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Traumatic Brain Injury, Neuroinflammation, and Post-Traumatic Headaches

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Abstract

Concussions following head and/or neck injury are common, and although most people with mild injuries recover uneventfully, a subset of individuals develop persistent post-concussive symptoms that often include headaches. Post-traumatic headaches vary in presentation and may progress to become chronic and in some cases debilitating. Little is known about the pathogenesis of post-traumatic headaches, although shared pathophysiology with that of the brain injury is suspected. Following primary injury to brain tissues, inflammation rapidly ensues; while this inflammatory response initially provides a defensive/reparative function, it can persist beyond its beneficial effect, potentially leading to secondary injuries because of alterations in neuronal excitability, axonal integrity, central processing, and other changes. These changes may account for the neurological symptoms often observed after traumatic brain injury, including headaches. This review considers selected aspects of the inflammatory response following traumatic brain injury, with an emphasis on the role of glial cells as mediators of maladaptive post-traumatic inflammation.

Keywords

traumatic brain injury; inflammation; glia; microglia; astrocytes; satellite cells; blood brain barrier; cytokines; post-traumatic headaches; inflammatory mediators

INTRODUCTION

Concussive head injury has been in the spotlight recently, with the high prevalence of disabling post-concussive symptoms in military service members who have sustained explosive blast-related traumatic brain injuries (TBIs) and with heightened attention to concussive injuries sustained in both professional athletes and school-age sports participants. Apart from these at-risk populations, concussions following head and neck injury are a significant cause of morbidity in the general population.¹ At least 75% of all concussions are

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classified as mild,² involving brief, if any, loss of consciousness and symptoms that are usually transient, with most patients recovering uneventfully.³ However, some patients have persistent or worsening cognitive, behavioral, or somatic symptoms, suggesting more profound, possibly progressive brain dysfunction. Headaches are common post-injury^{4,5} and are variably regarded to be more prevalent after mild TBI (mTBI) than after more severe TBI.^{5,6} Post-traumatic headaches (PTHAs) can have a variety of phenotypes, with migraine/probable migraine, tension-type, and mixed headache commonly reported, and other headache types, including cervicogenic and unclassifiable, also noted.^{7–14} PTHAs may progress in severity and frequency and persist to become chronic.^{4,14}

Despite the common occurrence of PTHAs, little is known about their pathogenesis. The balance of contributing factors likely varies case by case,¹⁵ given the diverse mechanisms of TBI, the complex biological and behavioral responses to it, and risk modifiers such as gender, genetic predisposition, and history of prior headaches or head injury. Inflammation is a plausible link between head/neck injury and the genesis of chronic PTHA. Following TBI, irrespective of mechanism or severity, inflammation is rapidly elicited as a response to the primary injury to brain tissues.¹⁶ This inflammatory response can become excessive or can persist beyond its beneficial effect, precipitating or being involved in secondary injury to the central nervous system (CNS).¹⁷ Such injury may at least in part account for the neurological symptoms often observed after TBI.^{18–20} This review considers maladaptive post-traumatic inflammation as a secondary injury mechanism in TBI and, potentially, in the genesis of PTHAs.

BRAIN INJURY AND NEUROINFLAMMATION

The immediate effects of TBI are complex and can include cell injury or death; neurovascular disruption; disturbances of ionic and neurotransmitter homeostasis; electrical, chemical, and energetic dysfunction; and other processes.^{3,21–24} The nature of the injury, eg, whether more focal or more diffuse, influences the pattern of these processes.¹⁶ Diffuse injury is associated with potentially widespread vascular damage and axonal dysfunction.²⁵ The initial inflammatory response to injury begins with activation of the innate immune system, production of an array of bioactive substances, alterations in the blood brain barrier (BBB), and involvement of the systemic immune system.^{16,26} Dynamic interactions between multiple cell types, including brain microvascular endothelia, glia, and peripheral immune cells, mediate these processes. Glial cells, in particular, are key to the initiation and the pathological prolongation of neuroinflammation.²⁷ This review will consider glial cells, followed by a brief discussion of the BBB and inflammatory mediators.

Glial Cells

Microglia are CNS-resident immune cells that, among other functions, monitor for pathogens or injury in the intraparenchymal space.²⁸ Microglia continuously probe their immediate surroundings with highly motile ramifications,^{28,29} detecting changes in the microenvironment via receptors for substances indicative of CNS threat or damage.³⁰ Under normal conditions, microglial activity is suppressed by peptide signaling from healthy neurons.³¹ Following injury, microglia become activated within minutes, evidenced by changes in morphology, increased motility, proliferation, aggregation to the area of injury,

upregulation of surface receptors,^{28,29} and release of inflammation-promoting mediators, including complement factors, cytokines, chemokines, proteolytic enzymes, and reactive oxygen and nitrogen species.²⁷ Parenchymal microglial activation can occur through contact with components of CNS injury or through interaction with perivascular microglia or with peripheral immune cells that infiltrate via the impaired or permissive BBB following injury.¹⁶ Adenosine triphosphate (ATP) released by damaged cells is thought to be an important activator of microglia.²⁹ Activated microglia can assume more pro- or anti-inflammatory phenotypes depending on stimuli in the local microenvironment.^{32,33} Pro-inflammatory processes involve the release of degradative, toxic, and activating autocrine and paracrine compounds, as well as other cell activities that are intended to clear the CNS of potentially harmful substances; outside the context of their defensive function, these activities are harmful to normal cells.²⁷ Anti-inflammatory processes involve reparative and regenerative functions considered to be beneficial to neuronal survival. Imbalanced or prolonged pro-inflammatory microglial activation, with continued release of cytotoxic pro-inflammatory substances injurious to neurons may perpetuate microglial activation,^{30,34} contributing to progressive CNS symptoms.³⁵ Aberrant microglial activation is associated with many CNS diseases, including brain and spinal cord injury, stroke, chronic pain syndromes, and neurodegenerative diseases.^{36,37}

TBI-related axonal injury with associated microglial activation has been a frequent histopathological finding in animal studies^{38,39} and human autopsy series.^{40–44} In particular, features of axonal injury, including demyelination, swelling and disconnection of the proximal axon bulb from its distal segment, and Wallerian degeneration, with evidence for associated inflammation including proliferation of activated microglia and the presence of myelin-containing macrophages have been observed after even mTBI.^{45–47} While expected as a response to injury in the short term, evidence for pathological denervation and re-innervation,⁴⁸ and thinning of white matter tracts (eg, corpus callosum) along with activated microglia has been observed in some individuals up to 18 years post-injury.⁴⁰ These findings implicate ongoing axonal damage and resultant impaired integrity of white matter tracts as important components of the clinical deficits observed after TBI^{49,50} possibly through disruption of functional neural networks.⁵⁰

Astrocytes, the most abundant cells in the brain, occupy a strategic position between microvascular endothelial cells and neurons,⁵¹ where they mediate interactions between those cells and are thus integrally involved in BBB regulation.⁵² Astrocytes support nearly all aspects of neuronal function, including maintaining ionic homeostasis, modulating neurotransmitter concentrations, and controlling synapse function.⁵³ They are interconnected via gap junctions and are believed to form a syncytial network in the brain that allows them to communicate by non-electrical calcium-mediated signaling.^{54–56} After CNS injury, astrocytes can become activated in response to substances released by injured neurons or by activated microglia, with morphological changes (hypertrophy, also called astrogliosis), increased glial fibrillary astrocytic protein expression, and the release of neuroregulatory molecules,^{57,58} eg, brain-derived neurotrophic factor. Like microglia, activated astrocytes can have both beneficial and deleterious effects. For example, following injury, activated astrocytes surround lesions and deposit a proteoglycan matrix, forming a

glial scar; this isolates the lesion but also forms a dense barrier that inhibits axonal regeneration and disrupts functional connections.^{59,60} The precise nature of the astrocyte response can vary and, as related to TBI, may be injury-specific.⁶¹ Astrocytes can themselves be injured in TBI, with structural alterations, loss of ion and neurotransmitter buffering capacity, and release of pro-inflammatory mediators.^{58,62}

Oligodendrocytes are increasingly recognized as being important to neuronal function; aside from myelination, oligodendrocytes also provide trophic support during axonal maturation and regeneration, and they play a role in modulating the effects of changes in the microenvironment.^{63,64} Dysfunction of oligodendrocytes is suspected to contribute to axonal degeneration in several CNS diseases.⁶⁵

Peripheral glial cells include *Schwann cells* and *satellite glial cells* (SGCs). Schwann cells, which can be non-myelinating or myelinating, can become activated, leading to alterations in the function and conduction properties of nociceptive fibers.⁵⁸ SGCs envelop the cell bodies of primary afferent sensory neurons^{66,67} and, like astrocytes, modulate the local microenvironment and respond to nerve injury by undergoing phenotypic and functional changes.⁶⁸ They are believed to produce inflammatory molecules that modulate neuronal excitability in the trigeminal and other sensory ganglia.⁶⁹

BBB and Peripheral Immune Cells

The BBB is a dynamic interface between the CNS and the peripheral circulation that under normal conditions restricts entry of potentially harmful substances from circulating blood and helps maintain an optimal interstitial environment for neuronal activity through astrocyte-mediated adjustments of cerebral blood flow (ie, neurovascular coupling) and permissiveness to nutrients.^{70,71} Altered BBB function caused by primary injury or by transient disruption leading to extravasation of peripheral blood components into the interstitial space has been implicated as central to the deleterious effects of TBI.^{72–74} Blood components, including proteins and pathogens, are cytotoxic, causing neuronal damage and glial activation with a consequent inflammatory response that can lead to further alteration of BBB permeability;⁷⁴ these effects can propagate well beyond the primary site of injury.⁷⁵ BBB microvascular changes occur at all severities of TBI, including mTBI, and can persist for months or years.^{76,77}

In addition to blood components, peripheral leukocytes can cross the BBB following injury.^{78,79} Having pro-inflammatory and neurotoxic effects, they are normally excluded from the CNS, but under pathological conditions, they can enter the brain interstitium and participate, along with resident CNS immune cells, in the inflammatory response.^{71,80} Their early post-injury appearance in the brain has been attributed to recruitment and BBB modifications that are induced by inflammatory mediators released by activated glia.^{26,81,82} Once in the brain, the presence of these normally extraparenchymal immune cells further stimulates inflammatory activity of CNS-resident cells, leading to the recruitment of additional peripheral immune cells.²⁶ Axonal degeneration and associated glial activation has been shown to be one trigger for their recruitment.⁸³

Cytokines, Chemokines, and Other Inflammatory Mediators

Inflammation in the CNS is regulated by an array of cytokines and other inflammatory mediators, which control intercellular signaling, activate immune cells, promote chemotaxis, and induce production of other inflammatory substances (reviewed as related to TBI in Ziebell et al,¹⁶ Hellewell et al,⁸⁴ and Helmy et al⁸⁵). Cytokines are normally present in low concentrations in the CNS, but in response to injury, their production, mainly by activated glia, increases markedly⁸⁶ in a generally stereotyped time sequence.^{86,87} Interactions between the mediators are complex, with positive and negative regulatory loops such that a given cytokine can produce pro-or anti-inflammatory effects that are context-dependent, ie, that vary depending upon microenvironmental factors.^{67,85} The complexity of these interactions has stymied efforts to identify reliable therapeutic targets for treating TBI-related inflammation;⁸⁸ current efforts are being refocused toward multipotential therapeutic strategies.⁶²

Among the cytokines investigated in particular depth with respect to TBI, as well as migraine and other headaches, are interleukin-1 (IL-1), especially IL-1 β ; tumor necrosis factor alpha (TNF α); IL-6; and IL-10.^{16,85} IL-1 β , considered to be pro-inflammatory, shows elevated expression within hours of TBI in both humans and animals,^{86,89} and it initially acts to promote the release of other cytokines,⁹⁰ including TNF α . TNF α appears to synergistically enhance the neurotoxic effects of IL-1 β ;⁹¹ both IL-1 β and TNF α can increase the permeability of the BBB,^{92,93} and both are involved in the initiation and maintenance of neuropathic pain.^{94,95} In addition to these proinflammatory activities, TNF α also subsequently acts as a neurotrophic factor that is vital for neuroprotection and repair.⁶² IL-6 is involved in a large number of physiological and pathophysiological processes, and, following injury, appears to be overall beneficial for neuronal survival,^{90,96} although it also has pro-inflammatory functions.²⁶ IL-6 has been shown to be necessary for astrocyte activation.⁹⁷ IL-10, upregulated early postinjury, has neuroprotective effects that may be the result of suppression of microglial activation.⁹⁸

A number of other substances are associated with secondary brain injury. Among those also implicated in inflammation-related pain include chemokines, matrix metalloproteinases (MMPs), P2X₇ receptors, and toll-like receptors (TLRs). Chemokines control immune cell recruitment and trafficking across the BBB,^{99,100} and in addition, they have a role in neuron-to-glia signaling during ongoing neuropathic pain states.^{101–103} MMPs mediate extracellular matrix turnover.¹⁰⁴ After injury, MMP synthesis increases to promote local repair but can concurrently degrade component proteins of the BBB.^{105,106} MMPs activate glia and thus can contribute to the development and maintenance of glia-mediated pathological pain after nerve injury.¹⁰⁷ MMP levels (MMP-2 and MMP-9) have been shown to be elevated post-TBI,¹⁰⁸ as well as in patients with migraine.^{109,110} Cortical spreading depression, which has been described in stroke, head trauma, and migraine,¹¹¹ has been shown to upregulate MMP-9, with associated alterations in BBB permeability.¹¹² P2X₇ is a purinergic receptor on microglia activated by extracellular neuron-derived ATP that is implicated in the induction and maintenance of both neuropathic and inflammatory pain by modulating the release of cytokines that sensitize sensory nerve terminals;^{113,114} P2X₇ plays a particularly important role in the release of IL-1 β .¹¹⁴ TLRs, a class of pattern recognition

receptors expressed by astrocytes and microglia, are activated by pro-inflammatory mediators, and in turn, they initiate the release of pro-inflammatory cytokines and modulate glia-neural communication.^{115–117} These activities appear to play a crucial role in chronic neuropathic pain after peripheral nerve injury.¹⁰⁷

INFLAMMATION AND PTHA

Processes mediating the pathophysiology of TBI may also be relevant to the development of PTHAs, possibly involving the trigeminovascular system.^{10,118} Although the endogenous mechanisms leading to the activation of meningeal nociceptors have not been definitively identified, neurogenic inflammation is one proposed hypothesis.¹¹⁹ Neurogenic inflammation is characterized by locally increased blood flow, plasma protein leakage from blood vessels, mast cell degranulation, and platelet aggregation.¹¹⁹ One stimulus for neuroinflammation may be direct injury to the trigeminal afferent nerves or to the leptomeningeal or cerebrovascular structures that are innervated by trigeminal nerves, with a local/regional inflammatory response mediated by glial cells.

Activated glial cells, with their increased production of pro-inflammatory substances, have been implicated in the development and persistence of pain.^{107,113,120–122} Cytokine-induced release of pain modulators from trigeminal neurons may subserve interactions between inflammatory and neuronal pathways.¹²³ For example, calcitonin gene-related peptide released from trigeminal nerve cell bodies has been shown to stimulate SGCs to release inflammatory substances,⁶⁷ which in turn can influence neuronal function and excitability through processes including upregulation of receptors for the inflammatory mediators and lowered activation thresholds¹⁰⁷ in a feed-forward loop.^{124,125} This neuronal-glial signaling is suspected to play a role in sensitizing afferent trigeminal nociceptors,^{122,126,127} potentially leading to sensitization of second-order neurons^{101,128} and mediating central pain sensitization.^{67,129} Prolonged inflammation and chronic hyperexcitability are thought to predispose to a pathological pain state.^{130–132}

These processes may be most relevant to post-traumatic migraines, as a number of shared pathological features between TBI and migraines have been identified,¹³³ including evidence for an inflammatory component and glial involvement.^{134–136} Evidence for inflammation in other headaches types, including tension-type headaches, new daily persistent headaches, cluster headaches, and variably cervicogenic headaches,^{123,137–140} has also been described but is less well characterized than for migraine headaches, being mainly limited to measurements of cytokine or neurotrophin levels. To what degree inflammation is a contributing causal factor to the headaches or a response to them is unclear. Neither these nor the migraine studies evaluating inflammatory markers have been specific to PTHAs. Further pressing questions include why individuals vary in PTHA type, what PTHAs may indicate about underlying brain pathology, which interventions may be of benefit in limiting secondary brain injury and preventing the onset of headaches or keeping them from becoming chronic, and whether those interventions may additionally be of benefit in limiting other post-concussive symptoms.

CONCLUSION

For some patients, TBI is a disease process rather than an isolated self-limited event,⁴⁸ with post-concussive symptoms, including PTHAs, reflecting persistent, potentially progressive brain dysfunction. Maladaptive inflammatory activity, particularly inflammatory activity that involves persistently activated glial cells, presents a plausible common denominator between the pathophysiology of TBI and the development of PTHAs, although the degree to which inflammation plays a role cannot be considered in isolation of all of the other changes that occur following TBI. A progressive inflammatory process with evolving sequelae is not inconsistent with the observation that PTHAs may have delayed onset well beyond the 7-day International Classification of Headache Disorders (ICHD) criteria¹⁴¹ and that headaches may become chronic. Delayed symptom onset has been viewed as a potential window of opportunity for therapeutic intervention before deleterious effects of secondary injury lead to intractable CNS damage.¹⁴² To date, there are few studies of glial activation in human chronic pain conditions. Importantly, human astrocytes differ greatly in morphology and relative number from those of other species,¹⁴³ suggesting that animal models may not realistically represent pathophysiological changes of glia-mediated TBI and chronic pain conditions in humans.⁵⁸ Future research directions should include carefully designed studies to further assess inflammation and glial activation in patients with TBI, with an eye toward identifying potential therapies that would interrupt processes predisposing to post-injury neurological deficits, including PTHA.

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