Mild closed head traumatic brain injury-induced changes in monoamine neurotransmitters in the trigeminal subnuclei of a rat model: mechanisms underlying orofacial allodynias and headache

Golam Mustafa1,2, Jiamei Hou1,2, Rachel Nelson1, Shigeharu Tsuda2, Mansura Jahan1, Naweed S. Mohammad1, Joseph V. Watts1, Floyd J. Thompson1,2,3*, Prodip Bose1,2,4,5*
1 Brain Rehabilitation Research Center of Excellence, Malcom Randall VA Medical Center, North Florida/South Georgia Veterans Health System, Gainesville, FL, USA
2 Department of Physiological Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL, USA
3 Department of Neuroscience, McKnight Brain Institute, College of Medicine, University of Florida, Gainesville, FL, USA
4 Department of Neurology, McKnight Brain Institute, College of Medicine, University of Florida, Gainesville, FL, USA

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Abstract
Our recent findings have demonstrated that rodent models of closed head traumatic brain injury exhibit comprehensive evidence of progressive and enduring orofacial allodynias, a hypersensitive pain response induced by non-painful stimulation. These allodynias, tested using thermal hyperalgesia, correlated with changes in several known pain signaling receptors and molecules along the trigeminal pain pathway, especially in the trigeminal nucleus caudalis. This study focused to extend our previous work to investigate the changes in monoamine neurotransmitter immunoreactivity changes in spinal trigeminal nucleus oralis, pars interpolaris and nucleus tractus soleitaries following mild to moderate closed head traumatic brain injury, which are related to tactile allodynia, touch-pressure sensitivity, and visceral pain. Our results exhibited significant alterations in the excitatory monoamine, serotonin, and inhibitory molecule norepinephrine in the nucleus tractus soleitaries, which might indicate the possibility of an alteration in visceral pain, and existence of other morbidities related to solitary nucleus dysfunction in this rodent model of mild to moderate closed head traumatic brain injury. Collectively, widespread changes in monoamine neurotransmitter may be related to orofacial alldynias and headache after traumatic brain injury.

Key Words: nerve regeneration; mild to moderate traumatic brain injury; trigeminal sensory system; neurotransmitters; facial and somatic allodynia; thermal hyperalgesia; headache; migraine; neural regeneration

Introduction
Traumatic brain injury (TBI) is a major cause of death and disability affecting more than 10 million people globally every year (Hyder et al., 2007). A large number of TBI patients undergo mild to moderate TBI (mTBI) which is often unattended clinically. mTBI causes multiple morbidities and neurological sequela including long-term sensory disabilities. Post-traumatic headache (PTH) is one of the most common and persisting sensory disabilities following TBI (Hoffman et al., 2007, 2011; Hyder et al., 2007; Theeler et al., 2013). Many patients with PTH and migraine also develop increased facial sensitization called facial allodynia (Burstein et al., 2010). The pathophysiology of this PTH or associated facial allodynia is unknown. However, the functional comorbidity of PTH and facial allodynia is consistent with a systemic sensitization affecting the significant anatomical viscerosomatic convergence of the trigeminal vascular afferents and facial cutaneous afferents within the trigeminal sensory system (Burstein et al., 2000; Sandkuhler, 2009; Sokolov et al., 2012; Noseda and Burstein, 2013). The cutaneous allodynia of extra cephalic regions seen in migraine and cluster headache patients (Edelmayer et al., 2009) often includes sensitization to thermal, touch, and pressure modalities.

A significant alteration in facial thermosensitivity/allodynia has been reported recently by us in this rodent model of closed head traumatic brain injury (cTBI) based on an operant avoidance behavior of reward/conflict to a noxious challenge temperature (Mustafa et al., 2016). We reported that cTBI causes significant loss of noradrenergic cells of the locus coeruleus (Bose et al., 2013; Tsuda et al., 2016) and noradrenergic fiber densities in the locus coeruleus, periaqueductal gray, and medial division of central nucleus of the amygdala (Tsuda et al., 2016). Physiologically, the noradren-
Autonomic dysregulation (e.g., loss of noradrenergic fiber)

Figure 1 Possible neurological sequelae following traumatic brain injury leading to the development of post-traumatic headache. Both trigeminal sensory system and trigeminal vascular system have potential to be affected by the inflammatory molecules and altered expression of excitatory and inhibitory neuromodulators.

Materials and Methods

Animals
Sprague-Dawley specific pathogen free (SPF) female rats (12 weeks old, weighing 240–270 g at the start of this study; Charles River Laboratory, USA) were used in this study. All procedures were performed in accordance with the U.S. Government Principle for the Utilization and Care of Vertebrate Animals, specifically following the National Institutes of Health “Guide for the Care and Use of Laboratory Animals”. Experimental protocols were approved by the Institutional Animal Care & Use Committee (IACUC) at the North Florida/South Georgia Veterans Health System, and the University of Florida, USA.

Surgical approach to create closed head mTBI
For producing closed head mTBI, a standardized 1.25 m/450 g weight-drop method (Marmarou model, Marmarou et al., 1994b) was used using the procedures as previously described in the original reports (Foda and Marmarou, 1994; Marmarou et al., 1994a) and in our recently published reports (Bose et al., 2013; Mustafa et al., 2016; Tsuda et al., 2016).

Tissue collection for immunohistochemistry
Brain tissues were collected 2 weeks following injury, and thus considered as acute. Briefly the animals were transcardially perfused with phosphate-buffered saline (PBS; 0.01 M, pH 7.4), followed by 4% paraformaldehyde in phosphate buffer (0.1 M, pH 7.4, 4°C) for immunohistochemistry. Briefly, the brain was dissected and post-fixed with fresh 4% paraformaldehyde for 24–48 hours. The whole brain was placed into 30% sucrose for 3 days and then cut serially into 40-µm-thick sections rostrocaudally by Cryostat (Leica CM 1850, Leica Biosystems, Bannockburn, IL, USA) approximately from Bregma: –10.68 mm to –11.04 mm for Sp5O; –12.84 mm to –13.20 mm for Sp5I, and –14.40 mm to –14.76 mm for NTS according to rat stereotaxic atlas of Paxinos and Watson (Watson, 2009).

Immunohistochemical analysis
A total of five sets of serial sections (approximately 80 µm apart from one another) for every specified region (SP5O, SP5I and NTS) were collected from each animal (3 normal and 3 mTBI). The sections were incubated with three antibodies for 24 hours at 4°C: rabbit anti-serotonin (5-HT) (1:6,000), mouse anti-dopamine beta-hydroxylase (DβH)
Figure 3 Immunofluorescence staining for 5-HT in the trigeminal subnuclei Sp5O (A), Sp5I (B) and NTS (C).

Mild to moderate cTBI altered the expression of 5-HT (red) in Sp5O (–10.84 mm to Bregma), Sp5I (–13.00 mm to Bregma) and NTS (–14.56 mm to Bregma) compared to the corresponding areas of the normal control animals. Scale bar: 50 µm. The position of Bregma was decided according to the rat brain atlas (Paxinos and Watson, 2007). 5-HT: Serotonin; Sp5O: spinal trigeminal nucleus oralis; Sp5I: spinal trigeminal pars interpolaris; NTS: nucleus tractus solitaries; cTBI: closed head traumatic brain injury.

Figure 4 Immunofluorescence labeling of the trigeminal subnuclei Sp5O (A), Sp5I (B) and NTS (C).

Mild to moderate cTBI altered the immunoreactivity of DβH (green) and the expression of NK1R (red) in Sp5O (–10.88 mm to Bregma), Sp5I (–13.04 mm to Bregma) and NTS (–14.60 mm to Bregma) compared to the corresponding areas of control animals. Scale bar: 50 µm in all figures. The position of Bregma was decided according to the rat brain atlas (Paxinos and Watson, 2007). cTBI: Closed head traumatic brain injury; DβH: dopamine beta hydroxylase; NK1R: neurokinin 1 receptor; Sp5O: spinal trigeminal nucleus oralis; Sp5I: spinal trigeminal pars interpolaris; NTS: nucleus tractus solitaries.

for norepinephrine (1:6,000), and rabbit anti-neurokinin 1 receptor (NK1R) (1:1,000). After washing with PBS, sections were then incubated with secondary antibodies (Alexa Fluor 594 goat anti-rabbit immunoglobulin G [IgG], 1:2,000 for 5-HT and NK1R; Alexa Fluor 488 goat anti-mouse IgG, 1: 2,000 for DβH), processed and mounted using procedure as described earlier (Watson, 2009; Bose et al., 2013; Mustafa et al., 2016). For microscopic observation, slides were viewed using a Zeiss Confocal microscope (LSM 710) with Zen software (version 2012; Carl Zeiss, Jena, Germany). The number of immunopositive cells (NK1R) and fibers (5-HT, DβH) in every 3rd equally spaced serial sections for 4 sections was counted in an investigator blinded semi-quantitative approach by using the petrimetric (sine-wave) probe to quantify immunoreactive cells and fibers as the procedure described earlier (Ducros and Wolff, 2016) in Sp5O, Sp5I and NTS. The procedure for acquiring images, and unbiased stereological analysis were the same as we previously reported or reported by others (West and Gundersen, 1990; Bose et al., 2005; Bernstein et al., 2011; Bernstein and O’Malley, 2013; Hou et al., 2014; Mustafa et al., 2016).

Results

Neurochemical alteration in trigeminal subnuclei

In both Sp5O and Sp5I, increased immunoreactive 5-HT expression was observed in closed head mTBI rats than in age- and sex-matched normal control rats (Figure 3A–C). The expression levels of DβH (a surrogate marker for norepinephrine) and NK1R were similar in both closed head mTBI rats and normal control rats (Figure 4A, B). However, the NK1R expression in Sp5O was greater in closed head mTBI rats than in the normal control rats (Figure 4A).

Neuromodulatory changes in the NTS

Following TBI, significant changes in the expression of 5-HT and the number of DβH immunoreactive fibers were observed in the caudal NTS. The expression of 5-HT was increased, and DβH immunoreactivity was decreased, in tissues from TBI animals than in normal tissues (Figure 3C, Figure 4C). NK1R expression was similar between closed head mTBI and normal control rats (Figure 4C).

Discussion

mTBI-caused diffuse axonal injury (Bose et al., 2012) results in widespread neurological sequelae in human and experimental animal models. PTH and cephalgic syndrome after TBI may be viewed as expression of surrogate symptomatic markers such as facial allodynia, tactile allodynia, and disturbance in circadian rhythm. PTH is very common in mTBI, so we used an mTBI animal model in our study. However, there are some controversies regarding mTBI models...
since the pioneer investigators (Marmarou and colleagues) and subsequent users of the Marmarou’s closed head injury model compared brain injuries using intensities sustained by 450 g weight drop from 1 m to 2 m; designations: 1 m: mild; 1.5 m: moderate; 2.0 m: severe. This classification was based upon, a) histological changes and b) neurologic deficits (Foda and Marmarou, 1994; Marmarou et al., 1994). However, a more comprehensive characterization of pre-clinical injury severity is needed so that the terms mild to moderate injury models will have more documented relevance to human TBI, for which duration of loss of consciousness and absence of detectable anatomical injury are standard criteria for mTBI. In this regard, it is worth noting that for the original closed head Marmarou TBI model, 1.25 m × 450 g weight drop was not an injury parameter in the original Marmarou report. The 1.25 m/450 g injury parameter was included in our studies to produce an injury that would potentially induce more detectable and enduring pain-like behavior within the setting of a mTBI model. Since this mTBI model exhibits injury patterns and detectable symptoms in pain-like behavior consistent with human mTBI, we extended our recently published work to provide better understanding in the possible pathophysiology of mTBI-induced pain and headache in this report.

We recently reported that several key neuromodulators related to pain perception were observed to be altered in the Sp5C following closed head mTBI (Mustafa et al., 2016). In the present study, we extended our investigation of the extent of neurochemical alteration in the trigeminal nucleus to include the subnuclei, Sp5O and Sp5I. It is known that caudal part of Sp5C receives afferents that transmit pain and temperature from the orofacial region. Whereas, the more rostral Sp5O and Sp5I are involved in the transmission of tactile sensitivity that would be more closely related to tactile allodynia (Sessle et al., 1986). The upregulation of 5-HT in Sp5O and Sp5I subnuclei in the current study is similar to what was observed in the nucleus caudalis in a study from Mustafa et al. (2016). Accordingly, this altered expression of 5-HT may relate to tactile alldynia in the orofacial region. Therefore, these observations suggest that comorbidity of visceral (PTH) and somatic sensitization (facial allodynia) is consistent with TBI-induced neurochemical alterations in both the caudal and more rostral trigeminal subnuclei. The changes in 5-HT expression in these two trigeminal subnuclei may be directly related to the physiological alteration in touch and pressure sensitivity (alldynia) in these closed head mTBI animals. This finding may be related to the changes in touch and pressure sensitivity in the periorbital region of the TBI patients as reported in several case reports (Hines, 1999; Walker et al. 2005; Ofek and Defrin, 2007).

Although the exact mechanism of PTH is unknown, the TBI-associated changes that lead to sensitization of trigeminal system to both vascular afferents (headache) and cutaneous afferents (facial allodynia) are promising candidates for the headache/allodynia related pain. Headache has been considered as a part of a systemic sensitization that includes facial allodynia (Ofek and Defrin, 2007; Bernstein and Burstein, 2012; Defrin, 2014). Accordingly, it is becoming progressively evident that headache (trigeminovascular) and facial alldynia (trigeminosomatic) are companion derivatives of sensitization at multiple levels of the trigeminal system (Ofek and Defrin, 2007; Bernstein and Burstein, 2012; Defrin, 2014). Results from this work exhibited significant alterations in the excitatory molecule, 5-HT, in the trigeminal subnuclei oralis and interpolaris regions, which may be related to the alterations in tactile and mechanical sensitivity from orofacial regions following TBI. Although etiologies associated with trigeminal sensitization are heavily weighting the balance, changes in vessel tone have also been suggested in association with several primary headache disorders (Couturier et al., 1997; Limroth et al., 2007; Asghar et al., 2011).

We further noticed that closed head mTBI injury caused significant alteration in the immunoreactive expression of some key neuromodulators in NTS. It is known that a group of fibers from the trigeminal nucleus project to the NTS, although the role of NTS in tactile sensation is not clear. However, NTS is well known to subserve afferent projection of general and special visceral afferent modalities including visceral pain, gag reflex, respiratory reflex, and taste sensation, projecting centrally through the cranial nerves VII, IX and X (Goldsmith, 2000; Machado et al., 2000; Cortelli and Pierangeli, 2003; Kitchen et al., 2006; Chen et al., 2008; Deyama et al., 2009). It is also known that general visceral afferent and special visceral (taste) modalities project to the caudal and rostral NTS regions, respectively. Accordingly, these current observations of TBI-induced changes in the caudal solitarius are consistent with the reports that many TBI patients develop neurogenic dysphagia which has been reported to be directly related to dysfunction of NTS (Saito et al., 2006). In patients with serotonergic symptoms, serotonergic hyperactivity at the NTS may inhibit swallowing reflex (Kessler and Jean, 1985). In addition, a direct innervation from mechanoreceptor, and chemoreceptor from carotid body are located near the bifurcation of the carotid artery. Reversible cerebral vasoconstriction syndrome is believed to be related to the use of vasoactive drug in about 50% of cases (Miller et al., 2015a, b). These drugs include selective 5-HT reuptake inhibitors, and other agents or their withdrawal such as nitroglycerin that induce headachе (Limroth et al., 1996; Couturier et al., 1997; Eriksen et al., 2004; Lipton et al., 2004; 2013). We predict that changes in serotonergic neurochemistry in the NTS may play a significant role in the development of PTH by altering the normal integrity of the cerebral blood vessel. In fact, we have recently observed a significant change in the vasculature of the middle cerebral artery following closed head TBI by an MRI-based angiogram study (data not shown). Future studies are needed to detail the changes in the solitary nucleus, which may provide important information regarding the role of solitary nucleus in the PTH, visceral pain, and gastroparesis following TBI.

Conclusion
The changes in immunoreactive markers, especially 5-HT, in
the trigeminal subnuclei Sp5O and Sp5I and solitary nuclei are similar to the initial observations made in trigeminal subcaudalis that we reported recently (Mustafa et al., 2016). Collectively, these injury-associated changes contribute to the functional understanding of the widespread facial allodynia, alteration in meningeal and cerebral blood vessels, and visceral pain/allodynia observed following TBI. Although the exact mechanism of PTH is not known, the injury-associated changes that lead to sensitization of trigeminal system are promising candidates for headache related pain. There has been no dependable preclinical model to date to measure the headache related pain. However, facial allodynia, a clinical manifestation of headache-like symptom considered to be manifested in the majority of TBI patients, is here considered as a highly relevant surrogate marker for pain associated with many forms of primary headaches including migraine; and behavioral quantitation of this allodynia is measurable by an operant based technology (Edelman et al., 2009). The involvement of trigeminal sensory system and trigeminal vascular system has already been documented by several researchers as key structures for headache related pain (Oshinsky and Gomonchareonsiri, 2007; Noseda and Burstein, 2013). In line to this, our findings show significant changes in several neuromodulators in the spinal trigeminal nuclei, and in the solitary nucleus. Accordingly, widespread changes in the trigeminal nucleus may significantly contribute to the tactile allodynia and facial pain in TBI patients. It is important to note that the level of 5-HT was altered in all three parts of the spinal nucleus of TSS. Accordingly, we predict that the changes in NTS after mTBI may be related to PTH development, and other posttraumatic complications like visceral pain. 5-HT is an excitatory neurotransmitter that is directly related to exacerbation of pain. Clinical data suggest that in addition to PTH, patients with mTBI report problems in gag reflex and in blood pressure, which are directly related to dysfunction of the NTS.

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