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From blast to bench: a translational mini-review of post-traumatic headache

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Abstract

Current events within the military and professional sports have resulted in an increased recognition of the long-term and debilitating consequences of traumatic brain injury. Mild traumatic brain injury accounts for the majority of head injuries, and post-traumatic headache is the most common adverse effect. It is estimated that between 30–90% of traumatic brain injuries result in post-traumatic headache, and for a significant number of people this headache disorder can continue for up to and over a year post-injury. Often, the most severe and chronic post-traumatic headache has a migraine-like phenotype, and is difficult to resolve. In this review we discuss the preclinical findings from animal models of post-traumatic headache. We also describe potential mechanisms by which traumatic brain injury leads to chronic post-traumatic headache, including neuroinflammatory mediators and migraine-associated neuropeptides. There are surprisingly few preclinical studies that have investigated overlapping mechanisms between post-traumatic headache and migraine, especially considering the prevalence and debilitating nature of post-traumatic headache. Given this context, post-traumatic headache is a field with many emerging opportunities for growth. The frequency of post-traumatic headache in the general and military population is staggeringly high, and further preclinical research is required to understand, ameliorate, and treat this disabling disorder.

Keywords

migraine; pain; mTBI; hyperalgesia; rodent

Introduction

The debilitating and often tragic consequences of traumatic brain injuries (TBIs) have received heightened and overdue attention following high-profile cases from both the military and professional sports. Consisting of blows, blasts, and jolts, TBIs are penetrating injuries to the head that disrupt normal functioning of the brain for any period of time (Gerberding 2003). TBIs are a serious public health concerns world-wide, and can often lead to persistent and disabling neuropsychological disorders. Globally, it is the leading cause of

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chronic disability among young adults and children (Feigin et al. 2013; Theeler et al. 2013). In the United States, the incidence of TBI has particularly risen in army personnel increasing four-fold since 2005, primarily due to combat in Iraq and Afghanistan (Theeler et al. 2013). With the improvement of protective gear and safety standards employed in modern combat, individuals are now surviving TBIs but consequently experiencing unprecedented adverse effects (Terri Tanielian 2008).

Mild TBI (mTBI), which is synonymous with concussion, is the most prevalent form of head trauma, and post-traumatic headache (PTH) is the most common symptom of mTBI. The incidence of PTH is highest following mTBI, and is less frequently observed following moderate or severe TBI (Hoffman et al. 2011; Lucas et al. 2012; Nampiaparampil 2008; Theeler et al. 2013). Up to 90% of mTBI patients have been reported to suffer from PTH, which can persist in a subset of patients for over a year post-injury (Couch and Bearss 2001; Hoffman et al. 2011; Lieba-Samal et al. 2011; Lucas et al. 2012; Nampiaparampil 2008; Okie 2005). Chronic PTH is defined by the International Classification of Headache Disorder (ICHD-3 beta version) as a secondary headache disorder, one which develops within seven days of TBI or within seven days after regaining consciousness from a TBI (ICHD 2013). While acute PTH is resolved within three months, persistent PTH is observed beyond this time frame. The persistence of PTH long after tissue healing suggests that some form of central sensitization and neuroadaptation has occurred. Often, the most severe and long-lasting PTHs have a migraine phenotype (Hoffman et al. 2011; Theeler et al. 2013), and migraine-like PTH is associated with greater cognitive impairment and increased recovery time. There is a staggeringly high number of civilians, veterans, and active duty military personnel suffering from PTH, and this has important implications for long-term health outcomes and quality of life. In this review we provide an overview of the epidemiology of PTH, current research models, and molecular mechanisms underlying this disorder.

Epidemiology of post-traumatic headache

TBI-related emergency department visits are increasing annually. According to the Center for Disease Control, at least 1.7 million TBI cases occur every year in the United States (Faul M 2010; Gerberding 2003; Lucas 2015). Furthermore, more than 2 million emergency room visits are made annually due to TBI (Coronado et al. 2012). In the general population, mTBI is most commonly due to falls, motor vehicle accidents, occupational hazards, recreational accidents, and assaults (D'Onofrio et al. 2014; Faul M 2010). Thus far, the only factors that predict the development of PTH following mTBI include female sex, prior headache disorder, and a family history of headache disorders (Mihalik et al. 2013; Walker et al. 2013). PTH is observed in 30–90% of cases following mTBI, and ~20–60% continue to suffer from this disorder for a year or longer post-injury (Couch and Bearss 2001; Lucas et al. 2014).

The incidence of TBI within the US military has dramatically increased in the last 10 years, and has become a signature injury of the Middle East conflicts (Theeler et al. 2013). Advancements in protective gear now allow military personnel to withstand blast injuries that would have once been fatal (Terri Tanielian 2008). These advancements have also

increased TBI-related side effects. Recent studies show that up to 78% of soldiers returning from combat with deployment-related TBI suffered from episodic headache, and 20% from chronic daily headache (Theeler et al. 2013). In the military population, PTH is a residual consequence of 67% of blast-induced TBI (bTBI) cases (Cernak and Noble-Haesslein 2010; D'Onofrio et al. 2014), and 77% of soldiers with chronic PTH experienced bTBI (Erickson 2011). Military-related TBI is distinct from civilian TBI, often occurring in combat-related deployment (Terri Tanielian 2008; Theeler et al. 2010) where additional factors such as irregular sleep patterns and emotional/psychological extremes can contribute to PTH development (Theeler et al. 2013). The relationship between post-traumatic stress disorder (PTSD) and PTH is of particularly relevance to the military population. For instance, longitudinal studies found that people with PTSD were more likely to report chronic or worsening PTH 1 year post-TBI (Sawyer et al. 2015; Tschiffely et al. 2015). Further research is required to fully understand the interplay between acute stress reactions, chronic psychiatric conditions such as PTSD, and the development and chronicity of PTH.

Treatment strategies for post-traumatic headache

To date, there are no specific pharmacological treatments for PTH. To the best of our knowledge, there has also never been a large scale clinical trial to test treatments for PTH specifically (Monteith and Borsook 2014). Due to the suboptimal diagnoses and treatment of PTH, many individuals turn to over-the-counter pain medications to self-treat their headaches. Pharmacotherapy is also based on the treatment strategy used for the primary headache condition the PTH most resembles (e.g. migraine, tension type headache). A small retrospective analysis in 167 patients found that more than 70% of non-military individuals with PTH used acetaminophen or a nonsteroidal anti-inflammatory drug for headache control, while only 8% used triptans (DiTommaso et al. 2014). Only 26% of individuals with PTH of a migraine phenotype reported complete relief, leaving 74% of individuals still suffering from PTH (DiTommaso et al. 2014). Interestingly, a retrospective cohort study in a 100 soldiers undergoing treatment for chronic PTH found that acute and preventative migraine therapies were effective treatment strategies; with triptans significantly aborting PTH, and topiramate acting as a preventative (Erickson 2011).

Alternative treatments have been proposed for the treatment of PTH, and warrant further study. A small retrospective cohort study evaluated the therapeutic effects of onabotulinum toxin A (OBA) for treatment of PTH (Yerry et al. 2015). Although a majority of soldiers reported feeling better, many ultimately stopped treatment for lack of continued progress (Yerry et al. 2015). Non-invasive therapy was also recently tested for the management of PTH (Leung et al. 2016). Repetitive transcranial magnetic stimulation (rTMS) is used to treat major-depressive disorder, and is currently being investigated for pain management. In a small study, 24 patients suffering from PTH received rTMS or sham stimulation, and a significant reduction in headache intensity was observed in the rTMS group which persisted 4 weeks post-treatment (Leung et al. 2016). In addition, adjunct behavioral therapies may be beneficial to PTH patients, particularly to supplement their pain management with psychological tools to overcome the after-effects of trauma (Dupin et al. 1991; Packard 1999). Focused research on mechanisms underlying PTH is necessary for the future development of novel therapies specifically targeting this condition.

Models of post-traumatic headache-associated pain

There are a number of limitations associated with modeling headache in animals, especially considering the subjective nature of the disease. Nevertheless, these types of models are necessary to understand the mechanism of PTH, and to screen novel drug therapies.

Currently, the majority of PTH models focus on assessing nociceptive responses in rodents following some form of TBI. There are numerous models of TBI, and the majority of PTH preclinical studies have used versions that produce a mild to moderate TBI. One thing to keep in mind is that for ethical reasons TBI is induced while the animals are anesthetized. Anesthetics are known to alter cortical networks and pain processing, and this factor should be considered when interpreting the findings. Considering the prevalence of PTH, it is surprising that there are so few preclinical studies investigating this disorder. We summarize the methods and findings below and in Table 1.

Lateral fluid percussion model

In this model, mTBI is induced through a wave of pressure applied onto the dura. Following craniotomy, a fluid percussion device is placed against the dura, and a wave of fluid is rapidly propagated through the device when a metal pendulum strikes a piston filled with saline (McIntosh et al. 1989). A detailed video of this procedure can be found within the following reference (Alder et al. 2011). An increase in mechanical, but not thermal, allodynia in the contralateral hindpaw was observed for up to 72h following unilateral, lateral fluid percussion. This increase was associated with a concomitant upregulation in brain derived neurotrophic factor (BDNF) mRNA and protein expression in the contralateral spinal cord (Feliciano et al. 2014). It has been previously shown that in models of dural inflammation, both cranial and hindpaw hypersensitivity is observed (De Felice et al. 2013; Edelmayer et al. 2012); and therefore in rodents disruption of the dura may sensitize pain mechanisms at peripheral sites. In addition, both cephalic and extra-cephalic allodynia has been observed in patients with chronic pain due to TBI (Ofek and Defrin 2007). It has yet to be determined whether the allodynia observed after the lateral fluid percussion injury is representative of chronic peripheral pain associated with mTBI or a correlate to PTH.

Closed head weight-drop model

The closed-head weight-drop model is one of the few mTBI models in which the skull and scalp are kept intact (Zohar et al. 2003). Briefly, anesthetized mice are positioned under a vertical metal guide tube and a cylindrical-shaped iron weight with a slight spherical tip is dropped from the full length of the tube onto one side of the mouse head. With the advantage of minimal damage to the intact crania, this mild closed head injury produces long-lasting learning and memory impairments, while keeping brain morphology intact (Zohar et al. 2003). With regards to PTH, this type of mTBI produced increased pain sensitivity to low doses of formalin injected into cranial tissue innervated by the trigeminal nerve. Interestingly, this heightened response was not observed to formalin in the hindpaw, indicative of a head-specific pain (Benromano et al. 2015). These studies were performed 48 hours after head injury, and it will be interesting to see if alterations in pain sensitivity persist at longer time points.

In a study using rats, a different closed head weight-drop model (Marmarou et al. 1994) was used to examine changes in pain-related behaviors in an operant testing paradigm. In this model, mTBI is induced by attaching a metal plate to the exposed cranium and dropping a 450 g weight from a height of 1.25m onto the plate. This technique is considered a model of mild vs. moderate/severe TBI, as the metal disk diffuses the force of the weight and decreases the probability of skull fracture (Marmarou et al. 1994). Two weeks post-injury, rats were tested in a reward-conflict test where the animal can choose to obtain a sweetened milk reward by pressing its face through plates which are warmed or cooled to produce varying levels of thermal nociception (Neubert et al. 2005). This pain test is thought to better model the human pain condition, as both the nociceptive and emotional components of pain are examined. Post-injury, rats showed decreased facial contact and lick behaviors to either warm or cool temperatures. This heightened thermal sensitivity was accompanied by an augmentation in the pain processing molecules: serotonin, norepinephrine, GABA, and the substance P receptor (NK1R) in the somatosensory cortex, thalamus and trigeminal nucleus caudalis (Mustafa et al. 2016). This study indicates that mTBI produces heightened facial pain sensitivity and/or decreased motivational drive, two factors that are also symptomatic of the human headache experience. Furthermore, this study also shows that injury at the level of the cortex produces adaptations in pain-processing regions distal to the site of injury.

Controlled cortical impact model

The controlled cortical impact (CCI) model, is one the most frequently used and best-characterized models of TBI (Petraglia et al. 2014; Xiong et al. 2013). This is a model of focal TBI and is highly reproducible across animals. Following a unilateral craniotomy, a controlled impact is applied to the intact dura with an electromagnetic or pneumatic impactor (Lighthall 1988). A video showing the detailed CCI procedure can be found in this reference (Romine et al. 2014). In a series of elegant studies by Elliott's lab, increased head pain sensitivity was observed following CCI. In these experiments mice showed increased mechanical allodynia in the periorbital region, both ipsi- and contralateral to the site of injury. Although peak nociception was observed 14 days following injury, allodynia persisted for up to 28 days post-TBI (Daiutolo et al. 2015; Elliott et al. 2012). To support that this nociception was associated with PTH, two migraine medications - sumatriptan and the calcitonin gene related peptide (CGRP) antagonist, MK8825 - blocked CCI-induced periorbital allodynia (Daiutolo et al. 2015). Furthermore, CCI also produced photophobia (Daiutolo et al. 2015), another frequently observed symptom of migraine (Rossi and Recker 2015). Interestingly, this group also found that periorbital allodynia was more pronounced in mice than rats following CCI, and that at earlier time points peripheral forepaw mechanical allodynia was also observed (Macolino et al. 2014). Compared to the clinical experience of mTBI, the CCI model is more severe – involving a craniotomy and a high pressure impact to a focal cortical region. However, this series of studies shows a number of links between head trauma and post-traumatic migraine, especially in terms of the chronicity and response to migraine-specific pharmacotherapies. Considering that PTH has so few preclinical tools, for the time being CCI is the best characterized model to screen for novel therapies.

Cell-based *in vitro* model of blast-induced TBI

Animal models are not ideal for the high-throughput screening techniques required for drug discovery, and to address this issue a cell-based blast-induced TBI (bTBI) model was recently developed (Arun et al. 2011). The *in vitro* bTBI model consists of using a compressed air-driven shock tube and mouse neuroblastoma/rat glioblastoma hybrid (NG108-15) or SH-SY5Y human neuroblastoma cells in tissue culture plates. Upon blast exposure, cells demonstrated significant cellular injury, with the highest damage resulting from one blast exposure instead of repeated blast exposures. Cells expressed a significant depletion of intracellular ATP levels, and increased reactive oxygen species formation, correlating with *in vivo* findings from prior literature (Arun et al. 2011). Theoretically, this *in vitro* system could be used to study complex cell-specific responses to blast injury, and may be used to initially screen pharmacotherapies for TBI and PTH. An interesting adaptation would be to use non-neoplastic cells in order to avoid differential protein expression and metabolic processing associated with cancer cells.

Proposed mechanisms underlying the development of post-traumatic headache

Neuroinflammation

Inflammation is rapidly elicited in response to brain injury, and neuroinflammatory mechanisms have been well characterized in TBI (Gyoneva and Ransohoff 2015; Mayer et al. 2013). In the brain, TBIs disturb ionic and neurotransmitter homeostasis, neurovascular processes, and result in cell injury and/or cell death (Ziebell and Morganti-Kossmann 2010). Similar biochemical changes in people suffering from mTBI and migraine have been noted, suggesting a shared mechanism (Solomon 1998; Solomon 2009). Inflammatory mediators have been at the crux of preliminary studies investigating PTH. Immediately after TBI, the immune system recruits various cell types to combat injury-induced disturbances, including mast cells, microglia, astrocytes and inflammatory cytokines. This neuroinflammatory response can ultimately trigger sensitization of the trigeminovascular complex resulting in PTH. In addition, cortical injury can trigger inflammatory responses in deeper neuroanatomical structures, including the thalamus (Hazra et al. 2014), a region that is also important for migraine-associated pain (Burstein et al. 2010).

The dura mater is heavily innervated by pain fibers, and is also densely populated by immune cells (Dimlich et al. 1991). Among the immune cells are mast cells, which are granulated cells that reside parallel to trigeminal nerve branches in the inner layer of the dura (Dimlich et al. 1991). Upon activation, mast cells release histamine and pro-inflammatory cytokines such as interferon gamma (IFN γ), and tumor necrosis factor alpha (TNF α); all of which can encourage a pro-nociceptive state. Early work demonstrated that dural mast cells play a role in neuroinflammatory responses to injury as well as to headache (Dimlich et al. 1991). *In vivo* electrophysiological recordings also showed that degranulation of dural mast cells induced a prolonged state of excitation in rat meningeal nociceptors (Levy et al. 2007). This excitation was accompanied by increased expression of the phosphorylated form of the extracellular signal-regulated kinase (pERK), a marker for nociceptor activation, and an increase in c-fos expression in the spinal trigeminal nucleus

(Levy et al. 2007). Peak mast cell degranulation was observed 72 hours post-trauma in a closed-head weight-drop model, and at 30 days in a bTBI model (Levy et al. 2016). Interestingly, acute treatment with sumatriptan, a migraine-specific medication, did not reduce dural mast cell degranulation at 7 or 30 days post-injury, which suggests an alternate mode of action for this drug (Levy et al. 2016).

Microglia also play a key role in the initiation and prolongation of neuroinflammation (Mayer et al. 2013; Nimmerjahn et al. 2005). Residing in the CNS, microglia monitor pathogens within the intraparenchymal space and are activated following injury (Nimmerjahn et al. 2005). An imbalance of microglial activation could result in continued release of cytotoxic inflammatory mediators, including reactive oxygen species and nitric oxide, contributing to progression of headache symptoms (Loane and Byrnes 2010; Olesen 2008). Aberrant microglial activation has been associated with many central nervous system disorders, including chronic pain (Grace et al. 2014; Ji et al. 2013; Taylor et al. 2016). Increased microglial and astrocyte activation was observed in the somatosensory cortex following CCI (Elliott et al. 2012). Peak activation preceded peak periorbital allodynia (7 days vs. 14 days), and microglial activation may be an early event that contributes to nociceptor sensitization resulting in PTH.

Numerous inflammatory mediators and cytokines are associated with TBI (Gyoneva and Ransohoff 2015). Cytokines have both pro- and anti-inflammatory effects depending on environmental factors (Ziebell and Morganti-Kossmann 2010). For example, interleukin-1 β (IL-1 β) is a pro-inflammatory marker that is elevated within hours post-TBI (Winter et al. 2002), and acts to promote the release of other cytokines, including TNF α (Ziebell and Morganti-Kossmann 2010). In a CCI model, an increase in TNF α mRNA expression was found 6 hours, 1 day, and 3 days post trauma (Amenta et al. 2014). Furthermore, the synergistic relationship between IL-1 β and TNF α results in increased permeability of the blood brain barrier, and is an important process in the initiation and maintenance of other pain states (Alves 2014).

The integrity of the blood brain barrier is often compromised following TBI both due to the actual injury and subsequent release of pro-inflammatory cytokines. Matrix metalloproteinases (MMPs) are a group of endopeptidase enzymes involved with the degradation of extracellular matrix proteins, and thus mediate blood brain barrier permeability (Rempe et al. 2016). MMPs regulate extracellular matrix turnover, and have been implicated in brain injuries (Lakhan and Avramut 2012). Synthesis of MMPs increases to promote local repair in response to neuronal injuries, but in parallel also contributes to the permeation of the blood brain barrier. Levels of MMP-2 and MMP-9 have been shown to be elevated post-TBI (Zhang et al. 2016), as well as in patients with migraine (Imamura et al. 2008; Lakhan and Avramut 2012). Interestingly, cortical spreading depression, a phenomenon related to migraine pathogenesis and aura; and observed following TBI, has also been shown to increase levels of MMP-9 (Imamura et al. 2008; Lakhan and Avramut 2012).

Migraine-associated neuropeptides and post-traumatic headache

The neuropeptide calcitonin gene related peptide (CGRP) is a well-characterized biomarker of migraine, and mTBI could increase migraine susceptibility through this mechanism. CGRP is upregulated in blood plasma and saliva during a migraine attack (Goadsby et al. 1990), and interictally in chronic migraine patients (Cernuda-Morollon et al. 2013). CGRP is also a known migraine trigger when administered intravenously (Lassen et al. 2002). CGRP has multiple sites of action within the trigeminovascular complex, spinal cord, and brain (Eftekhari et al. 2015). CGRP release at nerve terminals contribute to neurogenic inflammation by increasing vasodilation and mast cell degranulation, and activation of CGRP receptors in the brain stem can produce allodynia and central sensitization (Bigal et al. 2013). CGRP antagonists are effective migraine treatments (Bigal et al. 2013; Ho et al. 2010; Karsan and Goadsby 2015), and antibodies targeting CGRP or its receptor are currently being tested as migraine therapies (Bigal et al. 2015). CGRP may act as a link between brain injury and the development of PTH. To support this facilitatory role of CGRP, TBI induced by CCI has been shown to augment CGRP expression (Elliott et al. 2012; Theeler et al. 2013), and is part of a neuroinflammatory process which includes activation of inducible nitric oxide synthase (iNOS) initiated in response to injury Using CCI model of TBI, a significant increase in CGRP levels was observed in the brain stem of CCI mice when compared to control craniotomy counterparts (Elliott et al. 2012). This focal injury to the sensory cortex increased protein expression of CGRP in the trigeminovascular system for up to 2 weeks post-injury (Daiutolo et al. 2015). In addition, the anti-migraine medication, sumatriptan reduced this upregulation. Furthermore, the CGRP antagonist MK8825 inhibited both periorbital allodynia and photosensitivity evoked by CCI injury. These results suggest that upcoming CGRP-targeted therapies will be promising for the future treatment of PTH.

Pituitary adenylate cyclase-activating polypeptide (PACAP) is emerging as a key player in migraine pathophysiology. PACAP is a potent vasodilator of meningeal and trigeminal ganglia arteries, and like CGRP, is a known migraine trigger. In addition, inhibition of a PACAP receptor, PAC1, attenuated electrophysiological activity associated with dural nociception (Akerman and Goadsby 2015). Increased levels of PACAP in cerebrospinal fluid and plasma have also been observed following severe TBI (Bukovics et al. 2014). Further, PACAP also regulates cellular stress responses, and increased PACAP levels have been correlated with increased PTSD symptoms (Theeler et al. 2013). Post-traumatic headache and PTSD are often comorbid, especially in the military population; and PTSD appears to augment severity of PTH (Theeler et al. 2013). PACAP appears to be another convergent point by which mTBI could lead to post-traumatic migraine. In a closed-head weight drop model, exogenous administration of PACAP was found to be neuroprotective; and treatment with PACAP38 inhibited mTBI-induced upregulation of toll like receptor 4 and its downstream signaling molecules – important mediators of neuroinflammation. Further, PACAP38 also blocked the increase in levels of downstream inflammatory agents IL-1 β and TNF- α , in the brain tissue at and near the injury site (Mao et al. 2012); and PACAP activation may also protect from injury-induced oxidative stress (Miyamoto et al. 2014). In addition, the neuropeptide substance P (Corrigan et al. 2016; Elliott et al. 2012; Mustafa et

al. 2016), and the growth factor BDNF (Feliciano et al. 2014; Kaplan et al. 2010) have also been implicated in TBI.

There is an interaction between TBI and migraine, and further research into the factors mediating each condition could provide valuable insight on overlapping mechanisms shared by both conditions.

Conclusions and Future Directions

Many preclinical studies have been performed to investigate the pathophysiology of TBI. However, considering that PTH is the leading symptom of TBI, surprisingly little research has been done to understand how mTBI results in PTH. PTH often persists long after mTBI, and this suggests that the trigeminal nociceptive pathway is primed by neuroinflammatory and allostatic events triggered by injury. For the time being, our understanding of the complex mechanism regulating PTH remains limited. Deeper insight into the neurotransmitters, inflammatory mediators, and cellular and circuit adaptations that occur after mTBI, and how they relate to migraine, is critical to reveal novel therapeutic targets for PTH. A greater emphasis needs to be placed on the further characterization of already existing animal models, and the development of new animal models of PTH. In addition, *in vitro* models reflecting brain cell-specific changes that occur following trauma could be a promising strategy for high-throughput screening of emerging therapies. Furthermore, repetitive TBI has recently received a lot of attention in sports and the military, and animal models have been developed to study this type of injury (Kane et al. 2012; McAteer et al. 2016; Ojo et al. 2016; Semple et al. 2015; Winston et al. 2016). Future preclinical studies focused on the effect of repetitive TBI on PTH-associated symptoms would provide much needed insight on how the brain pain-processing regions adapt to repeated injury. Overall, a greater emphasis on well-characterized animal models of PTH would allow for the investigation of molecular mechanisms regulating this disorder, and subsequent rational drug design.

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References

- Akerman S, Goadsby PJ. Neuronal PAC1 receptors mediate delayed activation and sensitization of trigeminocervical neurons: Relevance to migraine. *Science translational medicine*. 2015; 7(308): 308ra157.
- Alder J, Fujioka W, Lifshitz J, Crockett DP, Thakker-Varia S. Lateral fluid percussion: model of traumatic brain injury in mice. *Journal of visualized experiments: JoVE*. 2011; (54)
- Alves JL. Blood-brain barrier and traumatic brain injury. *Journal of neuroscience research*. 2014; 92(2):141–147. [PubMed: 24327344]
- Amenta PS, Jallo JI, Tuma RF, Hooper DC, Elliott MB. Cannabinoid receptor type-2 stimulation, blockade, and deletion alter the vascular inflammatory responses to traumatic brain injury. *Journal of neuroinflammation*. 2014; 11:191. [PubMed: 25416141]

- Arun P, Spadaro J, John J, Gharavi RB, Bentley TB, Nambiar MP. Studies on blast traumatic brain injury using in-vitro model with shock tube. *Neuroreport*. 2011; 22(8):379–384. [PubMed: 21532394]
- Benromano T, Defrin R, Ahn AH, Zhao J, Pick CG, Levy D. Mild closed head injury promotes a selective trigeminal hypernociception: implications for the acute emergence of post-traumatic headache. *Eur J Pain*. 2015; 19(5):621–628. [PubMed: 25168788]
- Bigal ME, Walter S, Rapoport AM. Calcitonin gene-related peptide (CGRP) and migraine current understanding and state of development. *Headache*. 2013; 53(8):1230–1244. [PubMed: 23848260]
- Bigal ME, Walter S, Rapoport AM. Therapeutic antibodies against CGRP or its receptor. *British journal of clinical pharmacology*. 2015; 79(6):886–895. [PubMed: 25614243]
- Bukovics P, Czeiter E, Amrein K, Kovacs N, Pal J, Tamas A, Bagoly T, Helyes Z, Buki A, Reglodi D. Changes of PACAP level in cerebrospinal fluid and plasma of patients with severe traumatic brain injury. *Peptides*. 2014; 60:18–22. [PubMed: 25017241]
- Burstein R, Jakubowski M, Garcia-Nicas E, Kainz V, Bajwa Z, Hargreaves R, Becerra L, Borsook D. Thalamic sensitization transforms localized pain into widespread allodynia. *Ann Neurol*. 2010; 68(1):81–91. [PubMed: 20582997]
- Cernak I, Noble-Haesslein LJ. Traumatic brain injury: an overview of pathobiology with emphasis on military populations. *J Cereb Blood Flow Metab*. 2010; 30(2):255–266. [PubMed: 19809467]
- Cernuda-Morollon E, Larrosa D, Ramon C, Vega J, Martinez-Cambor P, Pascual J. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. *Neurology*. 2013; 81(14):1191–1196. [PubMed: 23975872]
- Coronado VG, McGuire LC, Sarmiento K, Bell J, Lionbarger MR, Jones CD, Geller AI, Khoury N, Xu L. Trends in Traumatic Brain Injury in the U.S. and the public health response: 1995–2009. *Journal of safety research*. 2012; 43(4):299–307. [PubMed: 23127680]
- Corrigan F, Vink R, Turner RJ. Inflammation in acute CNS injury: a focus on the role of substance P. *British journal of pharmacology*. 2016; 173(4):703–715. [PubMed: 25827155]
- Couch JR, Bearss C. Chronic daily headache in the posttrauma syndrome: relation to extent of head injury. *Headache*. 2001; 41(6):559–564. [PubMed: 11437891]
- D'Onofrio F, Russo A, Conte F, Casucci G, Tessitore A, Tedeschi G. Post-traumatic headaches: an epidemiological overview. *Neurol Sci*. 2014; 35(Suppl 1):203–206. [PubMed: 24867867]
- Daiutolo BV, Tyburski A, Clark SW, Elliott MB. Trigeminal Pain Molecules, Allodynia, and Photosensitivity Are Pharmacologically and Genetically Modulated in a Model of Traumatic Brain Injury. *J Neurotrauma*. 2015
- De Felice M, Eyde N, Dodick D, Dussor GO, Ossipov MH, Fields HL, Porreca F. Capturing the aversive state of cephalic pain preclinically. *Annals of neurology*. 2013; 74(2):257–265. [PubMed: 23686557]
- Dimlich RV, Keller JT, Strauss TA, Fritts MJ. Linear arrays of homogeneous mast cells in the dura mater of the rat. *Journal of neurocytology*. 1991; 20(6):485–503. [PubMed: 1869885]
- DiTommaso C, Hoffman JM, Lucas S, Dikmen S, Temkin N, Bell KR. Medication Usage Patterns for Headache Treatment After Mild Traumatic Brain Injury. *Headache: The Journal of Head and Face Pain*. 2014; 54(3):511–519.
- Dupin S, Tafani JA, Mazarguil H, Zajac JM. [125I][D-Ala²]deltorphin-I: a high affinity, delta-selective opioid receptor ligand. *Peptides*. 1991; 12(4):825–830. [PubMed: 1664947]
- Edelmayer RM, Le LN, Yan J, Wei X, Nassini R, Materazzi S, Preti D, Appendino G, Geppetti P, Dodick DW, Vanderah TW, Porreca F, Dussor G. Activation of TRPA1 on dural afferents: a potential mechanism of headache pain. *Pain*. 2012; 153(9):1949–1958. [PubMed: 22809691]
- Eftekhari S, Salvatore CA, Johansson S, Chen TB, Zeng Z, Edvinsson L. Localization of CGRP, CGRP receptor, PACAP and glutamate in trigeminal ganglion. Relation to the blood-brain barrier. *Brain research*. 2015; 1600:93–109. [PubMed: 25463029]
- Elliott MB, Oshinsky ML, Amenta PS, Awe OO, Jallo JI. Nociceptive neuropeptide increases and periorbital allodynia in a model of traumatic brain injury. *Headache*. 2012; 52(6):966–984. [PubMed: 22568499]
- Erickson JC. Treatment outcomes of chronic post-traumatic headaches after mild head trauma in US soldiers: an observational study. *Headache*. 2011; 51(6):932–944. [PubMed: 21592097]

- Faul, MXL., Wald, MM., Coronado, V. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths, 2002–2006. Atlanta, Georgia: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
- Feigin VL, Theadom A, Barker-Collo S, Starkey NJ, McPherson K, Kahan M, Dowell A, Brown P, Parag V, Kydd R, Jones K, Jones A, Ameratunga S. Incidence of traumatic brain injury in New Zealand: a population-based study. *The Lancet Neurology*. 2013; 12(1):53–64. [PubMed: 23177532]
- Feliciano DP, Sahbaie P, Shi X, Klukinov M, Clark JD, Yeomans DC. Nociceptive sensitization and BDNF up-regulation in a rat model of traumatic brain injury. *Neuroscience letters*. 2014; 583:55–59. [PubMed: 25246352]
- Gerberding, JL. Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem. National Center for Injury Prevention and Control; 2003.
- Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol*. 1990; 28(2):183–187. [PubMed: 1699472]
- Grace PM, Hutchinson MR, Maier SF, Watkins LR. Pathological pain and the neuroimmune interface. *Nature reviews Immunology*. 2014; 14(4):217–231.
- Gyoneva S, Ransohoff RM. Inflammatory reaction after traumatic brain injury: therapeutic potential of targeting cell-cell communication by chemokines. *Trends in pharmacological sciences*. 2015; 36(7):471–480. [PubMed: 25979813]
- Hazra A, Macolino C, Elliott MB, Chin J. Delayed thalamic astrocytosis and disrupted sleep-wake patterns in a preclinical model of traumatic brain injury. *J Neurosci Res*. 2014; 92(11):1434–1445. [PubMed: 24964253]
- Ho TW, Edvinsson L, Goadsby PJ. CGRP and its receptors provide new insights into migraine pathophysiology. *Nat Rev Neurol*. 2010; 6(10):573–582. [PubMed: 20820195]
- Hoffman JM, Lucas S, Dikmen S, Braden CA, Brown AW, Brunner R, Diaz-Arrastia R, Walker WC, Watanabe TK, Bell KR. Natural history of headache after traumatic brain injury. *J Neurotrauma*. 2011; 28(9):1719–1725. [PubMed: 21732765]
- ICHD. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia: an international journal of headache. 2013; 33(9):629–808. [PubMed: 23771276]
- Imamura K, Takeshima T, Fusayasu E, Nakashima K. Increased plasma matrix metalloproteinase-9 levels in migraineurs. *Headache*. 2008; 48(1):135–139. [PubMed: 18005141]
- Ji RR, Berta T, Nedergaard M. Glia and pain: is chronic pain a gliopathy? *Pain*. 2013; 154(Suppl 1):S10–28. [PubMed: 23792284]
- Kane MJ, Angoa-Perez M, Briggs DI, Viano DC, Kreipke CW, Kuhn DM. A mouse model of human repetitive mild traumatic brain injury. *Journal of neuroscience methods*. 2012; 203(1):41–49. [PubMed: 21930157]
- Kaplan GB, Vasterling JJ, Vedak PC. Brain-derived neurotrophic factor in traumatic brain injury, post-traumatic stress disorder, and their comorbid conditions: role in pathogenesis and treatment. *Behav Pharmacol*. 2010; 21(5–6):427–437. [PubMed: 20679891]
- Karsan N, Goadsby PJ. Calcitonin gene-related peptide and migraine. *Current opinion in neurology*. 2015; 28(3):250–254. [PubMed: 25887765]
- Lakhan SE, Avramut M. Matrix metalloproteinases in neuropathic pain and migraine: friends, enemies, and therapeutic targets. *Pain Res Treat*. 2012; 2012:952906. [PubMed: 22970361]
- Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J. CGRP may play a causative role in migraine. *Cephalalgia: an international journal of headache*. 2002; 22(1):54–61. [PubMed: 11993614]
- Leung A, Shukla S, Fallah A, Song D, Lin L, Golshan S, Tsai A, Jak A, Polston G, Lee R. Repetitive Transcranial Magnetic Stimulation in Managing Mild Traumatic Brain Injury-Related Headaches. *Neuromodulation: journal of the International Neuromodulation Society*. 2016; 19(2):133–141. [PubMed: 26555886]
- Levy D, Burstein R, Kainz V, Jakubowski M, Strassman AM. Mast cell degranulation activates a pain pathway underlying migraine headache. *Pain*. 2007; 130(1–2):166–176. [PubMed: 17459586]
- Levy D, Edut S, Baraz-Goldstein R, Rubovitch V, Defrin R, Bree D, Garipey H, Zhao J, Pick CG. Responses of dural mast cells in concussive and blast models of mild traumatic brain injury in

- mice: Potential implications for post-traumatic headache. *Cephalalgia: an international journal of headache*. 2016; 36(10):915–923. [PubMed: 26566937]
- Lieba-Samal D, Platzer P, Seidel S, Klaschetterka P, Knopf A, Wober C. Characteristics of acute posttraumatic headache following mild head injury. *Cephalalgia*. 2011; 31(16):1618–1626. [PubMed: 22116940]
- Lighthall JW. Controlled Cortical Impact: A New Experimental Brain Injury Model. *Journal of Neurotrauma*. 1988; 5(1):1–15. [PubMed: 3193461]
- Loane DJ, Byrnes KR. Role of microglia in neurotrauma. *Neurotherapeutics*. 2010; 7(4):366–377. [PubMed: 20880501]
- Lucas, S. Characterization and Management of Headache after Mild Traumatic Brain Injury. In: Kobeissy, FH., editor. *Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects*. Boca Raton FL: 2015 by Taylor & Francis Group, LLC; 2015.
- Lucas S, Hoffman JM, Bell KR, Dikmen S. A prospective study of prevalence and characterization of headache following mild traumatic brain injury. *Cephalalgia*. 2014; 34(2):93–102. [PubMed: 23921798]
- Lucas S, Hoffman JM, Bell KR, Walker W, Dikmen S. Characterization of headache after traumatic brain injury. *Cephalalgia*. 2012; 32(8):600–606. [PubMed: 22623761]
- Macolino CM, Daiutolo BV, Albertson BK, Elliott MB. Mechanical allodynia induced by traumatic brain injury is independent of restraint stress. *Journal of neuroscience methods*. 2014; 226:139–146. [PubMed: 24486873]
- Mao SS, Hua R, Zhao XP, Qin X, Sun ZQ, Zhang Y, Wu YQ, Jia MX, Cao JL, Zhang YM. Exogenous administration of PACAP alleviates traumatic brain injury in rats through a mechanism involving the TLR4/MyD88/NF-kappaB pathway. *J Neurotrauma*. 2012; 29(10):1941–1959. [PubMed: 22583372]
- Marmarou A, Foda MA, van den Brink W, Campbell J, Kita H, Demetriadou K. A new model of diffuse brain injury in rats. Part I: Pathophysiology and biomechanics. *Journal of neurosurgery*. 1994; 80(2):291–300. [PubMed: 8283269]
- Mayer CL, Huber BR, Peskind E. Traumatic brain injury, neuroinflammation, and post-traumatic headaches. *Headache*. 2013; 53(9):1523–1530. [PubMed: 24090534]
- McAteer KM, Corrigan F, Thornton E, Turner RJ, Vink R. Short and Long Term Behavioral and Pathological Changes in a Novel Rodent Model of Repetitive Mild Traumatic Brain Injury. *PloS one*. 2016; 11(8):e0160220. [PubMed: 27505027]
- McIntosh TK, Vink R, Noble L, Yamakami I, Fernyak S, Soares H, Faden AL. Traumatic brain injury in the rat: characterization of a lateral fluid-percussion model. *Neuroscience*. 1989; 28(1):233–244. [PubMed: 2761692]
- Mihalik JP, Register-Mihalik J, Kerr ZY, Marshall SW, McCrea MC, Guskiewicz KM. Recovery of posttraumatic migraine characteristics in patients after mild traumatic brain injury. *The American journal of sports medicine*. 2013; 41(7):1490–1496. [PubMed: 23696213]
- Miyamoto K, Tsumuraya T, Ohtaki H, Dohi K, Satoh K, Xu Z, Tanaka S, Murai N, Watanabe J, Sugiyama K, Aruga T, Shioda S. PACAP38 suppresses cortical damage in mice with traumatic brain injury by enhancing antioxidant activity. *Journal of molecular neuroscience: MN*. 2014; 54(3):370–379. [PubMed: 24907941]
- Monteith TS, Borsook D. Insights and advances in post-traumatic headache: research considerations. *Curr Neurol Neurosci Rep*. 2014; 14(2):428. [PubMed: 24435590]
- Mustafa G, Hou J, Tsuda S, Nelson R, Sinharoy A, Wilkie Z, Pandey R, Caudle RM, Neubert JK, Thompson FJ, Bose P. Trigeminal neuroplasticity underlies allodynia in a preclinical model of mild closed head traumatic brain injury (cTBI). *Neuropharmacology*. 2016; 107:27–39. [PubMed: 26972829]
- Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: A systematic review. *JAMA*. 2008; 300(6):711–719. [PubMed: 18698069]
- Neubert JK, Widmer CG, Malphurs W, Rossi HL, Vierck CJ Jr, Caudle RM. Use of a novel thermal operant behavioral assay for characterization of orofacial pain sensitivity. *Pain*. 2005; 116(3):386–395. [PubMed: 15982812]

- Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science (New York, NY)*. 2005; 308(5726):1314–1318.
- Ofek H, Defrin R. The characteristics of chronic central pain after traumatic brain injury. *Pain*. 2007; 131(3):330–340. [PubMed: 17689190]
- Ojo JO, Mouzon BC, Crawford F. Repetitive head trauma, chronic traumatic encephalopathy and tau: Challenges in translating from mice to men. *Experimental neurology*. 2016; 275(Pt 3):389–404. [PubMed: 26054886]
- Okie S. Traumatic brain injury in the war zone. *The New England journal of medicine*. 2005; 352(20):2043–2047. [PubMed: 15901856]
- Olesen J. The role of nitric oxide (NO) in migraine, tension-type headache and cluster headache. *Pharmacology & therapeutics*. 2008; 120(2):157–171. [PubMed: 18789357]
- Packard RC. Epidemiology and Pathogenesis of Posttraumatic Headache. *Journal of Head Trauma Rehabilitation*. 1999; 14(1):9–21. [PubMed: 9949243]
- Petraglia AL, Dashnaw ML, Turner RC, Bailes JE. Models of mild traumatic brain injury: translation of physiological and anatomic injury. *Neurosurgery*. 2014; 75(Suppl 4):S34–49.
- Rempe RG, Hartz AM, Bauer B. Matrix metalloproteinases in the brain and blood-brain barrier: Versatile breakers and makers. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2016; 36(9):1481–1507.
- Romine J, Gao X, Chen J. Controlled cortical impact model for traumatic brain injury. *Journal of visualized experiments: JoVE*. 2014; (90):e51781. [PubMed: 25145417]
- Rossi HL, Recober A. Photophobia in primary headaches. *Headache*. 2015; 55(4):600–604. [PubMed: 25790126]
- Sawyer K, Bell KR, Ehde DM, Temkin N, Dikmen S, Williams RM, Dillworth T, Hoffman JM. Longitudinal Study of Headache Trajectories in the Year After Mild Traumatic Brain Injury: Relation to Posttraumatic Stress Disorder Symptoms. *Arch Phys Med Rehabil*. 2015; 96(11):2000–2006. [PubMed: 26220236]
- Semple BD, Lee S, Sadjadi R, Fritz N, Carlson J, Griep C, Ho V, Jang P, Lamb A, Papolizio B, Saini S, Bazarian JJ, Prins ML, Ferriero DM, Basso DM, Noble-Haesslein LJ. Repetitive concussions in adolescent athletes - translating clinical and experimental research into perspectives on rehabilitation strategies. *Frontiers in neurology*. 2015; 6:69. [PubMed: 25883586]
- Solomon S. John Graham Senior Clinicians Award Lecture. Posttraumatic migraine. *Headache*. 1998; 38(10):772–778. [PubMed: 11279902]
- Solomon S. Post-traumatic headache: commentary: an overview. *Headache*. 2009; 49(7):1112–1115. [PubMed: 19583600]
- Taylor AM, Mehrabani S, Liu S, Taylor AJ, Cahill CM. Topography of microglial activation in sensory- and affect-related brain regions in chronic pain. *Journal of neuroscience research*. 2016
- Terri Tanielian, LHJ. *Invisible Wounds of War*. RAND Corporation; 2008. p. 538
- Theeler B, Lucas S, Riechers RG 2nd, Ruff RL. Post-traumatic headaches in civilians and military personnel: a comparative, clinical review. *Headache*. 2013; 53(6):881–900. [PubMed: 23721236]
- Theeler BJ, Flynn FG, Erickson JC. Headaches after concussion in US soldiers returning from Iraq or Afghanistan. *Headache*. 2010; 50(8):1262–1272. [PubMed: 20553333]
- Tschiffely AE, Ahlers ST, Norris JN. Examining the relationship between blast-induced mild traumatic brain injury and posttraumatic stress-related traits. *J Neurosci Res*. 2015; 93(12):1769–1777. [PubMed: 26346303]
- Walker WC, Marwitz JH, Wilk AR, Ketchum JM, Hoffman JM, Brown AW, Lucas S. Prediction of headache severity (density and functional impact) after traumatic brain injury: A longitudinal multicenter study. *Cephalalgia*. 2013; 33(12):998–1008. [PubMed: 23575819]
- Winston CN, Noel A, Neustadt A, Parsadani M, Barton DJ, Chellappa D, Wilkins TE, Alikhani AD, Zapple DN, Villapol S, Planel E, Burns MP. Dendritic Spine Loss and Chronic White Matter Inflammation in a Mouse Model of Highly Repetitive Head Trauma. *The American journal of pathology*. 2016; 186(3):552–567. [PubMed: 26857506]
- Winter CD, Iannotti F, Pringle AK, Trikkas C, Clough GF, Church MK. A microdialysis method for the recovery of IL-1beta, IL-6 and nerve growth factor from human brain in vivo. *Journal of neuroscience methods*. 2002; 119(1):45–50. [PubMed: 12234634]

- Xiong Y, Mahmood A, Chopp M. Animal models of traumatic brain injury. *Nature reviews Neuroscience*. 2013; 14(2):128–142. [PubMed: 23329160]
- Yerry JA, Kuehn D, Finkel AG. Onabotulinum toxin a for the treatment of headache in service members with a history of mild traumatic brain injury: a cohort study. *Headache*. 2015; 55(3):395–406. [PubMed: 25644249]
- Zhang S, Kojic L, Tsang M, Grewal P, Liu J, Namjoshi D, Wellington CL, Tetzlaff W, Cynader MS, Jia W. Distinct roles for metalloproteinases during traumatic brain injury. *Neurochemistry international*. 2016; 96:46–55. [PubMed: 26939762]
- Ziebell JM, Morganti-Kossmann MC. Involvement of pro- and anti-inflammatory cytokines and chemokines in the pathophysiology of traumatic brain injury. *Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics*. 2010; 7(1):22–30. [PubMed: 20129494]
- Zohar O, Schreiber S, Getslev V, Schwartz JP, Mullins PG, Pick CG. Closed-head minimal traumatic brain injury produces long-term cognitive deficits in mice. *Neuroscience*. 2003; 118(4):949–955. [PubMed: 12732240]

Significance Statement

Post-traumatic headache is one of the most common symptoms following mild traumatic brain injury, and can persist for months after the initial trauma. The most severe and long lasting post-traumatic headaches are usually classified as migraine; and are a major cause of disability. The mechanisms by which head trauma leads to migraine are currently unclear, and is the subject of current research. A better understanding of the mechanisms that lead from brain injury to chronic migraine would have important biological and therapeutic implications.

Table 1

Summary of best characterized mechanisms underlying post-traumatic headache

Molecule/Cascade	Observation	Model System Used	Reference
Peptides/Growth Factors			
CGRP	↑ CGRP mRNA and protein in brain stem/trigeminal nucleus and trigeminal ganglia	CCI	Elliot et al. 2012; Daiutolo et al. 2015
PACAP	PACAP38 ↓ inflammatory mediators, and ↑ antioxidants	Weight-drop with craniotomy; CCI	Mao et al. 2012; Miyamoto et al. 2014
BDNF	↑ BDNF mRNA and protein in spinal cord	Lateral fluid percussion model	Feliciano et al. 2014
Inflammatory Mediators			
Microglia and astrocytes	↑ microglial and astrocyte activation in the somatosensory cortex	CCI	Elliot et al. 2012
Dural mast cells	↑ mast cell degranulation observed after mTBI, and bTBI	Closed-head weight drop model; blast model	Benromano et al. 2015; Levy et al. 2016
Tumor necrosis factor α (TNF α)	↑ TNF α mRNA in injured cortex	CCI	Amenta et al. 2014
Matrix metalloproteinases (MMPs)	↑ MMP-2 and MMP-9 protein in cortex	Closed and open head injury models	Zhang et al. 2016