine frequency, migraine patients and their doctors very

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M. E. Bigal (✉)
Labrys Biologics Inc., 1810 Gateway Drive, Suite 230, San Mateo, CA 94404, USA
e-mail: mbigal@labrysbiologics.com

R. J. Hargreaves
Preclinical Research, Merck Inc., Whitehouse Station, NJ, USA

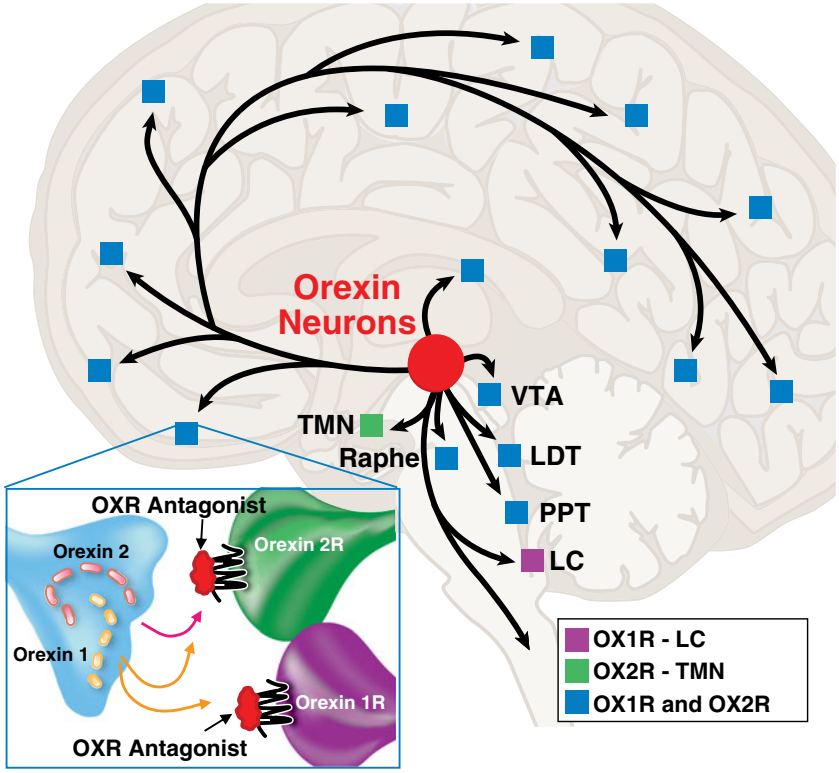

Fig. 1 Projections of orexin neurons and OX-R distribution. *Red circle* shows orexin neurons in the lateral and posterior hypothalamus. Squares show the orexin projections and receptor localizations that are widely distributed except the cerebellum with especially dense innervation of within the hypothalamus and of monoaminergic and cholinergic nuclei in the brain-stem. TMN = tuberomamillary nucleus (histaminergic), LDT/PPT = laterodorsal/pedunclopontine tegmental nucei (cholinergic), Raphe nucleus (serotonergic), LC = locus ceruleus (norepinehprinergic) and VTA is ventral tegmental area (dopamine). *Blue squares* show where OX-1R and OX2R are colocated with purple and green squares showing nuclei where OX-1R and OX-2R predominate. The call-out shows the preferential binding of orexin 1 (OX-A) to OX-1R and OX-2R and orexin 2 (OX-B) to OX-2R, respectively

consistently report that sleep relieves already established migraine attacks, although good quality evidence to support this statement is missing. Nonetheless, protocols for the non-pharmacological treatment of migraine often recommend sleep as an abortive. Dr. Marcia Wilkinson, one of the most respected headache specialists of our times and a past editor of the journal *Cephalalgia*, once recommended "that acute treatment depends mainly on sleep, an antinauseant, analgesics, ergotamine and more recently sumatriptan" [15, 16]. Additionally, relaxation therapies, which often induce sleep, are used in the acute treatment of migraine, with good evidence level [17].

The Physiology of Sleep

Sleep is a complex behavior that has been evolutionarily conserved among widely divergent species. Despite extensive studies on sleep and its role in animal physiology, sleep still remains one of the great mysteries of neuroscience. Even today, it remains relatively unclear as to why humans spend nearly 1/3 of our lives carrying out this behavior.

Human sleep is circadian based and is typically made up of oscillatory phases lasting about 90 minutes during which the brain moves through different frequencies of electrical activity. In a typical period of sleep the brain moves from being awake into progressively deeper sleep stages non-rapid eye movement sleep (NREMS, Stage 1 to Stage 4) and then into rapid eye movement sleep (REM or dream sleep). In a typical 8-hour sleep period there is about 20–25 % REM sleep whose periods lengthen towards the end of a sleep period before awakening. REMS sleep is associated with dreaming and muscle relaxation. NREMS stages 1 and 2 are collectively known as "light sleep" and stages 3 and 4 as "deep sleep". Normal sleep "architecture" in adults consists of a preponderance of NREMS, especially Stages 3 and 4 early in the sleep period, with a shift to an increasing proportion of time spent in light sleep and REMS as the sleep period progresses [7]. Slow-wave deep sleep (Stage 3 and 4) is thought to be essential for memory consolidation and learning and the amounts of time spend in these stages declines with age from childhood. It has been speculated that loss of slow wave sleep in teenagers and more profoundly in the elderly may result in an impairment of the ability to learn and remember new information. Several psychiatric conditions are associated with sleep deprivation and sleep disturbances are features of metabolic and

neuropsychiatric illness in patients suffering from obesity. Alzheimer's disease, Parkinson's disease, depression, bipolar disorder, schizophrenia, trauma and post-traumatic stress disorders. For an excellent overview of sleep physiology and its role in health and disease the reader is referred to a recent collection of articles in the *Nature Outlook* supplement "Sleep" [18••, 19].

Herein we will focus on one of the several potential relationships between sleep and migraine, by trying to answer the question, "Why does sleep stop migraine?" Since evidence for this relationship is largely based on empirical clinical observation, we will not provide a clinical review of the association. Instead, we will focus on the pathophysiology of migraine attacks and its intersections with sleep biology. We stress that many of the putative mechanisms discussed here are speculative.

The Pathophysiology of Migraine

For many years regarded as a vascular disorder, migraine is actually the prototype of a neurological condition. The fundamental problem in migraine pathogenesis is in the brain and this should be distinguished from migraine pain that may have both peripheral and central components. Herein we discuss important neurological phenomena related to migraine, as a framework to discuss the influence of sleep on its clinical symptoms.

Cortical Spreading Depression

Cortical spreading depression (CSD) is a slowly propagating (2–6 mm/min) wave of sustained neuronal depolarization, which is followed by potent, relatively long-lasting neural suppression [18••, 19]. CSD is considered to be the electrophysiological substrate of migraine aura [20, 21] and many consider it as being necessary for the development of headache [22, 23•]. However, evidence also questions this last assumption. Aura occurs in less than 30 % of migraine patients; aura can be experienced without pain at all, and is seen in the other primary headaches [24]. Indeed, most of the symptoms of migraine, including photophobia, phonophobia and osmophobia, may be explained by abnormal central processing of a normal sensory signal. Perhaps electrophysiological changes in the brain have been mislabeled as hyperexcitability whereas dyshabituation might be a simpler explanation, where symptoms may be explained by disturbance of sub-cortical sensory modulation system [25]. In migraine without aura, it has been suggested that sub-clinical CSD events may underlie the initiation of an attack although hard evidence for this phenomenon is lacking [26]. Nonetheless, in laboratory experiments CSD has been shown to activate the trigeminovascular system producing inflammation in the meninges and neuronal responses in the trigeminal nucleus caudalis, therefore its suppression has been suggested to enhance the probability of success of an anti-migraine preventative approach [27, 28]. Later in this paper we will explore the potential inter-play between sleep and CSD.

Subcortical Structures and Migraine

Subcortical structures are involved in the early mechanisms of migraine, where the hypothalamus seems to play a key role for the premonitory symptoms (for an excellent review, the readers are referred to [29•], and also in the genesis of pain.

The etiology of the premonitory phase of migraine is poorly understood, but data support the importance of changes in the activity of the hypothalamus, since symptoms such as changes in mood, appetite, and energy, can be attributed to dysfunctions in this region. Common premonitory symptoms include feeling groggy or sleepy [30]. Functional neuroimaging studies also indicate that the hypothalamus is activated in the early phases of migraine pain [31], suggesting that it may underlie the premonitory symptoms of migraine or is involved in early endogenous pain control responses to trigger stimuli [32]. The hypothalamus is activated by painful stimuli and is part of the endogenous descending pain control system. The descending pain control pathways originate in the amygdala and hypothalamus and terminate in the periaqueductal grey (PAG) where they activate neurons projecting to brainstem nuclei to control many of the antinociceptive and autonomic responses that follow noxious stimulation. The hypothalamus is also part of corticolimbic circuitry implicated in the affective and cognitive aspects of pain [33••]. Most importantly, as discussed below, the hypothalamus is in the core of the control system for many circadian behaviors such as onset and maintenance of sleep, thermoregulation, feeding and is responsive to light, stress and blood borne hormones.

Non-hypothalamic subcortical structures are also involved during migraine pain. Functional brain imaging with positron emission tomography (PET) has demonstrated activation of the dorsal midbrain, including the periaqueductal grey (PAG), and the dorsal pons, near the locus coeruleus, in studies during migraine without aura [34]. Dorsolateral pontine activation is seen with PET in spontaneous episodic [35] and chronic migraine [36], and with nitroglycerin-triggered attacks [37].

There has been debate over whether this PAG activation is due to heightened activity in the endogenous pain control systems during migraine or is a crucial part of the neuronal network dysfunction that underlies migraine. Evidence from surgical and pathological lesions, however, supports the view that the PAG may be involved in the initiation of migraine (and therefore called the migraine generator) since when stimulated in patients with electrodes implanted for pain control [38] or when there is pathology or lesions in the PAG [39], or the pons [40] migraine-like headache has been reported.

The Trigeminal System: Migraine Pain

During the pain phase of a migraine attack, activation of the trigeminal system occurs. When this system is activated, pro-inflammatory neuropeptides, including calcitonin gene-related peptide (CGRP), and substance P, are released from peripheral nerve endings in the cranium [41, 42]. These neuropeptides may play an important role in the generation and maintenance of headache pain and possibly other symptoms of migraine through actions at peripheral sites causing meningeal neurogenic inflammation (vasodilatation, plasma protein extravasation, and the release of proinflammatory mediators by mast cells) and central sites within pain relay centers in the brain [43, 44]. The relevance of neurogenic dural inflammation that can be produced experimentally by non-specific trigeminal activation has long been a subject of debate in the clinical setting [45]. The clinical anti-migraine activity of peripherally acting CGRP receptor antagonists however suggests that this system is in play during the headache pain phase of an attack [46]. Persistent trigeminal activation may in turn cause sensitization of peripheral trigeminal nerve fibers or central sensitization of second or third order sensory neurons in the brain stem and thalamus to produce the symptoms of allodynia (heightened sensitivity to innocuous sensory stimuli) that are often associated with a migraine attack.

Sleep in the Context of the Pathophysiology of Migraine

Sleep and Cortical Spreading Depression

The relationship between sleep and CSD events is poorly understood. CSD could indeed be called cortical spreading excitation (CSE) as it is characterized by first by a wave of intense excitation that precedes the quiescent phase when cortical activity is depressed. Indeed it is this excitation and depression that is thought to underlie the symptoms of the scintillating fortification spectra and subsequent scotoma of migraine aura. It is tempting to speculate that activation of sleep pathways could inhibit excitation in the cortex to prevent or ameliorate CSD events thereby abbreviating an attack by reducing the input function for migraine. Indeed slow wave sleep is thought to reflect oscillating activity in thalamo-cortical pathways that disrupts sensory-cortical transmission such that responsiveness to nociceptive stimuli is greatly reduced during these stages of sleep. Could it then be that CSD predisposes migraineurs to seek sleep? Non-clinical studies have shown that CSD increases non-rapid eye movement (NREM) sleep duration, suggesting an increased need for sleep [47]. Local energy depletion in the basal forebrain has been shown to increase NREM sleep comparable to the effect of 3-hours sleep deprivation [48]. Most recently, in a ground-breaking study, Faraguna and colleagues [49•] demonstrated that, in freely moving rats, unilateral CSD induction increased corticocortical evoked responses (synaptic potentiation) only in the affected cortical hemisphere. Large slow waves occurred in the affected hemisphere for several hours after CSD and were associated with quiet waking, disappearing during active exploration. They also found that NREM sleep duration increased after CSD. Since slow wave sleep reflects cortico-thalamic synchronization that reduces responsiveness to external sensory stimuli during sleep, these experimental studies suggest that CSD associated with a migraine attack may predispose an individual to seek restorative sleep.

What about the opposite? Does sleep prevent or reduce CSD? The answer to this is unknown and is difficult to address even in laboratory experiments. Conceptually however since CSD represents a state of intense neuronal activity that is known to activate subcortical pathways and deep sleep is characterized by slow wave thalamocortical oscillatory activity that alters sensory processing, it is certainly possible to conceptualize that sleep could reduce the effects of CSD and therefore help resolve a migraine attack giving headache pain relief. Perhaps a bidirectional homeostatic relationship exists between sleep and CSD. CSD predisposes to sleep, and sleep alleviates the consequences of CSD.

Subcortical Structures Relevant to Migraine Involved in Sleep

Our comprehension of the physiology of the daily cycles of sleep and wakefulness, as well as the neuronal circuitry and molecular basis of the biological clock that underpins human circadian rhythms (daily sleep–wake cycles), has increased substantially in recent years.

The wake promotion systems and the sleep promotion system are temporally controlled by the endogenous circadian pacemaker contained within the suprachiasmatic nuclei (SCN) that functions autonomously as the brain's master clock. The SCN receives information about light and dark periods from melanopsin expressing retinal ganglion cells during the day (the light entrainment system) and melatonin from the pineal gland at night to reset the human 24.5 hour circadian rhythm to our 24 hour day length. The molecular basis of the clock function involves transcriptional and translational regulation of the expression of genes such as period, clock, Bmal and cryptochrome that when mutated or deleted disrupt circadian rhythm cycles [50].

Daily oscillations in SCN activity signal through the subparaventricular zone and the dorsal medial hypothalamus to both GABA-ergic neurons of the ventrolateral pre-optic area of the hypothalamus (VLPO) and the wake promoting orexinergic neurons of the lateral hypothalamus. GABA-ergic neurons promote sleep by sending inhibitory projections both to orexin neurons as well as brain stem nuclei such as locus ceruleus (norepinephrine), Raphe nucleus (serotonin) and

tuberomamillary nucleus (histamine) that together with cholinergic projections from the basal forebrain form the ascending arousal systems. Attenuation of this inhibitory signal and increased excitatory input from the SCN to orexin secreting neurons that innervate these monoaminergic brain stem arousal nuclei promotes waking and somatosensory function [51].

Increasing evidence suggests that human circadian rhythms are regulated by a thalamic switch that can be activated or deactivated to regulate sensory information reaching the cerebral cortex and the degree of consciousness [52]. The transition from sleep to wakefulness comes as thalamocortical pathways activate the cortex that has been primed by neurotransmitters (serotonin, histamine, norepinephrine) released from ascending pathways originating in the brain stem. The extent of information passing to the cortex through the thalamus is "gated" based on the arousal level of the central nervous system that is in turn set by outputs from the brain stem and hypothalamus.

Orexin Systems in the Brain

Recent research has focused on a small number of orexinergic neurons that are clustered in the lateral hypothalamus [53]. It was not until recently in 1998 that it was discovered that these neurons produce a pair of closely related neuropeptides that were named orexin A (OX-A) and B (OX-B) by one group of investigators and hypocretin 1 and 2 by the other. OX-A and OX-B neuropeptides, are generated from the pre-pro-orexin peptide precursor encoded by the *HCRT* gene, are packaged into dense core vesicles of lateral hypothalamic neurons and are released via exocytosis from orexinergic neurons when they are activated. The orexin peptides bind to two different orexin receptors OX-1R and OX2R. The binding affinity of OX-A and OX-B for OX2R is similar, but the affinity of OX-B for OX1R is approximately 10 times lower than for OX2R. The primary mechanism of signaling from both OX-1R and OX-2R is through G-protein activation resulting in an elevation of intracellular Ca^{2+} from intracellular stores and neuronal activation [54].

OX-1 R and OX-2R are widely expressed throughout the cerebral cortex. OX2R are selectively expressed in the tuberomamillary nuclei (TMN) of the hypothalamus, and are thought to be predominantly involved in promoting arousal by triggering the release of histamine in cortical and sub-cortical brain areas. OX1R and OX2R are co-expressed in brain stem nuclei responsible for sleep/wake control and sub-cortical arousal, the exception being the noradrenergic locus ceruleus where OX1R are selectively expressed and are involved in REM sleep gating [55]. Interestingly (see above) it is these brain-stem regions that have been shown to be activated during migraine attacks.

Orexin neurons fire during active waking and virtually cease firing during sleep. Deficiencies in the expression of orexin peptide or its receptors lead to dysfunction in the mechanisms that determine sleep and arousal states in genetically altered mice, dogs and humans. Studies on human sleep syndromes where there is a loss of ability to control sleep states (narcolepsy) have shown the central involvement of impairments in the orexin producing systems [56].

In addition to their importance in wakefulness, recent studies in animals have linked the orexins to modulation of nociceptive processing, but the pharmacology of these interactions is still not fully understood and can be conflicting [57]. This may be because many of the studies have used direct injection of OX-A and OX-B at supra-pharmacologic doses so selectivity for OX-1R and OX2R is lost confounding allocation of receptor specificity to their pro and anti-nociceptive effects. Moreover, it is well known that OX-B is relatively unstable *in vivo* compared to OX-A especially after i.v. administration such that its effects or lack of them may be missed or underestimated after exogenous administration. Finally the selectivity of some of the early small molecule orexin antagonists may not be sufficient to provide confirmation of mechanism of action and new more selective pharmacologic tools will probably be required to provide definitive data [57]. This having been said in non-clinical studies, OX-1R has been localized to the spinal cord and dorsal root ganglion [58].OX-A and OX-B have been shown to be analgesic when given i.c.v. and intrathecally, but not subcutaneously, in line with their peptidic nature [59]. In animals, the efficacy of orexin-A acting at OX-1R (as defined by blockade of the response with the small molecule OX-1R antagonist SB334867, was found to be similar to that of morphine [60].

The orexins have also been recently linked with a possible role in migraine. Preclinical evidence suggests that OX-A acting at OX-1 receptors can modulate trigeminovascular nociceptive physiology such as dural vasodilatation [61] and input to the trigeminal nucleus caudalis after electrical stimulation [62]. Stimulation of the superior saggital sinus, an experimental maneuver for activating pathways relevant to migraine, was shown to activate neurons in the posterior hypothalamus [63] Injection of OX-A or OX-B into the posterior hypothalamus has been shown to differentially modulate nociceptive dural input to the TNC. Micro-injection of OX-A elicited an anti-nociceptive effect reducing A and C fiber responses to dural stimulation and spontaneous activity, in agreement with other analgesia studies whereas interestingly OX-B activation elicited the opposite "pro-nociceptive" effect enhancing nociceptive transmission and convergent sensory responses to facial thermal stimulation [64]. Most recently novel dual OX-1R/OX-2R receptor antagonists that have been developed for the treatment of primary insomnia [65] have been used to probe the pharmacology of the trigeminal system rather than the peptide orexin agonists. The dual orexin antagonists were shown [66] to inhibit electrically evoked trigeminal nociceptive transmission and neuronal

activity in the trigeminocervical complex supporting a pronociceptive role for orexins in trigeminal pain pathways. Delineation of the exact orexin receptor responsible for this effect awaits the study of OX-1R and OX-2R selective antagonists.

Given these data suggesting that orexins could promote trigeminovascular nociception, the propensity to sleep during migraine, and the possibility that migraine could be triggered by stimuli that activate the hypothalamus and increase orexin activity such as stress, fatigue, sleep deprivation or poor sleep hygiene [67, 68] there is the potential for orexin antagonism to treat or prevent migraine headaches. Finally, we must not forget that autonomic physiology changes during sleep as a function of time and sleep stage [69]. Sleep influences the cardiovascular, sensory, endocrine and thermoregulatory systems [70, 71]. During sleep there is a relative shift from sympathetic to parasympathetic tone with a decrease in blood pressure and reduction in muscle tone (atonia) with progressively deepening sleep stages that is regained upon waking. The orexin neurons of the hypothalamus fire during waking and are quiescent during sleep [72]. They innervate the brain regions that integrate sensory and autonomic systems with sleep behaviors [73]. Blockade of these systems by orexin receptor antagonists has the potential to mimic the physiological effects of sleep.

The use of current dual orexin receptor antagonists to treat migraine is however limited by their marked sleep promoting effects such that they cannot be given to treat migraines during the day unless induction of sleep is clinically acceptable. As a consequence, they will have to be dosed at bed time such that drug exposure during the day will be very low or absent, making these studies a test (in contrast to the acute non-clinical studies conducted to date) of migraine prevention through improvement of sleep hygiene rather than a test of orexin antagonism as a novel migraine treatment. Future studies on the role of the orexin peptides in the trigeminal system and the potential of OX-1R and OX-2R antagonists as anti-migraine agents will await the clinical development of receptor selective molecules as pharmacological tools.

Conclusion

The relationship of migraine and sleep disorders is complex. Sleep disturbances appear to be entwined with migraine pathophysiology (e.g., triggering individual attacks, or predisposing to migraine chronification), and clinical experience suggests that if patients are able to sleep during a headache attack, they often awake feeling better. The opposite explanations cannot be ruled out as well. It may be that the natural improvement of migraine is associated with sleepiness, which could be seen as a marker of migraine recovery. The reciprocal nature of these observations has not yet been disentangled and many of the associations remain purely observational. Many of the migraine premonitory symptoms that can occur well before an attack are thought to be mediated the hypothalamus and evidence is growing that hypothalamic brain nuclei that are involved in sleep –wake regulation such as the orexin secreting neurons of the hypothalamus can influence sensory processing. These intriguing juxtapositions of clinical observations and fundamental neuroscience suggest that the neurotransmitters and pathways of the hypothalamus and their role in nociception, and arousal are likely to be a fruitful area for future migraine research.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Marcelo E. Bigal is a full-time employee and holds stock/stock options with Labrys biologics incorporation.

Dr. Richard J. Hargreaves is a full time employee and holds stock/stock options with Merck & Co.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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