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Growing literature but limited evidence: A systematic review regarding prebiotic and probiotic interventions for those with traumatic brain injury and/or posttraumatic stress disorder

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ABSTRACT

Traumatic brain injury (TBI) is highly prevalent among a wide range of populations, including civilians, military personnel, and Veterans. TBI sequelae may be further exacerbated by symptoms associated with frequently occurring comorbid psychiatric conditions, including posttraumatic stress disorder (PTSD). This is particularly true among the population of military personnel from recent conflicts in Iraq and Afghanistan, with a history of mild TBI (mTBI) and PTSD. The need for efficacious treatments for TBI and comorbid PTSD is significant, and evidence-based interventions for these frequently co-occurring conditions are limited. Based on findings suggesting that inflammation may be an underlying mechanism of both conditions, anti-inflammatory/immunoregulatory agents, including probiotics, may represent a novel strategy to treat TBI and/or PTSD-related symptoms. The focus of this systematic review was to identify and evaluate existing research regarding prebiotic and probiotic interventions for the populations of individuals with a history of TBI and/or PTSD. Only 4 studies were identified (3 severe TBI, 1 PTSD, 0 co-occurring TBI and PTSD). Although findings suggested some promise, work in this area is nascent and results to date do not support some claims within the extensive coverage of probiotics in the popular press.

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1. Introduction

Over 2 million troops have been deployed in the Global War on Terror (Tan, 2009). Service Members are returning with physical injuries and co-occurring mental health conditions. Traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) have been described as the "signature wounds" of the recent conflicts. It has been estimated that approximately 11%–23% of those who served in Iraq or Afghanistan have a history of mild traumatic brain injury (mTBI), with around 8% reporting persistent post-concussive symptoms (PCS) (e.g., headaches, cognitive challenges, and emotional distress) (Bahraini et al., 2014; Terrio et al., 2014). Moreover, according to the Defense and Veterans Brain Injury Center (Defense and Veterans Brain Injury Center, 2016) over 35,000 individuals have sustained moderate and/or severe brain injuries since the year 2000.

Among those with a history of TBI, co-occurring psychiatric disorders are frequent. Data from both civilian and military populations suggest that a history of mTBI is associated with an increased likelihood of developing PTSD (Bahraini et al., 2014). Work by Brenner et al. (2010) also suggests that among Soldiers with physical injury, mTBI and PTSD are independently associated with persistent PCS reporting; however, those with both conditions are at greater risk for endorsing symptoms than those with either condition alone. For Veterans who served in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) (Richardson et al., 2010), PTSD prevalence estimates range from 4–17.1%. For

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individuals with a history of TBI with a loss of consciousness, the rate of PTSD has been reported to be as high at 43.9% (Hoge et al., 2008). Authors also highlighted that PTSD may be an "important mediator of the relationship between TBI and poor physical health outcomes" (p. 453) (Hoge et al., 2008).

At present, there is a dearth of evidence-based treatments to address persistent PCS, as well as co-occurring persistent PCS and PTSD symptoms (Bramley et al., 2016). As noted in a recent publication regarding TBI and PTSD (military/veteran/civilian) by Bahraini and colleagues, research on pharmacological and psychological interventions for those living with symptoms associated with these comorbidities is limited (Bahraini et al., 2014). In addition, though there is a compelling body of evidence in support of psychotherapeutic treatment for PTSD (e.g., Cognitive Processing Therapy, Exposure Therapy) a notable number of individuals are not significantly helped by traditional treatments. In exploring non-response and dropout rates in outcome studies for PTSD, Schottenbauer et al. found it was not unusual to find non-response rates as high as 50% (Schottenbauer et al., 2008).

Both patients and researchers have started to explore other strategies, including complementary and alternative medicine (CAM) interventions. The use of CAM, also called complementary and integrative health (CIH), in the United States has seen a steep rise over the past two decades (Barnes et al., 2004, 2008; Eisenberg et al., 1998). A national survey of over 31,000 adults in the United States found that 36% of respondents had used complementary therapies in the last month (Eisenberg et al., 1998), often to treat symptoms and illnesses associated with stress, such as depression, anxiety, back and neck pain, and gastrointestinal disorders. With the aim of increasing understanding regarding CAM usage among Veterans, Betthauser and colleagues utilized the Complementary and Conventional Medicine Attitudes Scale (CACMAS) to assess Veterans' attitudes and beliefs towards, and their use of, CAM (Betthauser et al., 2014). Findings suggest that the Veterans surveyed were open to, or are already using, CAM approaches. Interestingly, results also suggest that Veterans with mTBI and PTSD may be more accepting of CAM approaches than those without these conditions (Betthauser et al., 2014). While there are promising data showing the potential of CAM approaches for TBI *or* PTSD (McFadden et al., 2011; Hernández et al., 2016), studies of CAM treatments for co-occurring TBI *and* PTSD have been limited.

Mechanistically, the role that inflammation plays in the onset and perpetuation of psychiatric or post-TBI symptoms has garnered increased attention (Lozano et al., 2015; Miller and Raison, 2015). In a review article introducing the concept of "post-inflammatory brain syndrome [PIBS]", Rathbone et al. examine evidence suggesting that inflammation may play a role in the onset of post-concussive symptoms [PCS], including psychiatric symptoms (p. 1) (Rathbone et al., 2015). In specific, the authors suggest that if inflammation contributes to PCS, previous stressors, including psychological stressors, may "sensitize" individuals to "greater or earlier inflammatory stress" responses; thereby highlighting the potential role of PTSD as a "predisposing factor" in the onset of PCS. (p. 3) (Rathbone et al., 2015). Moreover, findings suggest that, among Soldiers, deployment-acquired TBI increases the risk of being diagnosed with PTSD approximately 3 or 9 months later, suggesting a relationship between the two conditions (Stein et al., 2015). Finally, animal studies support a role for neuroinflammation in anxiety-like behaviors following TBI (Rodgers et al., 2012, 2014).

According to the "Old Friends" hypothesis, problematic inflammatory processes in modern urban societies are posited to be at least in part associated with reduced exposure to commensal and environmental microorganisms that normally prime immunoregulatory circuits and suppress inappropriate inflammation (Lowry et al., 2016; Rook et al., 2004). As such, anti-inflammatory/immunoregulatory agents, including some probiotics, may have a role in treating TBI and PTSD-related symptoms. That is, emerging research suggests that probiotics may have the potential to decrease stress-induced inflammatory responses, as well as associated symptoms. For example, studies using a murine model of PTSD (Reber et al., 2016a) have demonstrated that immunization with a heat-killed preparation of the immunoregulatory bacterium, *Mycobacterium vaccae* (NCTC 11659), induces a more proactive behavioral response to a psychosocial stressor, prevents stress-induced colitis, and prevents stress-induced exaggeration of *ex vivo anti*-CD3-stimulated release of proinflammatory cytokines, including interferon gamma and interleukin (IL)-6, from freshly isolated mesenteric lymph node cells (Reber et al., 2016b). Furthermore, immunization with *M. vaccae* prevented stress-induced exaggeration of dextran sodium sulfate (DSS)-induced colitis, a model of inflammatory bowel disease (Reber et al., 2016b). As such, the goal of the systematic review is to elucidate existing findings regarding prebiotic and probiotic use among human populations of individuals with a history of TBI and/or PTSD.

2. Methods

Methods and presentation of results map onto Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.1. PRISMA stage: Identification

2.1.1. Search strategy

We conducted a systematic search of literature published between January 1, 1980 and June 17, 2016 in the following electronic databases: OVID MEDLINE, EMBASE, OVID PsycINFO, Web of Science, CINAHL, and Cochrane Library. The search strategy was developed using medical subject heading terms (MeSH) and relevant keywords in OVID MEDLINE, and then replicated in each database (see Table 1).

Google and Google Scholar were searched to identify grey literature studies that met inclusion criteria but were published outside of traditional academic distribution channels, or not yet indexed in electronic databases. Reference lists were also mined for relevant publications not already identified.

2.1.2. Study selection

Articles were selected in accordance with the Population, Intervention, Comparators, Outcomes, Timing/Setting (PICOTS) framework (Moher et al., 2009; Matchar, 2012).

Population(s): Adult humans with TBI of any severity, defined as a bolt or jolt to the head or a penetrating head injury that disrupts the function of the brain. The severity of such an injury may range from mild (a brief change in mental status or consciousness) to severe (an extended period of unconsciousness or amnesia) after the injury (Center for Disease Control and Prevention [CDC], 2017). Studies with human adults with PTSD were also included, with PTSD defined as a maladaptive response to a traumatic or stressful life experience that may be characterized by expressions of distress including intrusive thoughts or feelings, avoidance, negative cognitions and mood, and increased arousal and reactivity (VA National Center for PTSD, 2017; VA Health Services Research & Development, 2017; American Psychiatric Association, 2013). Child populations and animal models were excluded.

Intervention(s): An intervention was *not* required for inclusion. However, studies using randomized and non-randomized intervention approaches to study the administration of any prebiotic and/or probiotic supplements or consumption of food/beverage