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Sleep and headache: a bidirectional relationship

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Sleep and pain perception are two phylogenetically well-conserved functions, strictly influenced by environmental and psychological factors, and are able to interact reciprocally both in physiological and pathological situations. Sleep and head-pain perception share the involvement of several structures, such as the thalamus, the hypothalamus and brainstem nuclei, including the locus coeruleus and raphe nuclei. There ais clinical evidence indicating that sleep disorders can precede the appearance of certain headaches and that head pain, especially when frequent, can, in turn, affect sleep quality. In the present work the anatomy, physiology and pathology of sleep and head-pain perception will be reviewed with the aim of highlighting the points of contact and possible unifying treatment strategies

Keywords: headache • insomnia • migraine • pain • parasomnia • sleep

Sleep and pain perception are phylogenetically strongly conserved physiological functions that are strictly influenced by environmental factors, such as temperature and light, and by psychological aspects, such as previous experiences or mood situations. Clinical research correlates specific headache diagnoses and sleep disorders with chronobiologic patterns and sleep processes, suggesting that common anatomical structures and neurochemical processes are involved in the regulation of sleep and headaches. Sleep and pain perception share the involvement of several structures, such as the thalamus, the hypothalamus, and the brainstem nuclei, including the locus coeruleus and raphe nuclei. Understanding the anatomy involved and physiology of both conditions can improve our knowledge regarding this complex relationship and allow us to develop a more rational clinical and therapeutic approach [1].

Different clinical evidence supports the existence of mutual relationships between sleep and pain. It is well known that noxious stimuli and painful disorders interfere with sleep, however, sleep disturbances also affect pain perception [2]. Headaches seem to have a particularly strong link with sleep disturbances, but the common pathophysiologic substrate is poorly understood [1]. There is clinical evidence that sleep disorders may precede the appearance of headaches [3]. On the other hand, head pain, especially when frequent, seems to be able to modify sleep quality. Sleep fragmentation, insomnia and hypersomnia all have relationships with headaches. Epidemiologic data suggest that sleep disorders occur more frequently in more severe forms of headache. It has been recently demonstrated that the decreased quality of sleep in migraine patients may be a consequence of the migraine itself, rather than being an expression of comorbidity with affective disorders. There is clinical evidence that migraine attacks may be precipitated by sleep deprivation or excessive sleep, although sleep is also associated with relief of migraine attacks [4], and a substantial improvement in headache can result from the successful management of sleep disorders such as obstructive sleep apnea or insomnia [5].

More specific correlations between sleep and headache have been identified. Particular headache syndromes such as chronic paroxysmal hemicrania and cluster headache (CH) seem to be related to rapid eye movement (REM) sleep.

Sleep-associated headaches are often perceived to be the result of disrupted sleep [1]. By contrast, primary headache disorders such as migraine, CH, chronic paroxysmal hemicrania, and hypnic headache (HH), may cause themselves significant sleep disruption. In some cases, polysomnography may be helpful in assessing the cause–effect relationship [1].

A strong relationship between headache and allodynia – the perception of a painful sensation by a non-noxious stimulus – has been recently identified. Allodynia probably results from changes induced in nociceptive pathways

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and structures by repeated painful stimuli. This symptom can interfere with several daily activities and also with sleep. Starting from these observations, our group is evaluating allodynia as one of the possible bridges that links headaches and sleep disturbances.

Physiological functions of sleep & pain

In contrast to the opinion of most people, sleep is an active function under the control of different parts of the CNS. The primary function of sleep is to restore the body energy levels [6]. Sleep has also important roles in cognitive functions (mainly memory), maintaining mood equilibrium, and in hormonal and immune regulation. Sleep disorders may seriously affect health and prolonged sleep deprivation may even endanger life [6].

Pain – the unpleasant sensation(s) elicited by harmful stimuli – helps us to avoid external dangers and induces us to pay attention to a possible internal dysfunction that needs to be corrected. Malfunctioning of the pain-related systems can obviously give rise to a number of problems. There are conditions in which a painful sensation is generated after non-noxious stimuli or even in the absence of any internal or external stimulus, thus becoming a noxious element by itself. This is the case for primary headaches on which this review will be focused.

In order to help understand the underlying mutual relationship, the biology of sleep and pain perception by a physiologic, anatomic and pharmacological point of view will be briefly overviewed in the following section.

Sleep: physiological & pathological aspects

Physiology of sleep: a multilevel pathway

Throughout life, the wakeful state is cyclically interrupted by sleep. In turn, sleep shows an intrinsic cyclic pattern best characterized by electrophysiological means. The main element that characterizes the macrostructure of sleep is the subdivision between REM and non-REM (NREM) sleep. The three states of wakefulness, REM sleep and NREM sleep recur cyclically with variable proportions according to age [7]. Mutual (reciprocal) inhibition between sleep promoting and arousal promoting occurs in a way that resembles an electronic 'flip-flop' switch [8].

The preoptic area and other basal forebrain areas play a major role in the generation of NREM sleep [6]. Interaction of the pedunculopontine nucleus and the lateral dorsal tegmental area with the dorsal raphe nucleus and locus coeruleus in the brainstem is important for REM sleep generation. The hypothalamic suprachiasmatic nucleus (SCN) and the pineal gland synchronize the physiological near-24-h sleep-wave cyclicity with the circadian light–dark pattern. The principal effectors in the brainstem and midbrain include the ascending reticular activating system (ARAS), thalamus, hypothalamus and basal forebrain, namely the basal forebrain cholinergic complex (BFCC). These structures are responsible for the cyclic activation/inhibition of the supratentorial cortical areas – although it should not be forgotten that wake-dependent activation also affects the spinal cord through descending pathways. This is of particular relevance with regards to the modulation of ascending noxious stimuli.

Arousal is mediated by a number of neural pathways. Norepinephrine, histamine and orexin mediate the activity of neurons firing in the awake state and in behavior-related arousal. The firing rate of these neurons decreases in slow-wave sleep and ceases during REM sleep [9]. Cholinergic neurons, actively discharging during wake, decrease their firing rate during NREM sleep but again discharge at high rate in REM sleep in concomitance with rapid cortical activity. In turn, specific populations of GABAergic neurons in the basal forebrain and the preoptic area discharge during slow-wave NREM sleep, while others increase their activity concomitantly to behavioral quiescence and decreased muscle tone either during NREM and REM sleep. The reciprocating activities and interactions of wake-active and sleep-active cell groups determine the wake–sleep alternance [9].

Brainstem level

Activation and inactivation of cortical neurons are under the control of cholinergic and GABAergic pathways, respectively. The two major cholinergic activating areas are the aforementioned ARAS and BFCC. The ARAS gives rise to cholinergic, noradrenergic, and glutamatergic projections to the thalamus, hypothalamus, and basal forebrain. However, cortical activation induced by the ARAS is indirect, since it needs to be mediated by the intralaminar nuclei of the thalamus. Conversely, the BFCC has consistent direct projections to the cortex and only a minor proportion acts by the interposition of thalamus [10]. The BFCC and the ARAS act in tandem on the cerebral cortex giving rise to electroencephalogram (EEG) desynchronization, an increase in cerebral blood flow, modulation of cognitive processing function, and possibly modulation of pain threshold at the cortical level.

Brainstem-dependent modulation of sleep onset seems to be related mainly to the activity of the nucleus tractus solitarius. The noradrenergic projections from this nucleus to the midbrain and forebrain structures can inhibit the ARAS and activate inhibitory GABAergic thalamocortical projections to the cortex [7].

Thalamic level

Although the thalamus, as seen above, is an essential mediator of arousal originating in lower structures (mainly the ARAS), it should not be considered as a mere relay station. The intrinsic electrical properties of thalamic neurons make them capable of exerting a substantial control on the sleep–wake alternance [11]. The oscillatory activity in the thalamus is under the influence of afferent inputs from the neocortex and, to a lesser extent, from sensory pathways. As the membrane potential rises above -50 mV, thalamic neurons generate subthreshold oscillations with a frequency of approximately 40 Hz (γ band). This activity supports thalamo–cortical resonance and is the functional antithesis of the slow rhythmicity that is best evidenced in the deepest (slow-wave) stages of NREM sleep [11]. The thalamo–cortical activity has been demonstrated to be involved in the genesis of several neuropsychiatric conditions, collectively described as the 'thalamo–cortical dysrhythmia syndrome' [11], which includes among its symptoms headache and sleep disturbances.

Hypothalamic level

A sleep-promoting function for the rostral hypothalamus was initially inferred from the observation that chronic insomnia often followed damage to this structure [12]. Neurons in the preoptic area and adjacent basal forebrain are selectively activated during sleep. The hypothalamus is now recognized as a key center for sleep regulation [13]. A small population of GABAergic sleep-active neurons can be found in the ventrolateral preoptic area, lateral to the optic chiasm (vlPOA), and in the median preoptic nucleus (MnPN). In addition to GABA, vlPOA neurons also release galanin as an inhibitory neuromodulator [12]. Tracer studies revealed the existence of projections from the vlPOA and MnPN to arousal-regulatory systems in the posterior and lateral hypothalamus and rostral brainstem. There are cumulative lines of evidence that preoptic neurons promote sleep onset and maintenance by inhibiting these arousal systems. Cholinergic, histaminergic, serotoninergic and noradrenergic wake-promoting neurons are also present. They send axons back to the vlPOA, thus inducing neuronal inhibition, which gives rise to a mutually antagonistic network ensuring that specular changes in the activity of sleep- and wake-promoting neurons occur across the sleep–wake cycle. Besides being involved in the transition between sleep and wake, the same system also favors the stabilization of both sleep and wake states [14]. Neurons in the vlPOA are GABAergic and project to wake-promoting structures such as the serotonergic and noradrenergic neurons of the pontine and midbrain reticular formation, and histaminergic neurons in the posterior hypothalamus [15]. Their discharge rate increases at sleep onset and in the subsequent phases in a manner proportional to sleep depth. The vlPOA GABAergic neurons are in turn reciprocally inhibited by noradrenergic brainstem neurons. Thus, sleep induced through activation of the vlPOA inhibits wake-promoting structures, which in turn removes inhibition from vlPOA itself, thus facilitating the sleep-onset process with a feed-forward mechanism. On the other hand, stimuli capable of inducing arousal inhibit vlPOA, which would then remove inhibition from wake-promoting neurons. In this way the system can not only mediate the switch between sleep and wake, but also tends to sustain established sleep and wake states [14].

It has been recently found that the preoptic area is involved in the homeostatic aspects of the regulation of both REM and NREM sleep, probably through the effect of endogenous sleep-promoting mediators, such as some cytokines and adenosine [12].

The hypothalamus is also involved in the synchronization of the sleep cycles with the light–dark alternation. The hypothalamic circuitry is essential for the integration of photic and nonphotic environmental time signals that allow organisms to adapt to the patterns of rest–activity and sleep–wake cycles to environmental needs and seasonal variations [14]. The physiological circadian cycling of active life and wakefulness evolves over a precise 24-h rhythm that corresponds to the solar cycle. However, in the absence of a normal light–darkness alternation, as can be made in an experimental setting or has been sometimes observed in abnormal environmental conditions (i.e., prisoners and speleologists) the circadian cycles drift from the precise 24-h schedule. The SCN is a small group of hypothalamic neurons that covers the role of a circadian pacemaker controlling the timing of the sleep–wake cycle, providing synchronization with the light cycle and coordinating circadian rhythms in other brain areas and organs to enhance behavioral adaptation [16]. The SCN is also important for the homeostatic processes of sleep consolidation and the physiologic homeostatic sleep drive [8].

Pineal gland

Melatonin, the hormone secreted by the pineal gland, covers a major role in the regulation of sleep and other biological functions. As mentioned earlier, the SCN contains neurons with a circadian pattern of activity and its roles include helping to regulate melatonin secretion by the pineal gland in response to signals from the environment – namely the light–dark cycle [17]. The circadian changes of SCN are responsible for regulation of a number of physiological activities which include, besides the sleep–wake cycle, hormonal secretion and thermoregulation [18,19]. The GABAergic neurons in the SCN characteristically corelease other mediators such as arginine vasopressin (AVP) and vasoactive intestinal polypeptide (VIP) [19]. The GABA–AVP pathway regulates the circadian changes in the brainstem and other hypothalamic areas, such as the subparaventricular zone and the dorsomedial nucleus. The latter controls a wide range of circadian responses, including the sleep–wake cycle, via projections to other hypothalamic targets, particularly the ventrolateral preoptic area, the periventricular nucleus (PVN) and the orexinergic neurons of the posterior lateral hypothalamus [19]. The SCN also sends a direct inhibitory projection to the PVN controlling its sympathetic output to the pineal gland [20,21]. In this way, the pineal gland may extend, through the release of melatonin, this circadian control of the SCN to a number of different bodily structures.

Cortical level & EEG

In normal human sleep, the NREM and REM phases alternate cyclically. A typical sleep cycle lasts 60–120 min and consists of four subsequent NREM periods and one REM period. The transition between NREM and REM sleep is controlled by the so-called 'REM-off' noradrenergic neurons in the locus coeruleus and serotoninergic neurons in the raphe nuclei, and 'REM-on' cholinergic neurons in the pontine reticular formation.

The transition between the different phases of sleep is best evidenced using an EEG. As sensory inputs are attenuated, the EEG synchronizes giving rise to the normal α rhythm. Furthermore, synchronization of the EEG corresponds to moderately deep to deep stages of NREM sleep. At NREM stage 1, the α rhythm decreases and an EEG pattern of relatively low voltage and mixed frequency is observed. The appearance of the characteristic elements, which are sleep spindles and K-complexes, reveals the transition to stage 2, while the deepest sleep stages 3 and 4 show low-frequency EEG activity of increasing amplitude [7]. In the REM phase of sleep, characterized by rapid eyes movements and generalized hypotonus, the EEG is desynchronized.

Sleep disturbances: a brief picture

More than 100 sleep–wake disorders have been recognized as distinct clinical entities. Most of them can be ascribed to one of four principal diagnostic categories in accordance to the Association of Sleep Disorders. These consist of the following: alterations of the sleep–wake cycle, hypersomnias, parasomnias andinsomnias [2]. Primary sleep disorders are defined as the result of structural or functional (biochemical or metabolic) abnormalities arising within the CNS. A clear causal relationship has been demonstrated for a limited number of these disorders, as is the case for orexin receptor defects and narcolepsy [22–24]; for most of them, however, the pathophysiological features are not fully disclosed.

Abnormalities in the 'molecular clocks' and related regulatory genes have been recently identified in some patients with sleep disorders. Other genes have been shown to contribute to sleep disorders. A point mutation in the prion protein gene is the cause of fatal familial insomnia, and a mutation in the gene for the GABA-A β 3 subunit has been associated with chronic insomnia [25].

Attention has been drawn to conditions in which sleep, although normal by its quality, is quantitatively inadequate [26]. Chronic sleep restriction has severe adverse neurobehavioral effects, such as attention disorders, memory and other cognitive impairment, depressed mood [26], and pain syndromes, among which headache is preponderant. Sleep deprivation can also affect physiological variables, including glucose tolerance, blood pressure, sympathetic activation, and inflammatory mediators. The individual variability in neurobehavioral responses to sleep restriction appears to be related to a trait-like (possibly genetic) vulnerability.

Changes in the regular rhythm of the sleep–wake cycle often have negative influences on well-being, as is the case for shift-schedule workers or jet lag disorder, in which misalignment of circadian rhythms occurs after crossing time zones too rapidly for them keep pace [27]. In these conditions, the effects of sleep–wake cycle drift are often associated with those derived from sleep deprivation.

Primary headaches: pathophysiological aspects

Pathophysiology of sleep-related primary headaches: the case of CH & HH

Cluster headache

Cluster headache is included among the trigemino-autosomal cephalgias (TACs). It is characterized by recurrent brief attacks (15–180 min) of severe unilateral periorbitary pain associated to ipsilateral autonomic signs such as tearing, rhinorrhea, eyelid edema and ptosis, miosis and conjunctival injection. CH is infrequent, with a prevalence of approximately one in 1000, and affects mainly young adult men. Alcohol, intense smells, cigarette smoke and sleep alterations are common triggers of CH. Attacks are clustered in short periods and typically display a circannual and circadian periodicity [28], with peaks around solstices, related to changes in daylight duration [29]. Attacks frequently occur at a precise time during the sleep cycle, with notable regularity [28]. Restlessness during the attacks is associated to trigeminovascular activation and neuroendocrine and autonomic disturbances.

The pathogenesis of CH remains unclear. Neurovascular phenomena seem to be both permissive and triggering factors, as occurs in migraine, however, there is an increasing body of evidence that primary brain involvement predominates, whereas vasomotor changes occur secondarily [30]. Hypothalamic involvement can in part explain the cyclic aspects of CH. A causal role for the hypocretin receptor gene has been hypothesized and can be relevant regarding the association with night-time sleep. Deep brain stimulation (DBS) of the hypothalamus has been proven to have some efficacy in treating drug-refractory CH patients [28].

Hypnic headache

Hypnic headache, first described by Raskin in 1988, is a rare sleep-associated primary headache disorder that usually affects people over 50 years of age. It is also called 'alarm clock' headache and is characterized by single or multiple attacks of dull headache that occur exclusively during sleep and sometimes during a dream and constantly awaken the patient [31]. The reported female:male ratio is 1.7:1. Attacks are frequent (at least 15 a month) and autonomic symptoms are characteristically absent. The pain is bilateral in approximately two-thirds of cases, are usually of mild-to-moderate intensity, but can be severe in approximately a fifth of patients. The attacks usually last from 15 to 180 min but can occasionally be longer [32]. Exceptions to the described clinical spectrum may be represented by unilateral, often side-locked, pain, longer duration, or onset in young adults, and such exceptions are increasingly being reported.

Pathophysiology of migraine, an apparently sleep-unrelated primary headache largely influenced by sleep

Migraine, the most common form of disabling primary headache, is characterized by recurrent attacks of unilateral throbbing headache, variably associated with nausea, vomiting, photo- and phono-phobia, and enhanced irritability. In approximately 20% of migraineurs headache attacks are heralded by manifestations defined as the migraine aura.

Migraine is thought to arise from a dysfunction of the trigeminovascular system [33]. The intracranial pain-generating structures are innervated by branches of the trigeminal nucleus caudalis (TNC). The dilated blood vessels mechanically activate the trigeminal sensory afferents, inducing the release of glutamate, substance P, calcitonin gene-related peptide and other proinflammatory peptides from the sensory nerve endings. These self-maintaining mechanisms potentiate centripetal nociceptive transmission.

Besides the described neurovascular features, a role of CNS neurogenic mechanisms in migraine is supported by several lines of evidence. According to a neurovascular pathogenetic model [34], migraine attacks are precipitated by a lowering of the excitability threshold of brain cortex [35]. During the migraine aura, cortical hypoperfusion occurs in response to depressed neuronal function and tends to diffuse to contiguous regions giving rise to the so-called 'spreading depression'. Recently, Tottene *et al.* demonstrated that hyperactivity of P/Q-type calcium channel-mediated cortical

glutamatergic synaptic transmission represents a mechanism of susceptibility for cortical spreading depression in migraine [36]. The neurovascular theory also takes into account the role that neurochemical imbalances, the trigeminal system, meningeal blood vessels and noninfectious neurogenic inflammation can play in pain generation [37]. Hamada *et al.* recently showed that the level of plasma orexin-A in migraine patients during headache-free periods is lowered, suggesting that orexinegic neurons in the lateral hypothalamus may be generators of migraine [38]. The complexity of clinical manifestations in migraine therefore reflects the existence of an intricate pathway of neuronal circuits, the activity of which is modulated by environmental, psychological and hormonal elements besides being affected by a genetically determined predisposition. On this dynamic cerebral condition, characterized by the phenomena of habituation, sensitization and convergence of inputs, certain triggers can elicit migraine attacks [39].

Long-lasting activation and sensitization of neurons in the spinal nucleus of the TNC by nociceptive inputs from the whole trigeminal territory can sustain the development of head and face pain during the migraine attack [40]. Convergent inputs from intracranial and extracranial structures to the TNC are required to sustain the hyperexcitability that gives rise to allodynia [34,41].

The brain of migraineurs is characterised by a lack of habituation to evoked responses. Experimental data indicate that the sensory cortex of migraineurs reacts excessively to repetitive, but not to single, stimuli. Derangements of thalamo–cortical circuits may in part be responsible for such unbalance [42]. As described in previous sections, the thalamo–cortical activity is the product of the intrinsic electrical properties of neurons that, with their specific functional dynamics, regulate natural functional states such as sleep and vigilance. In this context, it is notable that besides being hypersensitive to external stimuli, migraine patients may also present with excessive daytime sleepiness [42].

Shared pathophysiologic features of sleep regulation & primary headaches

Modulatory molecules common to both sleep & headache regulation

As mentioned earlier, brain structures involved in sleep organization are largely implicated in primary headache genesis. Similar analogies emerge as concerns neurotransmitters that regulate sleep cyclicity and pain perception and modulation.

Several neurotransmitter systems are implicated in both sleep regulation and head-pain perception. Besides monoamines and acetylcholine, particular importance has been attributed to GABAergic structures, the orexin/hypocretin system and others including prostaglandins (in particular PGD2), cytokines (IL-1), and adenosine.

Hypocretins & orexins

Efficient wakefulness is essential for activities such as avoidance of dangers and thriving for food. Therefore, it is not surprising that specific systems, as the orexin (hypocretin) system, can supersede at these functions in an interdependent fashion [43]. Orexins are part of a recently characterized peptide family [44] primarily implicated in control of food intake and regulation of normal sleep processes [45]. They are synthesized in the lateral hypothalamus [13] and bind to the specific G-protein-coupled receptors, OX1R and OX2R, which are expressed by several neurons in brainstem, diencephalon, hippocampus and neocortex [46]. Orexin-sensitive structures include locus coeruleus, ventral tegmental area, and tuberomammillary nucleus (TMN). Through the activation of these monoaminergic areas orexins stimulate wake-active neurons in the hypothalamus and brainstem and allow the maintaining of a consolidated awake status, an effect that requires mediation by the limbic structures [44]. Dysfunction of the orexinergic system is a key feature of narcolepsy [47].

Orexins are also involved in energy homeostasis and neuroendocrine regulation [47,48], and modulation of orexinergic pathways also depends on metabolic variables such as glucose levels [49]. Orexins maintain the wake state and increase vigilance in response to several conditions, such as hypoglycemia, which can also trigger migraine attacks. Orexins are reduced in migraineurs, and orexinegic neurons in the hypothalamus have been hypothesized to be possible generators of migraine and CH.

Melatonin

There is evidence that melatonin, besides having a role in the biological regulation of circadian rhythms, sleep, mood and ageing, is also involved in various headache syndromes, including CM, CH and chronic tension-type headache (CTTH). Altered melatonin levels in migraine, CTTH, CM and CH patients during the cluster and an abnormal blunting of melatonin peaks during the active period have been documented [50]. Involvement of melatonin in the pathophysiology of headache may be related to its anti-inflammatory effects (i.e., free radical scavenging and reduction of proinflammatory cytokines upregulation), an increase of nitric oxide synthase activity, inhibition of dopamine release, membrane stabilization, potentiation of GABA- and opiate-induced analgesia, protection from glutamate neurotoxicity, neurovascular regulation and serotoninergic modulation [51].

Adenosine

Adenosine accumulates during wakefulness in the extracellular space of forebrain structures and can inhibit wakefulness-active neurons [52]. Prolonged sleep deprivation is accompanied by upregulation of adenosinergic A1 receptors. A1 receptor-mediated inhibition is therefore potentiated, thus increasing the gain of the sleep homeostat. Similar mechanisms can also take place in other cortical areas [52].

Cytokines

There is growing evidence that the processes of circadian timing are under the influence of the immune system and, *vice versa*, that the immune function is influenced by the circadian rhythm [53]. This can be manifested, for example, by the circadian rhythmicity of cytokine release and cytokine receptor expression in the SCN [54]. The immunoinflammatory system takes part in modulating the mechanisms giving rise to migraine, possibly by the intermediation of cytokines that are broadly expressed by several cells

of the CNS, including the neurons that are considered to mediate pain in neurovascular inflammation [55]. Activation of the immune system has been identified in CH in which an increase in IL-1 β, in particular during the ictal phase, can be found [56].

Calcium & sleep neurons: the cellular level of cyclicity

T-type Ca^{2+} channels are the main membrane structures the role of which is important in maintaining the characteristic oscillatory properties of thalamocortical circuitry, as can be best observed in NREM sleep [57]. In this physiological condition, the transient opening of T-type channels first gives rise to low-threshold Ca^{2+}-dependent potentials and then to high-frequency bursts of action potentials that are characteristically related to the appearance of sleep spindles and δ waves in the EEG. It also contributes to the high threshold bursts that underlie the thalamic generation of sleep θ rhythms.

Sleep-headache relationships: clinical & epidemiological evidences

Noxious stimuli and painful disorders on the one hand and sleep disturbances on the other hand are strictly inter-related [2]. It is well known that some primary headaches are related to specific sleep phases, as is the case for chronic paroxysmal hemicrania, HH and possibly CH, which are all related to REM sleep. The successful management of the sleep disorder usually ameliorates headache [2]. In other instances, headache and sleep seem to be linked to common and specific causative factors [58].

When investigating the relationships between specific sleep disorders and headache, the pivotal role of the hypothalamus should be remembered [59,60]. Thanks to its connections with a number of structures involved in autonomic and sleep mechanisms, as well as to the descending pathways controlling pain perception (brainstem periaquiductal grey, locus coeruleus, raphe nuclei), the hypothalamus is able to influence the chronobiological features of some headaches, in particular the sleep-related attacks in TAC, migraine and HH [59]. Hypothalamic involvement also takes place in CM, a condition characterized by a complex chronobiological dysregulation [61].

Migraine attacks may be precipitated by sleep deprivation or excessive sleep; on the other hand, relief from migraine is often brought on by sleep [62]. A particular link between sleep and migraine is represented by the typical elementary geometric imagery of the visual aura of migraine that can be experienced as a part of the oniric content which precedes awakening with a migraine headache. Furthermore, migraine aura can be represented by dreams, often recurrent, featuring complex and often unpleasant visual imagery (terrifying nightmares) [63]. In addition, sleep fragmentation, insomnia and hypersomnia all demonstrate a relationship to headache [64]. Finally, it should be remembered that headache and sleep disturbances can be symptoms of a common underlying disorder [58].

Headache in patients with sleep disturbances

The sleep disorders associated with headache are multiple and include obstructive sleep apnea syndrome (OSAS), periodic limb movement disorder, circadian rhythm disorder, primary insomnia, hypersomnia, and circadian phase abnormalities [65]. Headaches that occur during or after sleep may be primary or, less often, secondary to a sleep disorder, as is the case for hypoxemia-related headache [65].

Sleep-disordered breathing

Sleep-disordered breathing is the best example of a specific sleep disorder related to headache. OSAS occurs frequently in the general population. Chronic headache is seven-times more common among individuals with OSAS than in the general population [66]. Morning headache is a typical clinical finding in OSAS, with a prevalence ranging between 20 and 70%, it is significantly higher in moderate-to-severe forms, and can also be presented by heavy snorers [67]. Although common in OSAS, morning headaches are not specific for this syndrome, and their relationship with nocturnal respiratory patterns and architectural sleep parameters is poorly established [68]. In a comparative study by Grenough *et al.*, OSAS patients with and without headache did not differ in the percentage of sleep time (either REM or NREM) spent with oxygen saturation less than 90%, thus negating the hypothesis that the duration of nocturnal hypoxemia relates to headache [69]. These findings have been contradicted in another recent study in which it emerged that the oxygen saturation nadir during REM and NREM sleep as well as mean oxygen saturation during total sleep time are significantly lower in OSAS patients with morning headache compared with headache-free patients [70].

Patients (especially if male, middle-aged and overweight) suffering from chronic refractory headache associated with sleep apneas or snoring should be considered for polysomnography in order to rule out OSAS. The effect of nocturnal continuous positive airway pressure (C-PAP) ventilation on headache is still an open question given the controversial results of different studies regarding this issue [71,72]. It has been hypothesized that nighttime fluctuations of oxygen saturation determining hypercapnia, vasodilatation and increased intracranial pressure can impair sleep quality but, as mentioned, the exact mechanisms remain only partially identified.

Insomnia

Insomnia is the most often cited sleep-related complaint in headache patients [73]. It is particularly frequent in episodic morning migraine and seems to influence the circadian pattern of migraine attacks that are preponderant in the morning hours. The exact causal relationships between migraine and insomnia remain unclear [74]. Transient recurrent situational insomnia, reversible after remission of headache, has been reported in association with chronic CH [75].

Narcolepsy

Narcolepsy is associated with different types of headaches. In 1991 it was described the case of a patient who first presented with episodic CH and later developed narcolepsy. The frequency and distribution of pain attacks did not change once the narcolepsy crises had begun, suggesting that narcolepsy-related changes of

REM sleep – a common trigger for cluster pain – do not seem to be able to modify the CH pattern [76]. In a study by Dahmen *et al.* on 68 narcoleptic patients interviewed for the presence of headache symptoms, headache was reported by 81% of them. In a more specific manner migraine defined according to ICHD-I criteria was found in 54% (65% women, 35% men) [77]. The increased prevalence of migraine in narcoleptic patients was confirmed by the same authors in a larger population. Migraine prevalence was two- to four-fold greater in narcoleptic patients than in a reference population, reaching 44.4% in women and 28.3% in men [78]. The onset of narcolepsy preceded by 12.3 ± 11.4 years that of migraine.

A multicenter case–control study evaluating the comorbidity of narcolepsy and different headaches did not found differences in migraine frequency between patients and controls, whereas tension-type headache was significantly more frequent in narcoleptic patients. The authors concluded that narcolepsy is associated with nonspecific headaches rather than to migraine [79].

Parasomnias

Wakefulness, REM sleep and NREM sleep may sometimes occur almost simultaneously, oscillate rapidly, or appear in dissociated or incomplete forms to produce primary sleep parasomnias [80]. Most of these often bizarre and frightening experiences constitute a diagnosable and treatable disturbance. Somnambulism is one of the most frequent parasomnias. A significant proportion of people with somnambulism also suffers from migraine, especially young women and patients with ophthalmic migraine. Somnambulism and migraine generally appear at different ages, the former in the late infancy, the latter in childhood; both seem to be related to a disorder of serotonin metabolism [81].

Sleep disorders in primary headaches: clinical & experimental evidence

A significant risk for sleep disturbances, particularly as concerns initiating and maintaining sleep, is presented by sufferers of migraine with aura, and a similar association exists between CTTH and sleep breathing disorders [82]. Additionally, headache disorders are associated with excessive daytime somnolence.

Migraine & sleep disorders

Insomnia is the most common sleep disorder in migraine, being present in approximately half to two-thirds of migraineurs. A large proportion of migraineurs report, at least occasionally, difficulty in the induction and maintainance of sleep, and very often a chronically shortened sleep pattern, similar to that observed in people with insomnia. Migraine attacks are often triggered by sleep disturbances. Awakening owing to headache is reported by the majority of patients [83], and sleep deprivation has been reported to be the most common trigger of migraine, with (44%) and without (38%) aura [84]. Furthermore, the prevalence of excessive daytime sleepiness (even in interictal periods) among migraineurs is significantly high [85] and its presence correlates with disability, nocturnal sleep problems and anxiety.

Sleep habits in patients with headache are often considerably abnormal since childhood. Snoring, sleep talking, bruxism, pavor nocturnus, nightmares, breathing pauses, and awakening in the night are often reported [86]. Parasomnias, night-time sweating, and daytime sleepiness are more common in children with migraine than in controls [87]. Gender influences headache–sleep relationships mainly in the young: girls with headache have poorer sleep quality, whereas the same has not been confirmed in boys [88]. In adolescents suffering from headache, sleep-related disturbances are also relevant. The most frequent complaint is insufficient total sleep (65.7%), followed by difficulty in falling asleep (40.6%), night awakenings (38%) and daytime sleepiness (23.3%) [89]. Changes in sleep pattern are also reported, particularly in the night preceding a headache attack. Migraineurs show a lower cyclic alternating pattern (CAP) rate in NREM sleep and a low index of high-frequency EEG arousals during REM sleep, suggesting a dysfunction in neural structures involved in the control of REM sleep and migraine generation and located within the hypothalamus and the brainstem [90]. By means of actigraphic studies, it has been also shown that in young migraineurs the sleep onset latency is slightly prolonged during the interictal period, and that the nocturnal motor activity decreases in the imminence of an attack [91], suggesting that cortical activation during sleep decreases before migraine attacks.

The role of the hypothalamus in migraine has been better outlined in a study evaluating some migraine-triggering conditions. These include stress (79.7%), neuroendocrine factors in women (65.1%), fasting (57.3%), a warm environment (30.3%), meals (26.9%) and sexual activity (5.2%) [92]. These data suggest that migraine is, at least in part, a problem of adaptation to environmental elements. The pineal gland may also be involved in the pathogenesis of migraine and other headaches [93]. Melatonin levels are low in plasma from migraine patients and show an abnormal circadian pattern in CTTH, CM and CH during the cluster period. These findings therefore corroborate the involvement of hypothalamus and pineal gland particularly in chronic-type headaches rather than episodic ones [50].

Whereas defective or disordered sleep can trigger migraine attacks, conversely sleep can provide relief from headache and is thought to be an important protective factor for migraine [83]. Besides drug treatment, lifestyle changes should always be considered for migraine prophylaxis. Patients should be advised to make efforts in order to maintain regular life habits with special regards for meals, physical exercise, management of stress and, of course, sleep [94].

Chronic daily headaches & sleep disorders

The relationship between primary headaches and poor quality of sleep is also evident in chronic daily headaches, including transformed migraine. Chronic daily headache usually evolves from an episodic headache, mostly migraine. Psychopathological factors, such as personality traits or stressful life events, systemic conditions such as hypertension, and sleep disturbances have been identified both as causes of transformation and consequences of chronicization. Patients frequently report a poor sleep quality and drowsiness during the morning [95,96].

An intriguing hypothesis regarding a possible common mechanism underlying migraine transformation and sleep changes is related to the hypersensitivity to nitric oxide. Circulating nitric oxide increases towards the end of the sleep cycle and can be further increased by factors, such as stress and old age, that reduce sleep continuity. The sleep fragmentation-dependent nitric oxide release is probably mediated by cortisol. Nitric oxide-dependent vasodilation may therefore be a relevant mechanism that can sustain headache or even contribute to the switch towards CM in association with sleep disturbances. This can be particularly relevant since the brain of patients suffering from migraine seems to be supersensitive to nitric oxide [97].

CH & sleep disorders

The nocturnal predominance of CH in REM sleep, its association with sleep apnea in approximately a third of patients and the efficacy of oxygen therapy are features that underline the association between CH and sleep problems [98]. The hourly rate of sleep apneas and hypopneas in CH patients exceeds 80%, and minimum oxygen saturation is frequently reduced. All these findings are more evident in the active phase of CH [99]. Hypothalamic (dys)regulation seems to be responsible for both sleep apnea and CH [100]. During the headache clusters, sleep–wake pattern becomes irregular and abnormalities of REM sleep occur. An association has been hypothesized with dysregulation of the 'biological clock' and the arousal mechanisms, particularly in relationship with REM sleep [101]. In patients with sleep apneas and CH, C-PAP treatment is able to prevent headaches as well as nocturnal oxygen desaturation [98].

Besides obstructive sleep apnea, other sleep disorders, including insomnia and narcolepsy, can be associated with CH [102]. Treatment strategies addressed at these associated conditions have been attempted. Melatonin levels are decreased in CH similarly to migraine. Defective melatonin secretion seems to predispose CH patients to nocturnal, and possibly daytime, attacks. Melatonin and other treatments that affect the circadian rhythm have been suggested for the simultaneous treatment of CH and the associated sleep disorder [102]. Leone *et al.* demonstrated that melatonin could rapidly alleviate cluster attacks in episodic cluster patients [103], and Peres *et al.* reported that melatonin administration could be beneficial in CH patients with both daytime and nocturnal attacks [104].

In patients with drug-resistant chronic CH, DBS of the posterior hypothalamus has been evaluated as a possible treatment option. DBS abolished nocturnal CH attacks, demonstrating an improvement of sleep structure and quality [105]. Again, these findings underline the central role of the hypothalamus in CH pathophysiology. More recently, the involvement of the hypothalamic orexinergic system as a possible key pathway in CH pathophysiology has been emphasized [106], again reinforcing the hypothesis of a common origin for CH and the associated sleep disturbances.

HH & sleep disorders

Pure sleep-related headaches are quite rare and include hypoxemia-related headache and HH [107]. Polysomnographic recordings in patients with HH allow the observation of an increased frequency of attacks during REM sleep, together with the appearance of the so-called ponto-geniculo-occipital spikes (PGOs), which are considered to be potential triggers of cortical spreading depression [108]. A NREM HH has also been described [109]. REM and NREM HH attacks are not associated with sleep-related breathing abnormalities [110]. As concerns treatment, lithium is particularly effective, but caffeine, an adenosinergic antagonist influencing sleep-promoting structures, may also be useful [111].

Tension-type headache

Tension-type headache is probably the most common of the head-pain syndromes. Its prognosis is fairly favorable, especially for the episodic forms. Indicators of a poorer outcome include chronicity, coexisting migraine, and sleep problems [112]. Data about sleep disorders in tension type headache are limited. An association has been found with narcolepsy [79], and CTTH has been indicated as a trigger for sleep-breathing disorders [82], however, these findings require further confirmation.

Drug overuse headache

Drug overuse headache generally complicates chronic headaches, especially the transformed forms, and the overuse of certain drugs is recognized as one of the major triggers for the transformation. In this form of headache, that is essentially treated by drug washout, a low sleep quality was found to be associated with a poor outcome of withdrawal therapy [113], evidencing that before considering drug washout, attention needs to be paid to sleep problems and proper sleep treatment should be instituted.

Mood: one of the bridges between headache & sleep

In this section, we will make a brief overview of the changes in the psychological profile that can be observed in both headache and sleep disorders and that might constitute, at least in part, a common background of headache and sleep disturbances. Taking into account the full constellation of headache, sleep and affective symptom may yield opportunities to ameliorate treatment [73]. Cognitive–behavioral therapies aimed at treating pain and insomnia in patients with chronic pain can reduce pain severity while improving sleep quality [114].

Chronic pain is often associated with disordered mood. Depression and anxiety are frequently comorbid with both headache and sleep disorders, especially insomnia, giving rise to a headache–sleep-affective syndrome [73]. Migraine with aura is associated with hypomania, recurrent depressive episodes and anxiety disorders, whereas phobic disorders and panic attacks have been correlated to migraine without aura. The onset of the mood disorders generally precedes that of migraine. Affective disorders including anxiety do not seem to be significantly related to tension-type headache [115].

The impact of anxiety disorders and migraine on sleep quality has been the object of several studies. Subjects suffering from panic disorder have poorer sleep quality as assessed by Pittsburgh sleep quality index (PSQI) scores; when panic disorder was associated with migraine, patients scored worse for sleep quality items in the Hamilton Depression Rating scale [116]. Multidimensional

evaluation performed in migraine patients by PSQI, fatigue severity scale (FSS), Epworth Sleepiness Scale (ESS), the Self-Rating Depression Scale and the Self-Rating Anxiety Scale confirmed that, although the quality of sleep was negatively affected, the incidence of fatigue and daytime sleepiness did not differ from healthy controls [117]. The poor quality of sleep in migraineurs is therefore a consequence of the migraine itself and can be only partially related to comorbidity with depression or anxiety. It is noticeable that the association between sleep disorders and migraine persists after successful treatment of anxiety and mood disorders [118]. In another study, however, a strong association was found between the occurrence, severity and frequency of headache on the one hand, and sleep problems and psychological distress on the other hand, reinforcing the evidence that poor sleep and anxiety make a substantial contribution to the impact of headache on life quality and well being [119].

A greater relevance of psychiatric comorbidity has been found in transformed migraine compared with episodic forms. The coexistence of depression and migraine calls for an effective treatment of depression in order to reduce the risk of shifting towards transformation of migraine [120]. Somatic symptoms, among which fatigue and altered sleep predominate, are more common in patients with chronic headache associated with anxiety or depression, especially in those with more frequent and severe attacks [121]. Behavioral intervention on the sleep changes in patients with transformed migraine is capable of inducing significant reductions in headache frequency and severity [122].

Seasonality of headache & sleep

Both sleep quality and headache show a circadian and seasonal periodicity. In arctic countries it was observed that patients with migraine, but not with other headaches, were more likely to have attacks during the bright summer season [123]. Migraine attacks tend to recur in a 24-h cyclic fashion, with a peak around the middle of the day in both aura and nonaura patients [124]. In the Northern Hemisphere, migraine attacks are more frequent during the summer. In geographic areas where the light-darkness cyclicity changes widely throughout the year this effect is more evident, and migraineurs present more attacks during the luminous seasons than during the dark ones. Interictal light hypersensitivity and light exposure can be precipitating factors in these patients. Notwithstanding, no significant difference was observed between aura and nonaura patients as regards circadian or circannual changes in sleep disturbances [125]. Seasonal periodicity of migraine is therefore a characteristic of aura migraineurs. This effect is likely to be related to increased light sensitivity and cortical hyperexcitability in migraineurs [123]. Interestingly, when insomnia-related attacks were successfully treated the seasonal changes were minimized [126].

Quality of sleep & allodynia among primary headache patients

Allodynia is the perception of pain induced by a non-noxius stimulus. Allodynia is commonly reported by patients with disease states, such as neuropathic pain and fibromyalgia, in which chronic pain is a main feature. Allodynia is far from being uncommon in primary headaches, especially in migraine, where it results from an altered regulation of the central nociceptive pathway and persistent pain-induced central sensitization in the caudal nucleus of the TNC. Although an increasing amount of evidence is reinforcing this theory, it is still unexplained why the frequency of allodynia in migraine patients is not constantly related to the number or severity of migraine attacks. Moreover, since a significant proportion of patients with episodic migraine also complain of interictal allodynia, central sensitization alone presumably cannot explain the occurrence of allodynia [127].

Many recent studies in allodynic subjects have demonstrated changes in CNS nociception-related processes that can induce neuroplastic changes resulting in central sensitization. Additional factors, above all poor sleep possibly related to changes in thalamic activity, have been shown to significantly contribute to these processes [128,129].

Allodynia-related changes of sleep parameters have been studied in animal models. In allodynic animals sleep was only partially altered in basal conditions but became disturbed with regard to controls when aversive environmental conditions where present, suggesting that allodynia may exacerbate the detrimental effect of environmental factors on sleep [130]. Our group found poorer quality of sleep, as defined by a brief semi-structured questionnaire, in allodynic headachers, either tension type and migraine patients, compared with non-allodynic ones [Lovati C, Unpublished Data].

Expert commentary

The clinical implications of sleep disturbances in headache patients deserve a thorough examination, in analogy with other typical comorbidities. Evaluating the quality of sleep by a detailed anamnestic collection, and possibly with the aid of specific questionnaires can help to detect the presence of sleep abnormalities that may unfavorably affect the headache symptoms or even trigger headache. In some forms of primary headache, such as CH or HH, a detailed and quantitative evaluation of sleep quality, also in terms of time, frequency of disruptions, and daytime somnolence, is fundamental for a correct therapeutic approach to headache as well as to sleep disorders.

A systematic application of sleep-quality assessment will allow practitioners to better characterize patients and consequently, to prescribe the appropriate therapeutic regimens. This approach is likely to produce a reduction in the failure rate of therapy and possibly to prevent chronicization.

The assessment of allodynia together with sleep quality would also be beneficial. There is emerging evidence that allodynia and a poor sleep quality often coexist in headache patients: this stimulates the hypothesis that the two conditions may be mutually reinforcing, and that the correct treatment of one may also improve the other.

Five-year view

Central sensitization, considered to be pivotal in the development of allodynia in headaches, is known to involve primarily the caudal nucleus of TNC and consequently to influence

nearby structures, including brainstem nuclei and the thalamus: this extension of central sensitization may possibly also induce changes in sleep quality and/or architecture among headache patients. On the other hand, it is possible that primary sleep alterations may facilitate both pain perception and central sensitization.

There are several areas that need further explanation; the following deserve particular attention in our opinion:

- Sleep disturbances and allodynia may be present in some headache patients since their first attacks, while in others, even with chronicized forms, they may never have been experienced;
- A poor quality of sleep and allodynia are more frequent in chronic headaches but may also be reported by patients with sporadic episodic forms;
- The temporal relationship between sleep disturbances and headache complaints is not constant; sometimes one precedes the other, while other times they appear contemporary;
- Some molecules that improve sleep may be useful in headache prevention, at least for some specific headache forms, while other drugs, with a similar efficacy on sleep, have not shown to be beneficial in the treatment of headache.

These and other unsolved questions reinforce once more the concept that primary headaches, sleep control and allodynia are multifactorial conditions with several common and interconnected elements that are still not completely understood.

In the next 5 years these aspects will be studied and we can expect that a great number of these questions will be answered. A better knowledge of the interaction of sleep and headache generators will be very useful for a better diagnostic and prognostic definition, as well as for more personalized treatments.

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Key issues

- Nearly all types of primary headache seem to be frequently associated with a poor quality of sleep.
- Clinical research correlates specific headache diagnoses and sleep disorders with chronobiologic patterns and sleep processes, suggesting that the same anatomic structures (namely the brainstem and diencephalon) are involved in the regulation of sleep as well as in headache generation. The hypothalamus has a central role in the chronobiological cyclicity of several processes and may provide a common pathophysiological substrate for these conditions. The role of sleep mediators, such as orexins, adenosine and melatonin, needs to be thoroughly evaluated in primary headaches and in particular in forms that are strongly related to the sleep cycle, such as cluster headache, hypnic headache and migraine.
- Similarly to cutaneous allodynia, sleep disturbances are more frequent in chronic than in episodic forms of headache. Both allodynia and sleep disorders, although being more often present during headache, can also occur inbetween attacks.
- Susceptibility to allodynia and possibly to the development of anti-migraine drug overuse may have a genetic background on which environmental and hormonal factors act in variable fashion, giving rise to headache transformation. In this condition, sleep disturbances seem to be at the same time a causal factor and one of the most frequent clinical features.
- Instrumental methods, such as polysomnography, are the only way to precisely assess the abnormalities in sleep pattern but have evident limitations for a widespread use. As is the case for allodynia, validated questionnaires allow us to detect and, in some measure, to quantify the presence of sleep disturbances.

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