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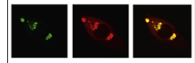
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Review

Common biochemical defects linkage between post-traumatic stress disorders, mild traumatic brain injury (TBI) and penetrating TBI

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ABSTRACT

Post-traumatic stress disorder (PTSD) is a complex mental disorder with psychological and emotional components, caused by exposure to single or repeated extreme traumatic events found in war, terrorist attacks, natural or man-caused disasters, and by violent personal assaults and accidents. Mild traumatic brain injury (TBI) occurs when the brain is violently rocked back and forth within the skull following a blow to the head or neck as in contact sports, or when in close proximity to a blast pressure wave following detonation of explosives in the battlefield. Penetrating TBI occurs when an object penetrates the skull and damages the brain, and is caused by vehicle crashes, gunshot wound to the head, and exposure to solid fragments in the proximity of explosions, and other combat-related head injuries. Despite clinical studies and improved understanding of the mechanisms of cellular damage, prevention and treatment strategies for patients with PTSD and TBI remain unsatisfactory. To develop an improved plan for treating and impeding progression of PTSD and TBI, it is important to identify underlying biochemical changes that may play key role in the initiation and progression of these disorders. This review identifies three common biochemical events, namely oxidative stress, chronic inflammation and excitotoxicity that participate in the initiation and progression of these conditions. While these features are separately discussed, in many instances, they overlap. This review also addresses the goal of developing novel treatments and drug regimens, aimed at combating this triad of events common to, and underlying, injury to the brain.

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1. Introduction

Post-traumatic stress disorder (PTSD) is a complex disorder which is caused by exposure to single or repeated traumatic events such as those found in war, terrorism, in natural or human-caused disasters, and in violent personal assaults, such as rape, mugging, domestic violence and accidents. The symptoms of PTSD include unwanted re-experiencing of the traumatic memory (flashbacks, nightmares, triggered emotional responses), passive and active avoidance of the experience (emotional numbing, avoidance of discussions about the traumatic event), and hyperarousal. In addition, PTSD often includes other psychiatric and medical comorbidities, including depression, substance abuse, cognitive dysfunction, and other health-related problems. These symptoms may lead to impairment of the ability to function in normal life, including occupational failure, marital stress, and family problems.

Traumatic brain injury (TBI) occurs when the brain is violently rocked back and forth within the skull following a blow to the head or neck such as observed in contact sports like football, or when in close proximity to a concussive blast pressure wave after detonation of explosives. TBI can occur as a mild TBI (concussion) or TBI with penetrating head injury. TBI without penetrating head injury is also called concussive injury and may be expressed as a mild, moderate or severe form. Mild TBI is characterized by temporary loss of memory, confusion, poor balance and reflexes, and hearing loss. In addition, cognitive dysfunction and abnormal behavior may occur after mild TBI.

Penetrating TBI occurs when an object penetrates the skull and damages the brain. This can be caused by vehicle crashes, gunshot wound to the head, or exposure to explosions and combat-related injuries. Progression of damage in penetrating TBI occurs into three phases. The first phase involves injury to the brain tissue that cannot be reversed, because the damaged tissue is irreversibly lost. The second phase of injury continues for days to weeks after the initial event and eventually leads to neurological disorders and neuronal death. During this period, administration with appropriate agents may slow down the progression of the damage. The third phase of penetrating TBI

appears as delayed behavioral abnormalities, which depend upon the initial areas of the brain damaged. These may include cognitive dysfunction, PTSD, and other behavior defects

Despite the availability of standardized treatment guidelines, and improvements in understanding the mechanisms of cellular damage, prevention and treatment strategies for patients with PTSD and TBI remain unsatisfactory. In order to develop a logical plan for reducing the development and progression of PTSD and TBI, it is important to identify underlying biochemical changes that may play key role in the initiation and progression of these disorders. One issue that remains to be addressed, concerns whether there are common biochemical deficits that relate to PTSD and TBI. The identification of these may provide targets for the development of new mitigating agents that can reduce the risk of development and progression of these disorders.

This review discusses studies that support the hypothesis that increased oxidative stress, chronic inflammation and glutamate release represent events common to post-traumatic disorders (PTSD), and traumatic brain injury (TBI) and that these events play important role in the initiation and progression of these disorders.

2. Common biochemical defects in PTSD, mild TBI and penetrating TBI

Several reports using tissue culture and animal models together with limited human studies revealed that increased oxidative stress, chronic inflammation and extracellular glutamate play an important role in the initiation and progression of PTSD and TBI. Direct evidence for these biochemical deficits comes from investigations in which markers of oxidative stress and chronic inflammation in various tissues including brain were measured. However, the types of markers were not the same in PTSD and TBI. Nevertheless, each of these markers of oxidative stress and chronic inflammation indicates the presence of these biochemical defects. Indirect evidence for these biochemical changes comes from studies in which agents that reduce oxidative stress and

chronic inflammation, can improve some symptoms, and reduce neurodegeneration. Direct evidence for glutamate release in the initiation and progression of PTSD and TBI comes from studies in which the levels of glutamate in CSF and brain were measured; however, the tissues in which glutamate levels measured were not the same in PTSD and TBI. Indirect evidence comes from investigations in which the antagonists of NMDA receptors reduced the symptoms and neurodegeneration associated with PTSD and TBI, whereas the agonist of NMDA receptors aggravated them. In addition, the types of NMDA receptor antagonist and agonist were not the same in PTSD and TBI. Nevertheless, the overall data suggest that glutamate plays a significant role in the initiation and progression of PTSD and TBI. The references for the above studies have been provided under the individual section. Some relevant findings suggesting that free radicals, undesirable inflammatory changes and the presence of excitatory neurotransmitter free glutamate ions are biochemical defects common to PTSD and TBI are briefly described here. Fig. 1 presents a diagrammatic representation of the biochemical defects in PTSD, mild TBI and penetrating TBI.

2.1. Increased oxidative stress

2.1.1. Oxidative stress in PTSD

There are several reports that increased oxidative stress may be a factor in the evolution of some enduring neurological and psychiatric disorders and PTSD (Bremner, 2006). Stress, a risk factor for developing PTSD, evokes a sustained increase in nitric oxide synthase (NOS) activity that can generate excessive amounts of nitric oxide (Harvey et al., 2004). Oxidation of nitric oxide produces peroxynitrite that is very toxic to nerve cells (Ebadi et al., 2001). Elevated levels of peroxynitrite and its precursor nitric oxide have been observed in patients with PTSD (Tezcan et al., 2003). Platelet monoamine oxidase activity, which generates excessive amounts of free radicals while degrading catecholamines, was also elevated in patients with PTSD (Richardson, 1993). This may bear a relation to the depletion of catecholamines that has been observed in patients with PTSD (Pivac et al., 2007). These reports support the possibility that increased levels of oxidative stress may

contribute to the development of PTSD and associated cognitive dysfunction.

Major stressors can induce PTSD-like symptoms in animal models of PTSD. The impact of severe life stress in animals including sleep deprivation and social isolation has been described. Such stressed rats showed apoptosis in the hippocampus region of the brain and impaired spatial memory (Schivavone et al., 2013). These biological effects of stress, a risk factor for PTSD, were mediated by Bcl2 (B-cell lymphoid-2) and Bax genes (Li et al., 2010). Immature rats exposed to two stressors, namely foot shock and maternal separation exhibited impaired spatial memory and increased number of DNA breaks in the hippocampus (Diehl et al., 2012). In a rat model of PTSD, levels of markers of oxidative stress and chronic inflammation increased in hippocampus, amygdala, and pre-frontal cortex, both of which are involved in the development and progression of PTSD (Wilson et al., 2013). In addition, these markers were also elevated in the whole blood and adrenal glands. In another rat model of PTSD, treatment with valproic acid, a histone deacetylase inhibitor, normalized the levels of indices of oxidative stress and of pro-inflammatory cytokines in hippocampus and pre-frontal cortex of stressed animals. In addition, valproic acid treatment reduced anxiety in experimental animals, and restored neurotransmitters levels to normal values (Wilson et al., 2014). Valproic acid has several functions, including raising GABA levels, blocking Na⁺ channels, and maintaining IP3 levels. Increased levels of GABA may attenuate the excitotoxicity of glutamate.

2.1.2. Oxidative stress in mild TBI

Elevated levels of protein carbonyls (a marker of oxidative damage), and reduced levels of superoxide dismutase (SOD) and silent information regulator-2 (Sir2) in the rat hippocampus following mild TBI were observed (Aiguo et al., 2010). Poor behavioral performance of the animals was associated with reduced levels of brain-derived neurotrophic factor (BDNF), which facilitates synaptic function and learning ability. Oral administration of a diet supplemented with vitamin E for 4 weeks before the TBI insult prevented both impairment in the learning ability and the biochemical changes described above (Aiguo et al., 2010).

Treatment with methylene blue, a FDA approved drug with a variety of clinical applications, which exhibits energy-enhancing and antioxidant properties, reduced lesion volume, behavioral abnormalities and neuronal degeneration following mild TBI in rats (Talley et al., 2014). Extended stress followed by mild TBI produced synergistic adverse effects on brain mitochondrial electron transport chain function leading to more severe behavioral deficits (Xing et al., 2013). Using a magnetic resonance imaging (MRI) technique, focal microhemorrhage and an accumulation of free iron in the gray matter were observed (Nisenbaum et al., 2014). Free iron is known to generate free radicals; and the prolonged presence of excess levels of free iron may contribute to the progression of neurodegeneration following TBI.

In a rat model of blast-induced mild TBI, fiber-tract degeneration, axonal injury, increased oxidative stress, and neuroinflammation with a sustained chemokine response occurred, together with marked increases in activated astrocyte number

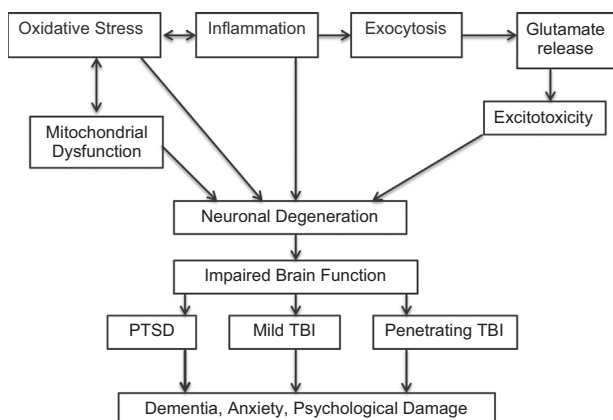


Fig. 1 – A diagrammatic representation of the common biochemical defects in post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI).

(Kochanek et al., 2013). Blast-induced TBI also caused oxidative damage to blood–brain barrier (BBB) associated with induction of NADPH oxidase and inducible nitric oxide synthase (iNOS) both of which increase the production of free radicals (Kochanek et al., 2013). Cerebral vascular injury occurred prior to the development of neurological deficits in mild TBI and was accompanied by the activation of caspase-3 and apoptosis in the perivascular region around the lesion (Abdul-Muneer et al., 2013).

In transgenic mouse model of Alzheimer's disease amyloidosis using Tg2576 mice, repetitive concussive brain injury induced by a modified cortical impact model of closed head injury increased the levels of brain lipid peroxidation, accelerated beta amyloid deposition, and caused learning deficits. Oral administration of a diet supplemented with vitamin E for 4 weeks before the TBI prevented increased lipid peroxidation, reduced learning ability and decreased BDNF levels in these transgenic mice (Conte et al., 2004). Conversely, oral administration of a high-fat diet decreased hippocampal plasticity and cognitive function and reduced BDNF levels in rats subjected to TBI (Wu et al., 2003). Oral administration of a diet supplemented with curcumin, which has antioxidant and anti-inflammatory properties, restored BDNF and improved cognitive function in rats with a mild TBI (Wu et al., 2006). Similar results were obtained by feeding a diet supplemented with omega-3-fatty acid docosahexanoic acid (DHA) prior to inducing TBI in rats (Wu et al., 2011). Repetitive concussive injuries increased the levels of markers of lipid peroxidation, levels of oxidized glutathione and reduced ascorbic acid levels in rats (Tavazzi et al., 2007).

No clinical studies are available on the markers of oxidative damage or the levels of antioxidants before or after concussive injury, in active or retired football players or in veterans. In post mortem tissue, levels of inducible nitric oxide synthase (iNOS) in human neurons, macrophages, neutrophils, astrocytes and oligodendrocytes were increased within 6 h after trauma to the brain, and peaked at about 8–23 h (Gahm et al., 2002). Increased levels of iNOS can lead to excessive amounts of NO that can form oxidant peroxynitrite.

2.1.3. Oxidative stress in penetrating TBI

Increased levels of oxidative events occur after TBI (Bayir et al., 2006; Rael et al., 2009; Shao et al., 2006; Mikawa et al., 1996). In rats subjected to TBI, the extent of oxidative damage was directly proportionate to the severity of the insult (Petronilho et al., 2009; Tavazzi et al., 2005). The total antioxidant reserves of brain homogenates such as tissue concentrations of ascorbate, glutathione, and sulfhydryl proteins were reduced after TBI in rats (Singh et al., 2007). TBI increased nitric oxide (NO) production and this impairs mitochondrial function by inhibiting cytochrome oxidase, a key enzyme of the electron transport chain essential for energy generation (Huttemann et al., 2008). Loss of this enzyme can retard anabolic regenerative processes. Excess levels of NO produced by TBI also lead to increased peroxynitrite content (Louin et al., 2006). In a rat model of TBI (unilateral moderate cortical contusion), increased oxidative damage occurred as early as 3 h after the injury resulting in defective synaptic function and plasticity of hippocampal neurons, and disruption of cognitive function (Ansari et al., 2008). In a fluid concussion brain injury model of

TBI in the rat, protein carbonylation and thiobarbituric acid-reactive substances (TBARS) levels increased in parietal cortex one and three months after injury and this evidence of oxidative damage was associated with a progressive decrease of Na⁺, K⁺-ATPase activity (Lima et al., 2008). Thus, increased oxidative stress together with reduced Na⁺, K⁺-ATPase may contribute to the development of cognitive dysfunction after TBI.

A few human studies also confirm the role of oxidative stress in the progression of TBI. The levels of F₂-isoprostane, a marker of lipid peroxidation, and neuron-specific enolase (NSE), a marker of neuronal damage, increased in the cerebral spinal fluid (CSF) samples of children and infants following TBI (Varma et al., 2003). Levels of ascorbate and glutathione were both decreased in the CSF of infants following TBI (Bayir et al., 2002). The levels of 3-nitrotyrosine, a marker of nitrosylative stress, increased in the CSF of adult patients with TBI (Darwish et al., 2007). After severe TBI, the levels of beta-amyloid fragments (A β 1-42) were enhanced in the CSF (Emmerling et al., 2000). Amyloid peptides have been implicated in causing neuronal damage in Alzheimer's disease. One of the mechanisms of injury induced by amyloid beta fragments generated from splicing of amyloid precursor protein (APP), involves increased oxidative stress (Pappolla et al., 1998; Butterfield, 2002; Schubert et al., 1992; Varadarajan et al., 1999).

There are parallels in some of the long-term consequences of PTSD and TBI. Both of these conditions in humans have been associated with delayed events including an increased risk of developing dementia (Burri et al., 2013; Ikonovic et al., 2004; Vincent et al., 2014), and this is supported by data derived from animal studies (Uryu et al., 2002; Tran et al., 2011). The animal studies also suggest that anti-inflammatory and antioxidant compounds such as simvastatin, or the flavonoid, luteolin can blunt the effects of TBI (Abrahamson et al., 2009; Sawmiller et al., 2014).

Increased oxidative stress contributes to the mitochondrial dysfunction that plays an important role in causing cognitive impairment and eventually neuronal death following TBI, in part by increasing production of free radicals (Robertson et al., 2009; Mazzeo et al., 2009). Experimental TBI causes a significant loss of cortical tissue at the site of injury (primary damage) that is followed by a secondary damage involving mitochondria that enhances the primary injury leading to neurological dysfunction. Generally, oxidative stress-induced mitochondrial dysfunction in rat model of TBI is observed 1–3 h after TBI, suggesting the importance of an early intervention (Gilmer et al., 2009). In a mouse model of TBI, cortical mitochondrial damage included swelling, disruption of cristae and rupture of outer membranes, a decrease in calcium-buffering capacity, and an increase in oxidation of protein and lipids were observed, and levels of cortical 3-nitrotyrosine were elevated as early as 30 min after injury (Singh et al., 2006).

In a clinical study on 14 patients (6 patients with diffuse brain injury and 8 with focal brain lesions), reduction in the brain levels of n-acetylaspartate in the absence of ischemic insult reflected mitochondrial dysfunction (Aygok et al., 2008). TBI-induced glutamate release during acute phase of injury can cause an overload of Ca⁺ leading to mitochondrial dysfunction; therefore, it was thought that treatment with

mitochondrial uncouplers after TBI may be useful in preventing Ca⁺ overload. Treatment of animals with mitochondrial uncouplers, 2, 4-dinitrophenol (2, 4-DNP) and p-trifluoromethoxyphenylhydrazine (FCCP), significantly reduced loss of cortical damage and reduced the intensity of behavioral deficits following TBI in rats (Pandya et al., 2007). This paradoxical effect may result from preventing Ca⁺ overload in the mitochondria before they become dysfunctional.

2.2. Increased inflammation

2.2.1. Increased chronic inflammation in PTSD

In addition to heightened oxidative stress, increased chronic inflammation due to activation of microglia may be associated with PTSD. The serum levels of interleukin-6 (IL-6) were elevated in patients with PTSD (Yehuda, 2001) and increased levels of IL-6, and IL-6 receptors were present in patients with PTSD (Maes et al., 1999). Levels of tumor necrosis factor-alpha (TNF- α) and IL-1 β were similarly elevated in patients with PTSD (von Kanel et al., 2007). Psychological stress, a risk for developing PTSD, also induced a chronic inflammation (Sutherland et al., 2003). Chronic terror in women, but not in men, is associated with elevated levels of C-reactive protein (CRP) that may contribute to increased risk of cardiovascular disease in PTSD patients (Melamed et al., 2004).

In a clinical study on severely traumatized PTSD patients, spontaneous production of pro-inflammatory cytokines IL-1 β , IL-6 and TNF- α by peripheral blood mononuclear cells (PBMCs) was significantly elevated compared to control subjects. Furthermore, the extent of increase in the levels of these pro-inflammatory cytokines correlated with the severity of PTSD symptoms (Gola et al., 2013). These studies suggest the presence of low-grade inflammation in patients with PTSD.

In a clinical study on 48 patients with an established pain disorder or PTSD, pro-inflammatory cytokines were at detectable levels in the serum of 87% of patients (men and women), but in only 25% of healthy controls (Hoge et al., 2009). In another study on 50 patients with PTSD, the levels of pro-inflammatory cytokines (IL-2, IL-4, IL-6, IL-8, and TNF- α) were elevated in the serum relative to age- and gender-matched controls (Guo et al., 2012).

In a study on 51 combat-exposed males with PTSD and 51 combat-exposed males without PTSD, the overall score of levels of pro-inflammatory cytokines (combining the results of IL-6, IL-1 β , TNF- α , interferon- γ and C-reactive protein) were correlated with the levels of Clinical Administered PTSD Scale (Lindqvist et al., 2014). In order to determine whether the plasma levels of CRP can be considered as a biomarker for PTSD risk, 2600 war zone-deployed Marines were evaluated for PTSD symptoms and various physiological and psychological parameters after 3 and 6 months following a 7-month deployment. Increased plasma levels of CRP were associated with PTSD symptoms (Eraly et al., 2014). In a study on 139 urban women who are likely to experience interpersonal violence, the relationships between such violence, psychological distress, and the plasma levels of CRP were determined. Women with symptoms of stress have significantly higher plasma levels of CRP and this relationship

existed after adjusting for depression (Heath et al., 2013). The reduced levels of cortisol found in those suffering from PTSD (Horn et al., 2014) may underlie the appearance of inflammatory processes. High dose hydrocortisone is effective in reducing both the behavioral and morphological consequences of PTSD (Zohar et al., 2011). Thus, increased levels of chronic inflammation may also contribute to the development of cognitive dysfunction and behavior abnormalities associated with PTSD.

2.2.2. Increased chronic inflammation in mild TBI

Rats exposed to repetitive concussions (1, 3 or 5 times, spaced 5 days apart), displayed increased anxiety and depression-like behaviors, short- and long-term cognitive dysfunction, inflammation in the brain and cortical damage (Shultz et al., 2012). Treatment with anti-CD11d integrin antibody after this TBI reduced the levels of neutrophil and macrophages in the damaged area of the brains of rats. In addition, this treatment reduced lipid peroxidation, astrocyte activation, accumulation of amyloid precursor protein (APP), and loss of neurons. Cognitive function and sensorimotor ability were improved, while indices of anxiety were reduced (Shultz et al., 2013). Exposure to brief hypoxia after TBI in a mouse model, enhanced systemic and brain inflammation, while administration of neutralizing antibody to cytokine IL-6, inhibited inflammation and neuronal injury in the brain, and prevented motor deficits (Yang et al., 2013). Treatment of mice with resveratrol, which exhibit antioxidant and anti-inflammation properties, after mild TBI reduced activation of microglia in the cerebral cortex, corpus callosum, and dentate gyrus regions of the brain (Gatson et al., 2013). Increased levels of chronic inflammation may thus contribute to the development of behavioral and cognitive dysfunctions associated with TBI.

Changes in inflammatory cellular response following cortical contusion were investigated by immunohistochemistry during first 30 weeks after blunt head injury in humans (Hausmann et al., 1999). CD-15 (3-fucosyl-N-acetyl-galactosamine)-labeled granulocytes were detected as early as 10 min after brain injury. Increased numbers of mononuclear leukocytes labeled with LCA (leukocyte common antigen), CD-3 and UCHL-1, a clone of CD45RO that is an isoform of LCA, were detected at 1.1 days, 2 days and 3.7 days after injury in cortical contusions. The above changes reflect TBI-induced inflammatory cellular responses.

In another study, time-dependent alterations in inflammatory cellular responses in patients undergoing surgery for brain contusions 3 h to 5 days after trauma were determined by immunohistochemistry (Holmin et al., 1998). When the inflammatory responses were determined during surgery performed less than 24 after injury, they were limited to the vascular margins of polymorphonuclear cells. However, samples from patients undergoing surgery 3–5 days after injury revealed an extensive inflammatory cellular response consisting of monocyte/macrophages, reactive microglia, polymorphonuclear cells, and CD-4 and CD-8-labeled T lymphocytes. At these later stages, human lymphocyte antigen-DQ was expressed on reactive microglia and infiltrating leukocytes. These delayed inflammatory reactions following contusions may produce several potentially harmful effects, including acute- and long-

term degeneration of nerve cells. In patients undergoing surgery in less than 24 h after injury, marked expression of the pro-inflammatory cytokines interleukin-1 beta (IL-1 beta), IL-6, and interferon-gamma (INF-gamma) and the anti-inflammatory cytokine IL-4 was already present. However, in patients undergoing surgery 3–5 days after injury, expression of IL-4 was lower compared to those who were operated earlier while expression of IL-1beta and IFN-gamma remained high compared to IL-6. The persistence of pro-inflammatory cytokines may underlie subsequent long-term neurodegeneration after TBI (Holmin and Hojeberg, 2004).

In a study on the brain tissue obtained at autopsy from 24 patients dying after TBI, changes in CD-14, a pattern recognition receptor of the immune system, were investigated. In brains derived from control subjects, CD-14 expressed constitutively in perivascular cells, but not in parenchymal cells. However, after TBI, expression of CD-14 in perivascular cells and parenchymal cells reached maximal levels within 4–8 days and remained elevated until weeks after injury (Beschoner et al., 2002). Thus, extended increased expression of CD-14 is one of the major responses of acute inflammatory reaction in the brain following TBI.

2.2.3. Increased inflammation in penetrating TBI

Following TBI, cells with immune capacity in the brain such as microglia and astroglia can become activated. These cell responses can be associated with repair but can also become a source of deleterious changes since this activation can result in excessive amounts of pro-inflammatory cytokines, prostaglandins, reactive oxygen species, complement proteins and adhesion molecules that are highly toxic to neurons. Evidence of inflammation in the post-TBI brain is also found by the infiltration and accumulation of polymorphonuclear leukocytes (Goodman et al., 2008; Hutchinson et al., 2007; Hein and O'banion, 2009). Pro-inflammatory cytokines increase the synthesis of iNOS which can produce excessive amounts of NO that may in turn become oxidized to form peroxynitrite that contribute to the pathogenesis of TBI (Dietrich et al., 2004; Potts et al., 2006; Hall et al., 2004). An inhibitor of iNOS provides neuroprotection against damage produced by peroxynitrite (Gahm et al., 2006). The levels of pro-inflammatory cytokine interleukin-6 (IL-6) were elevated in patients with acute TBI, and a significant relationship existed between the severity of TBI and the transcranial IL-6 gradient (Minambres et al., 2003). In addition, activation of nuclear factor-kappa B (NF-kappaB) occurred after TBI in both animals and humans (Xiao and Wei, 2005; Hang et al., 2006). Treatment with beta-aescin (a natural triterpenoid isolated from the seed of Chinese horse chestnut) inhibited activation of NF-kappaB and expression of TNF-alpha (Xiao and Wei, 2005). In a study on 75 patients with moderate to severe TBI, the role of cytokines on patient outcomes using the criterion of 30-day mortality was evaluated. Levels of cytokines (IL-6 and IL-8) increased in all patients compared to controls and the levels of these two cytokines were higher in non-survivors than in survivors (Venetsanou et al., 2007).

The levels of inflammatory markers such as iNOS and cyclooxygenase 2 (COX-2), and indices of oxidative stress (reduced levels of glutathione and elevated oxidized/ reduced glutathione ratio, 3-nitrotyrosine, and 4-hydroxynonenal)

increased after TBI in an animal model, but were reduced after treatment with fenofibrate, a cholesterol-lowering drug (Chen et al., 2007). A delayed elevation of soluble TNF receptors p75 and p55 was observed in CSF and plasma after TBI of rats (Maier et al., 2006). Motor performance and spatial memory acquisition were better in TNF-alpha and Fas deficient transgenic mice (TNF-alpha/Fas^{-/-}) compared to wild type mice after subjecting them with a controlled cortical impact (a model of TBI), suggesting that TNF-alpha and Fas play an important role in TBI-induced neurological dysfunction. Indeed, inhibition of TNF-alpha and Fas expression in immature normal mice subjected to controlled cortical impact, protected against histological changes and defective spatial memory acquisition in adulthood (Berpohl et al., 2007). In a rat model of TBI, animal received minor or severe head injury by impact-acceleration. Levels of NO decreased in the cortex, cerebellum, hippocampus and brain stem in both groups after 5 min. The decrease in NO levels depended upon the extent of injury, NO content being lowest in the brain regions where the direct trauma was most severe (Tuzgen et al., 2003). This was linked to the global decrease in cerebral blood flow that occurs in the initial stages of TBI. Thus, NO can both exert a beneficial action by improving circulation yet excessive levels can promote peroxynitrite-induced oxidative damage. Using transgenic mice deficient in nuclear factor erythroid-2-related factor 2 (Nrf2 (-/-)) compared to the wild type Nrf2 (+/+), TBI led to activation of NF-kappaB, increased levels of pro-inflammatory cytokines, TNF-alpha, IL-1beta and IL-6, and expression of intracellular adhesion molecule 1 (ICAM-1) and these were higher in the brains of mutant mice relative to wild type (Jin et al., 2008, 2009). This implies that the presence of Nrf2 prevents the elevation of pro-inflammatory cytokines after TBI.

The role of pro-inflammatory cytokines in the progression of damage after TBI is further supported by the fact that inhibitors of these cytokines prevent neuronal loss and cognitive dysfunction. For example, IL-1 beta neutralizing antibody (IgG2a/k) (Clausen et al., 2009), dexanabinol (HU-211, an inhibitor of TNF-alpha at a post-transcriptional stage, (Shohami et al., 1997), antioxidants (Trembovier et al., 1999), Minoxac and a synthetic analog of tripeptide glypromate (NNZ-2566, inhibitors of glial activation and pro-inflammatory cytokines, (Lloyd et al., 2008; Wei et al., 2009), and simvastatin, an inhibitor of activation of astrocytes and a cholesterol lowering drug (Wu et al., 2009), all provided protection by reduction of neuronal loss and neurological deficits.

2.3. Increased excitotoxic events

2.3.1. Increased glutamate release and gamma-aminobutyric acid (GABA) inhibition in PTSD

The glutamatergic system plays an important role in the pathophysiology of PTSD. The effect of glutamate is mediated by increasing the release of corticotropin-releasing factor (CRF) and subsequently activating the stress-response hormone cascade, which increases extracellular levels of glutamate and NMDA receptor expression (Nair and Singh Ajit, 2008). Increased levels of CRF have been found in the CSF of patients with PTSD (Bremner et al., 1997). Stress-induced glutamate release and glucocorticoids have been suggested to

cause hippocampal atrophy in patients with PTSD (Nair and Singh Ajit, 2008). This is logical because glutamate at high doses is known to be neurotoxic. Glutamate and nitric oxide (NO) released during stress play a central role in maintaining anxiety disorders (Joca et al., 2007; Harvey et al., 2004). Stress activates glutamate-NMDA receptors and decreases BDNF, and excessive amounts of glutamate can cause death of cholinergic neurons. This may account for the cognitive dysfunction associated with PTSD (Harvey et al., 2004; Nair and Singh Ajit, 2008). The antagonists of NMDA receptors and alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate receptors (AMPA receptors) are useful in reducing anxiety-related disorders (Riaza Bermudo-Soriano et al., 2012; Walker and Davis, 2002). Therefore, blocking the release of glutamate or its action would be useful in tempering the risk and progression of PTSD symptoms. Indeed, anti-glutamatergic agents such as lamotrigine improve some of the symptoms of PTSD (hyperarousal and avoidance) (Nair and Singh Ajit, 2008).

The levels of GABA in the insular cortex were lower in PTSD patients than in control subjects and were associated with higher state of anxiety (Rosso et al., 2013). Plasma levels of GABA were also lower in PTSD patients than in control subjects (Vaiva et al., 2006). In study of patients with PTSD and trauma exposed controls without PTSD, the parieto-occipital and temporal cortices of PTSD patients had lower levels of GABA (assayed by in vivo proton magnetic resonance spectroscopy) than those in patients without PTSD (Meyerhoff et al., 2014). The patients with PTSD had higher depressive and anxiety scores as well as a higher Insomnia Severity Index (ISI) score. The higher ISI score correlated with lower levels of GABA and higher levels of glutamate. In a study on an animal model of PTSD, apoptosis of hippocampal neurons after severe traumatic stress has been related to imbalance between GABA and glutamate (Gao et al., 2014).

2.3.2. Glutamate release in mild TBI

Mild brain concussive injury can cause cognitive and emotional dysfunction and increase the risk for the development of anxiety disorders, including PTSD (Carlson et al., 2011; Wilk et al., 2012). The N-methyl-D-aspartate (NMDA) glutamate receptors in the amygdala appear to regulate fear and anxiety. In a rat model of mild TBI, the levels of NMDA receptors in the amygdala increased while the levels of gamma-aminobutyric acid (GABA) decreased (Reger et al., 2012). Excitatory events created by an elevation of NMDA receptors levels and a decrease in GABA activity may increase the risk for developing fear and anxiety. Following mild TBI, excessive amounts of glutamate are released that can cause a massive efflux of K⁺ ions via stimulation of excitatory amino acid-coupled ion channels and increased accumulation of lactate. This was confirmed by the fact that administration of ouabain, an inhibitor of Na⁺/K⁺-ATPase, before injury, reduced lactate accumulation (Kawamata et al., 1995). Relatively mild TBI enhanced levels of extracellular glutamate in the dentate gyrus and dorsal striatum, whereas moderate TBI enhanced the amplitudes of KCl-evoked glutamate release in the dorsal striatum (Hinzman et al., 2010). Cellular damage and neurological deficits are mediated through glutamate by activating NMDA receptors. Interestingly, preconditioning with low doses

of NMDA prior to inducing mild TBI prevented all motor and behavior deficits (Costa et al., 2010).

2.3.3. Glutamate release in penetrating TBI

The excitatory amino acids play a significant role in the progression of injury following major TBI. Levels of extracellular glutamate and aspartate increase in the brain following TBI in animals due to increased synaptic release of glutamate which occurs at the site of injury (Gopinath et al., 2000). Excessive amounts of glutamate in the extracellular space may lead to elevated levels of intracellular calcium and hyperactivity, and to excessive influx of sodium ions that can cause edema and eventually cell death (Yi and Hazell, 2006). In a study on 80 patients with severe head injury, levels of free excitatory amino acids increased and it was proposed this may enhance neuronal damage (Bullock et al., 1998). In patients with focal or diffuse brain injury, the levels of glutamate were elevated in both CSF and extracellular space following TBI (Yamamoto et al., 1999). In another clinical study, it was found that patients, who subsequently died of their head injury, had higher levels of dialyzable glutamate and aspartame compared to those who recovered. The highest levels were present in patients with gunshot wounds, followed by those who had massive lesions while patients with more diffuse brain injury had lower levels of free glutamate and aspartame (Gopinath et al., 2000). Excessive amounts of glutamate and aspartame were released in severely head injured patients, the patients with the most severe contusions having the highest levels of glutamate and aspartate (Koura et al., 1998). In a clinical study on 28 severely brain injured patients, the levels of glutamate and taurine in ventricular CSF were elevated in those patients with subdural or epidural hematomas, contusions, and generalized brain edema. The simultaneous release of taurine, which has inhibitory and anti-excitotoxic functions, with glutamate suggests that the injured brain is attempting to counteract the action of glutamate (Stover et al., 1999). Parallel results have been obtained in a rat model of TBI (Stover and Unterberg, 2000). In a clinical study on 27 children with severe TBI, the levels of adenosine and glutamate in the ventricular CSF were elevated relative to a control group. The release of adenosine following TBI may reflect an attempt by adenosine to maintain homeostasis by providing neuroprotection against glutamate-induced toxicity (Robertson et al., 2001).

Levels of two high-affinity sodium-dependent glial glutamate transporters, glutamate transporter 1 (GLT-1) and glutamate-aspartate transporter (GLAST), decreased following TBI in the rat (Rao et al., 1998; Yi and Hazell, 2006). This suggested that reduced glial glutamate transporter activity may contribute to the increased levels of extracellular glutamate. Treatment with hypothermia reduces the neuronal damage in cortical and sub-cortical regions following TBI. Hypothermia reduced the level of brain hydroxyl radicals and extent of glutamate release following TBI in a rat model (Globus et al., 1995). The involvement of glutamate in the progression of damage in the rat following TBI is further suggested by the fact that administration of NMDA antagonists, significantly reduced glutamate release, and improved motor function and cognitive function after TBI (Panter and Faden, 1992; Obrenovitch and Urenjak, 1997). Activation of presynaptic group II metabotropic glutamate (mGlu II) receptor,

reduced synaptic glutamate release, while (–)-2-oxa-4-aminobicyclo (3.1.0) hexane-4, 6-dicarboxylate (LY379268), a selective agonist of mGlu II receptors, reduced cell death following TBI in mice (Movsesyan and Faden, 2006). In another animal model of TBI (lateral fluid percussion-induced brain injury), administration of a mGlu II receptor agonist also protected against behavioral deficits following injury (Allen et al., 1999). These studies suggest that mGluII receptors play a significant role in protecting against TBI.

3. Relationship between mild TBI and PTSD

The relationship between mild TBI and PTSD has been reviewed in two recent epidemiologic studies of US soldiers returning from Iraq and Afghanistan (Hoge et al., 2008; Schneiderman et al., 2008). In one study on 2525 soldiers, 4.9% reported injury with loss of consciousness, 10.3% reported injuries with altered mental status, and 17.2% reported other injuries during deployment. Among those who reported loss of consciousness, the incidence of PTSD was 43.9%, among those reporting altered mental status, it was 27.3%, and those reported other injuries, it was 16.2%. In contrast, those soldiers reporting no injury in combat, the incidence of PTSD was only 9.1% (Schneiderman et al., 2008). Because of likely common biochemical defects, as discussed in previous sections, it is not surprising that a direct relationship between mild TBI and PTSD exists.

4. An integrative approach to mitigation of PTSD, mild TBI and penetrating TBI

Since increased oxidative stress, chronic inflammation and glutamate release represent common biochemical vulnerability in three neurological disorders, PTSD, mild TBI and penetrating TBI, attenuation of the activities of these biochemical defects alone or in combination with standard therapy, may be a logical scientific choice for prevention and improved management of these neurological abnormalities. The question arises how to reduce these biochemical defects simultaneously. Increasing the levels of antioxidant enzymes through activation of a nuclear transcription factor Nrf2 by ROS-dependent and -independent mechanisms, as well as enhancing the levels of dietary and endogenous antioxidant chemicals simultaneously may optimally decrease oxidative stress, and indirectly reduce chronic inflammation, and glutamate release and its toxicity (Prasad and Bondy, 2014). Such a strategy may prevent the often-worsening sequel of these disorders in combination with standard therapy, and may improve their management more effectively than that produced by standard therapy alone.

5. Conclusions

Increased oxidative stress, inflammation and glutamate release are common biochemical defects in PTSD, mild TBI and penetrating TBI. Therefore, attenuation of these defects simultaneously may improve the current management of these neurological disorders.

Conflict of interest

Stephen C. Bondy has no conflict of interest.

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Kedar N. Prasad is an employee and owns stocks of the Premier Micronutrient Corporation.

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