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SECONDARY HEADACHE (M ROBBINS, SECTION EDITOR)

Linking Traumatic Brain Injury, Sleep Disruption and Post-Traumatic Headache: a Potential Role for Glymphatic Pathway Dysfunction

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Abstract

Purpose of the Review Traumatic brain injury (TBI) is a major public health concern in the USA and worldwide. Sleep disruption and headaches are two of the most common problems reported by patients after TBI. In this manuscript, we review the current knowledge regarding the relation between post-traumatic sleep disruption and headaches. We also describe the role of the glymphatic system as a potential link between TBI, sleep, and headaches.

Recent Findings Recent studies show a reciprocal relation between post-traumatic sleep disruption and headaches: patients with sleep disruption after TBI report more headaches, and post-traumatic headaches are a risk factor for developing disrupted sleep. Despite this clinical association, the exact mechanisms linking post-traumatic sleep disruption and headaches are not well understood. The glymphatic pathway, a newly described brain–wide network of perivascular spaces that supports the clearance of interstitial solutes and wastes from the brain, is active primarily during sleep, and becomes dysfunctional after TBI. We propose a model where changes in glymphatic function caused by TBI and post-traumatic sleep disruption may impair the clearance of neuropeptides involved in the pathogenesis of post-traumatic headaches, such as CGRP.

Summary The relation between TBI, post-traumatic sleep disruption, and post-traumatic headaches, although well documented in the literature, remains poorly understood. Dysfunction of the glymphatic system caused by TBI offers a novel and exiting explanation to this clinically observed phenomenon. The proposed model, although theoretical, could provide important mechanistic insights to the TBI-sleep-headache association.

Keywords Glymphatic system · Traumatic brain injury · Concussion · Headaches · Sleep

Background

Traumatic brain injury represents a major public health concern, with an estimated 1.7 million cases of TBI occurring per year in the USA [1]. TBI is classified as mild, moderate, or severe based on the level of responsiveness, duration of loss of consciousness, and duration of post-traumatic amnesia, as well as findings on neuroimaging [2]. Mild TBI (mTBI, also referred to as concussion) accounts for 70% of all TBI [1]. TBI has a bi-modal distribution, with highest rates among patients

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75 years and older and among those 21 years and younger [3]. According to the Centers of Disease Control and Prevention, symptoms following TBI (known as post-concussive symptoms) can be grouped into four often overlapping categories: sleep, physical (headaches, dizziness, fatigue, disequilibrium, photophobia), cognitive (difficulties with attention, concentration, and memory), and emotional (irritability, depression, and anxiety) [4].

Post-traumatic headaches (PTH) and sleep-wake disturbances (SWD) are the most common acute and chronic complaints, respectively, after TBI of all severities [5–7]. Moreover, there is a bi-directional relation between the two: subjects with post-traumatic SWD report increased headaches, and headaches are a risk factor for SWD after TBI. Despite the available studies addressing the role of SWD in post-traumatic morbidity [8, 9], the mechanisms linking SWD to PTH remain poorly understood. Without this knowledge, it will remain difficult to create interventions to reverse the long-term damages of TBI.

The glymphatic pathway, a recently described brain-wide network of perivascular spaces that supports the clearance of interstitial solutes and wastes from the brain, is active primarily during sleep [10••, 11••]. Recent studies demonstrate that glymphatic function is impaired in rodent models of TBI [12•]. The relationship of glymphatic function to SWD and PTH in humans is not known, but could provide important mechanistic insights to the relationship between TBI, SWD, and PTH.

In this review, we will analyze the current understanding of the interaction between TBI, post-traumatic SWD, and PTH. We will also review the recent advances in our understanding of glymphatic biology. Last, we will outline model that incorporates glymphatic dysfunction as a putative link between TBI, SWD, and PTH.

Post-Traumatic Sleep Disturbances

Epidemiology and Presentation

Poor sleep quality is one of the most commonly reported chronic complaint in patients with history of TBI, and a major contributor to morbidity and long-term sequela [5, 13–15, 16•]. Insomnia, fatigue, and somnolence are the most common complaints in patients with TBI. Insomnia is reported in 30–65% of patients with TBI of all severities, and it is more common following mTBI [17–19]. Increased daytime sleepiness is reported by 50–85% of patients with TBI of all severities. Although these complaints decrease over time, they persist in 10–53% of head-injured individuals [17, 18, 20–24]. Obstructive sleep apnea (OSA) has been reported in 35–61% of patients with TBI [18, 25]. In patients with TBI and OSA, there is an increased incidence of memory and attention deficits [26]. On polysomnogram, patients with mTBI demonstrate increased sleep fragmentation, delayed sleep onset, increased awakenings, and reduced sleep efficiency [27].

Although the exact mechanisms linking TBI and SWD are not fully understood, there is a clear clinical link between post-traumatic SWD and prolonged recovery after TBI. In adolescents with mTBI, post-injury sleep difficulties are correlated with a greater report of post-concussive symptoms [8, 9]. Post-traumatic SWD can affect neurorehabilitation and exacerbate many of the consequences of TBI, including fatigue, depression, anxiety, post-traumatic stress symptoms, and chronic pain including post-traumatic headaches.

Mechanism

Several pathological processes may contribute to post-traumatic sleep dysregulation. Alterations in the production and secretion of melatonin observed after TBI have been proposed as potential mechanism for post-traumatic insomnia and disordered circadian rhythmicity [28]. Damage to orexin (hypocretin)-secreting cells in the hypothalamus after TBI can lead to a centrally mediated hypersomnia [20, 24, 29]. Other structures and pathophysiologic processes involved in sleep and circadian rhythm generation can potentially be disrupted after mTBI. At the cellular level, subtle injury to certain neuronal populations such as galanin and γ-aminobutiric acid (GABA)-secreting neurons in the ventrolateral preoptic nucleus, orexin- and histamine-secreting neurons in the tuberomammilary nuclei, serotonin-secreting neurons in the dorsal raphe nuclei, and noradrenaline in the locus coeruleus can interfere with the processes involved in initiating and sustaining sleep. Alternatively, damage to these structures can alter these pathways in ways that increase sleep drive [29]. TBI can also affect cerebral metabolism causing alterations in neurotransmitter function, dysfunction of cerebral autoregulation, release of neuroinflammatory mediators, and alteration of circadian hormones [28, 30–36]. Last, co-morbid conditions such as PTSD and chronic pain can promote autonomic dysregulation and affect circadian rhythms [37].

Clinical Treatment

Melatonin is a common first–line medication in post-traumatic insomnia, although evidence of its efficacy in treating this condition has not been well established. In addition to melatonin, sedative medications such as benzodiazepines are commonly used in the treatment of post-traumatic insomnia. However, current guidelines recommend avoiding the use of benzodiazepines due to potential risk for dependence and withdrawal symptoms [2]. Non-pharmacologic interventions such as cognitive-behavioral therapy (CBT) have been used successfully to treat post-traumatic insomnia in adults [38–41].

There are currently no medications specifically approved for the treatment of post-traumatic somnolence. In addition to treating post-injury co-morbidities such as physical injuries, depression/anxiety, and PTSD, modafinil, armodafinil, methylphenidate, and amphetamines are often prescribed to improve daytime sleepiness [42, 43]. Bright light therapy has also been used to treat fatigue in patients with mTBI, with some success [44].

The treatment of OSA in patients with TBI is similar to that in the general population, with continuous positive airway pressure (cPAP). It is not known, however, how the treatment of OSA improves cognitive symptoms in patients with TBI and co-morbid OSA.

Post-Traumatic Headache

Epidemiology and Presentation

Headaches are the most common acute symptom in patients with TBI of all severities. Headaches become chronic in a significant proportion of those patients. Eighteen to 58% of patients with TBI will complain of a significant headache up to 1 year after the trauma [6, 7]. The incidence of PTH is higher after mTBI compared to moderate or severe traumatic brain injuries [45]. Women, patients with premorbid history of headache, adolescents, and those with a family history of migraine are at a higher risk for developing PTH [45–47]. Psychological factors such as depression and anxiety are also risk factors, both in children and adults [48, 49]. In the International Classification of Headache Disorders 3 beta (ICHD-3 beta), PTH are classified according to the severity of injury and the duration of the headaches following the injury [50]. Headaches usually begin within 7 days following injury, although longer asymptomatic periods have been reported. PTH can have different presentations, but migraine or probable migraine is the most common presentation for PTH of all severities [7, 51]. Migraine headaches usually present with throbbing pain, typically exacerbated by physical activity, and associated with nausea/vomiting and photo/phonophobia [50]. Tension-type headaches present with a tight, squeezing, bilateral pain that is not exacerbated by movement, and is not associated with photo/phonophobia [50]. Other headache phenotypes seen after TBI include cluster headaches, cervicogenic headaches, and hemicrania continua [52]. In a series of pediatric patients presenting to a concussion clinic with complaints of post-traumatic headaches, Kuczynski et al. reported that 61% had daily headaches, 39% had migraine, and 9% had tension-type headaches [53]. At follow-up, 44% of subjects had migraine, 44% had daily headaches, and 26% had new onset of a migraine-like disorder which was attributed to the mTBI. In adults with PTH, 15–85% have tension-type headache, 10–63% have migraine, and 10% have cervicogenic headaches, but there is significant overlap between these phenotypes [6, 51, 54].

Mechanism of PTH

Both physiologic and psychologic causes may contribute to the appearance and persistence of PTH. A comprehensive review of the pathophysiology of TBI is beyond the scope of this review. In the following section, we will focus on changes that happen after mTBI, as this is the most common form of TBI, and the one most closely associated with PTH. In patients with mTBI, PTH are often seen in association with other post-concussive symptoms such as sleep disturbances, dizziness, anxiety, and depression. Although much is known about the changes that occur after mTBI at the cellular level, none of these processes has been directly linked to the pathogenesis of PTH. Immediately after mTBI, there is intracellular ion influx, cell swelling, axonal injury, release of neurotransmitters, and increase in blood-brain barrier permeability [55]. These acute processes cause an initial mismatch between cerebral metabolism and cerebral blood flow. The acute phase is followed by more subacute changes such as release of neuroinflammatory mediators, neuroendocrine responses, and changes in cerebral blood flow [56]. All of these processes could potentially initiate or propagate PTH.

Neurovascular and Metabolic Function The symptoms seen acutely after mTBI could be, at least in part, explained by a mismatch between cerebral metabolic demand and cerebral blood flow. Both reduced and increased cerebral blood flow have been documented after mTBI [57]. These changes may persist for weeks and even months after symptoms have resolved [58]. However, a direct link between alterations in cerebral blood flow and post-traumatic symptomatology has not been established. The notion of disrupted cellular energy metabolism as a cause of PTH has supported the use of several supplements used for non-traumatic headaches such as riboflavin and CoQ10 in the treatment of PTH [59].

Glutamate Animal studies demonstrate that after mTBI there is substantial release of glutamate, and alterations in its receptors [55]. Glutamate has also been implicated in migraine pathogenesis [60]. Topiramate, an antagonist of the glutamate kainate receptor, is commonly used for migraine prophylaxis [61]. Memantine, an NMDA receptor antagonist, has also been used in the treatment of migraine, and has shown some efficacy in animal models of TBI [62, 63].

ATP and Adenosine ATP is released during cortical spreading depression, and although not fully characterized, it is likely that a similar release of ATP occurs in response to TBI [64]. Activation of purine receptors, particularly the P2X receptors, is linked to pain and inflammation [65]. The role of adenosine,

a metabolite of ATP, after TBI is also poorly understood. Activation of the A1 subtype adenosine receptor can be neuroprotective, whereas activation of the A2 receptor subtypes can be deleterious [66, 67]. Caffeine, a non-specific adenosine receptor antagonist, is commonly used in the acute treatment of migraine [68]. However, the effect of caffeine on PTH has not been well established.

Inflammation Inflammatory mediators are released after mTBI [34]. Some of these mediators have also been found to be elevated in patients with headache disorders. NSAIDs are commonly used in the setting of PTH; however, their efficacy has not been well established.

Neuropeptides (Calcitonin Gene–Related Peptide [CGRP], Pituitary Adenylyl Cyclase Activating Peptide [PACAP], Substance P) Perhaps the clearest link between PTH and other headache types, particularly migraine, relates to the role of neuropeptides in these two entities. CGRP pays a central role in migraine pathogenesis [69]. Importantly, CGRP is also released after trauma in animal models of TBI, and mediates some of the migraine-related behaviors such as hyperalgesia and light avoidance [70–73]. Moreover, antibodies targeting CGRP signaling have been recently approved for clinical use in migraine [74]. Their efficacy in PTH, however, has not yet been established. Another promising neuropeptide is PACAP. Elevated levels of PACAP are observed in the external jugular vein during migraine attacks [75]. Antibodies against the PACAP receptor are in the early stages of clinical trial for migraine prevention. Substance P is also released during traumatic brain injury and it is known to play a role in increased blood-brain barrier permeability, and brain edema [76]. However, several substance P neurokinin receptor antagonists have shown no efficacy in migraine prevention [77].

Other potential targets for the link between PTH and other headache types include abnormalities in the levels of brain-derived neurotrophic factor (BDNF), changes in neuroendocrine function, cervical root pathology, and cerebral edema/increased intracranial pressure [78]. Despite extensive literature, the role of these processes in the generation or propagation of PTH remains to be determined.

Clinical Treatment

Currently, no single therapy has proven particularly beneficial in the treatment of PTH. As noted above, most patients with acute PTH will improve over time. However, there is a significant minority who continue to experience symptoms for months or even years after injury. Sleep disturbances, depression, anxiety, PTSD and other co-morbidities complicate the management of these patients. Given the lack of evidence-based guidelines, the treatment of PTH is often similar to that of other primary headache disorders, and can be broadly divided into non-pharmacologic and pharmacologic. Non-pharmacologic approaches include psychotherapy, physical therapy, biofeedback, and cognitive restructuring [79, 80]. Pharmacologic approaches for acute PTH include acetaminophen and NSAIDS (although NSAIDS are typically avoided within 24 h after injury because of the risk of bleeding). Opioids are usually avoided due to the risk of dependency and overuse. Triptans, which are serotonin 5T-1B/1D receptor agonists, have been used successfully in the acute treatment of migraine, and can be used acutely in PTH, although there is a theoretical risk associated with vasoconstriction [81, 82]. Very few prophylactic medications have been studied in the setting of PTH. Supplements, such as melatonin, magnesium, riboflavin, and butterbur, are often used as first line [80, 83]. Prescription medications such as tricyclic antidepressants, anticonvulsants, beta-blockers, calcium channel blockers, and muscle relaxants are also commonly used as second-line alternatives. In a study of children with PTH on a variety of medications, 64% reported some improvement in their symptoms, with 45% reporting complete symptoms resolution. Interestingly, 75% of patients who used melatonin reported improvement [53]. It remains unclear if the symptom improvement was related to improvements in sleep. In adults with PTH, topiramate was associated with a response rate of 48% [82].

The Relationship Between Sleep Disruption and Headache

Epidemiology and Presentation

Sleep disturbances and headaches are prevalent across the lifespan. Migraine and tension-type headaches occur in approximately 12% of children, whereas 25% of the pediatric population has experienced at least one sleep problem [84, 85]. Stress and sleep disturbances are the two most commonly identified headache triggers: 48–74% of patients with migraine and 26–72% of patients with tension-type headaches identify "lack of sleep" as a common headache trigger [86–88]. The most common sleep disturbances reported by children with chronic headaches are insufficient sleep, anxiety related to sleep, restless sleep, night walking, nightmares, fatigue during the day, and parasomnias [89–93]. Children with migraine and tension-type headaches have shorter sleep duration, increased sleep latency, and increased sleep disruption with more than 2 awakenings per night [89].

The relationship between sleep disruption and PTH has also been well documented. In a study of 93 adults with mTBI, Tkachenko et al. found a significant correlation between headaches and sleep problems (fatigue, drowsiness, and difficulty falling asleep) [94]. In a study of veterans with TBI, headaches, anxiety, and depression were higher risk

factors for insomnia than injury severity [95]. A third study of 98 adults reported that headaches, along with dizziness, and anxiety/depression were higher risk factors for insomnia than the initial Glasgow Coma score [96].

Association of Different SWD Phenotypes with Migraine or Tension-Type Headache

There is a relationship between sleep stage and the onset of certain headache types: cluster headaches usually present during REM sleep, migraine attacks that wake patients up are often associated with vivid dreams, suggesting an onset during REM as well. Hypnic headaches often awake patients 1–3 h after falling asleep. Chronic paroxysmal hemicrania also awakens patients from sleep [97].

Insomnia is the most prevalent sleep disorder in patients with chronic headaches, both migraine and tension-type headaches. Approximately 50% of individuals with migraine report at least occasional symptoms of insomnia, 38% report sleeping less than 6 h/night [98]. The prevalence of insomnia is 1.8 times higher in individuals with tension-type headaches than controls [99]. Insomnia is also considered a risk factor for higher headache frequency, particularly in tension-type headaches and migraine [100]. Non-REM sleep parasomnias are also a common complaint of patients with headaches. Forty percent of adolescents with chronic migraine reported a history of sleep terrors during childhood versus 8% of controls [101]. In addition to these frequent problems, sleep-disordered breathing, periodic limb movement/restless legs syndrome, and narcolepsy have all been documented in patients with chronic headaches [102–106].

The relation of headaches and sleep disturbances is bi-directional. Sleep disturbances (increased or decreased sleep, inappropriate sleep timing, or abnormal sleep behaviors) can trigger headaches; on the other hand, headaches can also promote sleep disturbances [107, 108].

Mechanism

The mechanisms linking sleep and headaches, even in the absence of TBI, are poorly understood, with genetic, pathophysiological, and behavioral causes proposed as possible links between them. However, the specific factors have not yet been identified [89, 109]. Sleep deprivation, even in the absence of TBI, has been linked to several pathogenic processes, including changes in glutamate concentrations, brain temperature, and decreased levels of cerebral glycogen [110–112]. In addition, sleep deprivation leads to elevation in pro-inflammatory cytokines (IL-1 beta, IL-6, TNF alpha), which can independently impair neuronal function [113, 114]. As noted above, sleep is a complex process, which involves several anatomical regions of the central nervous system. Some of these regions also participate in the generation and perpetuation of headaches: the thalamus, hypothalamus, and brainstem nuclei, including the locus coeruleus and raphe nuclei [115]. In addition, several neurotransmitters are involved in sleep and headache generation, particularly GABA, orexin/hypocretin, acetylcholine, melatonin, prostaglandins (PGD2), cytokines (IL-1), and adenosine [116]. Several of the structures and pathways involved in both headaches and sleep can be damaged during TBI.

Clinical Treatment

Given the pathophysiological commonalities between sleep and headaches, it is not surprising that drugs used to improve sleep, such as anti-histamines, serotoninergic agents, and melatonin, are also beneficial for headaches. The effect of anti-histamines and melatonin in improving migraine may be indirect, through the improvement of sleep [117]. However, a more direct effect of melatonin on headaches has also been proposed, based on the demonstrated lower levels of nocturnal melatonin in patients with migraine and cluster headaches [118, 119]. Serotonin is involved in central nociceptive pathways, as well as modulating the sleep-wake cycle. Lower serotonin levels can promote pain, but they can also disrupt normal sleep architecture [120]. Serotonin agonists such as amitriptyline and L-5-hydroxy-tryptophan are routinely used as migraine prophylactics, and to improve sleep [121].

The Glymphatic Pathway: a Possible Link Between TBI, Sleep and Post-Traumatic Headaches

Anatomy and Physiology of Glymphatic Exchange

The blood-brain barrier (BBB) prevents the ready exchange of fluid and solutes between the brain interstitium and periphery. As a result, solutes and wastes released to the brain interstitium that are not specifically transported across the BBB, or degraded locally be neural or glial cells, must exit the cranium through exchange with the cerebrospinal fluid (CSF) compartment and subsequent clearance along CSF efflux pathways [122]. Recent experimental studies have dramatically altered our understanding of this process, with the description of the glymphatic system, a brain-wide network of perivascular spaces that supports rapid exchange of fluid and solutes between the CSF and brain interstitium [10••, 123], and meningeal lymphatic vessels that support the clearance of solutes from the CSF to the deep cervical lymphatic drainage [124, 125]. Glymphatic exchange along perivascular spaces is driven in part by arterial pulsation [126], and is supported by astroglial water transport via the aquaporin-4 (AQP4) water channel that is localized to perivascular astroglial endfeet that ensheathed the cerebral microvasculature [10••, 127].

Although initially characterized in mice, glymphatic exchange has now been defined in human subjects by evaluating the movement of intrathecally injected gadolinium–based contrast agents from the CSF to the interstitial compartment by dynamic contrast–enhanced (DCE)-MRI [128, 129]. Similarly, MRI-based imaging and histological approaches have confirmed the presence of meningeal lymphatics in humans [130, 131], while DCE-MRI following intrathecal contrast agent injection confirms that drainage of CSF solutes along deep cervical lymphatics occurs in human subjects [132]. Thus, although characterized only recently, perivascular pathways provide key routes for the rapid exchange of interstitial and CSF solutes, supporting the clearance of metabolites, proteins, and other solutes from the brain.

The Glymphatic System Is Active during Sleep

Soon after the glymphatic system was described, Xie et al. showed that glymphatic exchange is markedly increased during sleep. Using 2-photon microscopy, the investigators demonstrated that CSF influx into the brain parenchyma is reduced by 90% in awake versus anesthetized mice. Similar results were observed in naturally sleeping mice [11••]. Radio-tracer studies further demonstrated that the clearance of interstitial solutes, including amyloid β, is more rapid during sleep. More rapid glymphatic exchange during sleep appeared to be supported by an increase in the volume of the brain extracellular space, which supports more rapid diffusion of metabolites and proteins between perivascular compartments. Sleep-wake regulation of glymphatic exchange and extracellular volume fraction are regulated at least in part by central noradrenergic tone, as administration of noradrenergic antagonists increased glymphatic exchange in the waking brain to levels similar to those observed during sleep or under anesthesia [11••].

Impairment of Glymphatic Exchange After Traumatic Brain Injury

In addition to the metabolic and chemical disturbances, experimental data suggests that TBI causes glymphatic dysfunction. In an animal model of moderate-severe TBI, influx of CSF into the brain parenchyma and the clearance of interstitial solutes from the brain were significantly impaired starting 1 day and persisting up to 28-day post-injury [12•]. Impairment of glymphatic exchange after TBI was associated with loss of perivascular localization of AQP4, which is sufficient to impair glymphatic exchange [127]. It is noteworthy that the clearance of proteins released from the brain following TBI, including S100b, glial fibrillary acidic protein (GFAP), and neuron-specific enolase, to the plasma compartment is dependent upon glymphatic exchange [133], a process slowed following TBI. Similar mislocalization of AQP4 and slowing of glymphatic exchange is observed in other models of brain injury such as ischemic stroke, although in these cases function resumes approximately 24-h post-injury [134]. Lastly, cortical spreading depression (CSD), a common sequelae following traumatic and ischemic injury and believed to be neurophysiological basis for migraine aura [135], was observed to almost completely abolish glymphatic exchange through the cortex [136].

Proposed Role of Post-Traumatic Glymphatic Disruption in Post-Traumatic Headaches

As discussed above, glymphatic exchange along perivascular spaces during sleep supports the clearance of metabolites, peptides, and proteins out of the brain. Following TBI and associated pathological conditions such as CSD and ischemic injury, glymphatic exchange is profoundly impaired. In addition to direct effects on glymphatic exchange, TBI may also impair overall glymphatic activity indirectly through SWD, thus reducing both the *opportunity* for glymphatic exchange during sleep in addition to the *efficacy* of exchange that can occur during sleep. These findings suggest that impairment of glymphatic exchange may be one mechanism at the center of the interactions between TBI, sleep disruption, and post-traumatic headaches.

One potential explanation for the link between glymphatic dysfunction and post-traumatic headaches involves the clearance of CGRP from the perivascular compartment. As detailed above, CGRP is an important mediator of headaches. Although the exact mechanism by which CGRP promotes the initiation or persistence of headaches is not yet known, in recent years, its central role in headache, particularly migraine generation, has been demonstrated by the fact that antibodies against CGPR or its receptor have been effective in the treatment of migraine [137]. CGRP is released both by trigeminal afferents innervating meningeal, pial and intracerebral arteries, and by central projections in the spinal trigeminal nucleus at the level of the medulla oblongata [138–141]. Once released peripherally at perivascular trigeminal afferents during injury or during migraine, the specific anatomical pathway along which CGRP is cleared from the perivascular compartment to the blood has not yet been defined [142]. Contrary to central CGRP clearance in the trigeminal nucleus, whose supplying vessels lack a BBB [143], CGRP released from perivascular trigeminal afferents cannot readily cross the BBB or blood-meningeal barrier. It must therefore exchange into the CSF within the subarachnoid space, a processes presumably mediated by glymphatic exchange. This notion is supported by the fact that the concentration of CGRP is 5 times higher in CSF than in plasma after activating dural afferents with depolarizing KCl^{-} [144].

If neuropeptides released from perivascular trigeminal afferents are cleared from the CSF-filled perivascular compartment through glymphatic exchange, then this may provide a

mechanistic explanation for the clinical observation that sleep disruption (impairing the clearance of perivascular CGRP or PACAP) is a frequently reported migraine trigger [86], while sleep (which increases the clearance of perivascular neuropeptides) is frequently reported to be an effective migraine abortive [97]. In this way, impairment of sleep-associated perivascular fluid movement may further link post-traumatic SWD with the development or persistence of PTH.

By impairing perivascular glymphatic exchange [12•], TBI may also slow the clearance of perivascular migraine–associated neuropeptides during both waking and sleeping, providing a second direct mechanistic link between TBI and post-traumatic headache. The effect of CSD, a neurophysiological sequelae frequently associated with TBI [145], on glymphatic exchange [136], would be predicted exacerbate such an effect on perivascular neuropeptide clearance.

Conclusion

We have discussed the relationship between TBI, sleep-wake disturbances, and post-traumatic headaches. We have also outlined the bi-directional link between sleep-wake disturbances and post-traumatic headaches, and the proposed mechanisms for such relationship. The recent description of the glymphatic system, a network of perivascular spaces that support the clearance of interstitial solutes to the CSF that is active primarily during sleep and is impaired following TBI, may provide a novel framework to explain these associations. In this model, glymphatic dysfunction is one common factor linking TBI, sleep disturbances, and headache. This may be a direct connection, as impairment of glymphatic clearance of perivascular migraine–associated neuropeptides promotes post-traumatic headaches, or indirectly as post-traumatic sleep disruption reduces overall glymphatic clearance of these neuropeptides. If such a model were substantiated, then modulation of post-traumatic glymphatic function, including through inhibition of central noradrenergic tone by centrally acting drugs such as prazosin, may provide a useful therapeutic target for the prevention and treatment of post-traumatic headaches.

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Compliance with Ethical Standards

Conflict of Interest Juan Piantino, Miranda M. Lim, Craig D. Newgard, and Jeffrey Iliff declare no conflict of interest.

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.

Disclaimer Interpretations and conclusions are those of the authors and do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

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