Brain, Behavior, and Immunity xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Review Article

The influence of immunological stressors on traumatic brain injury

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ARTICLE INFO

Article history:
Received 18 September 2017
Received in revised form 13 January 2018
Accepted 14 January 2018
Available online xxxx

Keywords:
Polytrauma
Infection
Sepsis
Toxoplasma gondii
Age
Immunosenescence
Concussion
Inflammation

ABSTRACT

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide, and typically involves a robust immune response. Although a great deal of preclinical research has been conducted to identify an effective treatment, all phase III clinical trials have been unsuccessful to date. These translational shortcomings are in part due to a failure to recognize and account for the heterogeneity of TBI, including how extracranial factors can influence the aftermath of TBI. For example, most preclinical studies have utilized isolated TBI models in young adult males, while clinical trials typically involve highly heterogeneous patient populations (e.g., different mechanisms of injury, a range of ages, presence of polytrauma or infection). This paper will review the current, albeit limited literature related to how TBI is affected by common concomitant immunological stressors. In particular, discussion will focus on whether extracranial trauma (i.e., polytrauma), infection, and age/immunosenescence can influence TBI pathophysiology, and thereby may result in a different brain injury than what would have occurred in an isolated TBI. It is concluded that these immunological stressors are all likely to be TBI modifiers that should be further studied and could impact translational treatment strategies.

Contents

1. Introduction

Traumatic brain injury (TBI) is induced by biomechanical forces to the brain, and is a leading cause of mortality and morbidity worldwide (Blennow et al., 2012). Significant research efforts have been made to better understand the complex pathophysiology of TBI and identify pharmacological interventions (Xiong et al., 2013; Shultz et al., 2017). Despite these efforts, all phase III clinical trials in TBI have been unsuccessful, and there are still no treatments known to improve long-term outcomes in TBI patients (Stein, 2015). A number of factors have likely contributed to the translational failures in the TBI field, and in-depth discussion on each of these is beyond the scope of this paper (see Maas et al., 2012; Menon and Maas, 2015; Stein, 2015 for other relevant reviews). However, one of the major reasons for the lack of translational success is the failure to account for the heterogeneity of TBI in both the preclinical and clinical settings (Xiong et al., 2013; McDonald et al., 2016; Shultz et al., 2017). TBI is often not

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https://doi.org/10.1016/j.bbi.2018.01.007
0889-1591/

an isolated injury; yet the majority of preclinical research has utilized isolated TBI models such as the controlled cortical impact, fluid percussion, and weight-drop methods. Although TBI-related factors (e.g., brain structures affected by injury, focal versus diffuse injury, mechanism of injury, etc.) can affect TBI pathophysiology, how concomitant extracranial stressors might influence TBI is still largely unknown. Amongst the possible extracranial stressors that could affect TBI, some of the most common include extracranial trauma (i.e., polytrauma) (McDonald et al., 2016), infection (e.g., bacterial, viral, parasitic) and sepsis (Tenter et al., 2000; Semmler et al., 2008; Marks et al., 2013; Semmler et al., 2013), and aging (i.e., immunosenescence) (de la Plata et al., 2008; Sendroy-Terrill et al., 2010). Each of the abovementioned stressors involve a significant immune response, which is also a pathological hallmark of TBI. This review article will summarize how these common extracranial immunological stressors have potential to affect TBI and discuss how this might influence future research, both in terms of preclinical TBI modeling and treatment strategies.

2. Traumatic brain injury (TBI)

It is estimated that over 10 million people worldwide suffer a TBI each year (Humphreys et al., 2013), and TBI often results in death or disabilities (Gennarelli et al., 1989; Werner and Engelhard, 2007). Depending on the nature and severity of the injury (i.e., focal versus diffuse; mild versus severe), outcomes from TBI range from transient to long-term neurological deficits (e.g., cognitive, emotional, and motor abnormalities) that can involve significant grey and white matter damage (Blennow et al., 2012). TBI is also linked to the later development of other neurological conditions, including posttraumatic epilepsy (Webster et al., 2017), Alzheimer's disease (AD) (Jellinger, 2004), amyotrophic lateral sclerosis (Chen et al., 2007; Schmidt et al., 2010), and chronic traumatic encephalopathy (McKee et al., 2009, 2015). The brain damage induced by TBI is generally categorized as being caused by either primary or secondary injury mechanisms. Primary injury is the result of the direct mechanical insults at the moment of impact, and due to the rapid onset is largely considered irreversible (Blennow et al., 2012; Xiong et al., 2013). The primary insult, however, also initiates a series of pathological secondary injury pathways, including activation of the immune system (Taupin et al., 1993; Shohami et al., 1994; Frugier et al., 2010), apoptosis (Miñambres et al., 2008), lipid peroxidation (Awasthi et al., 1997; Ansari et al., 2008), excitotoxicity (Werner and Engelhard, 2007), numerous proteopathies (e.g., tau, amyloid) (Blennow et al., 2012; Zheng et al., 2014; Shultz et al., 2015b), and further injury to the blood-brain barrier (BBB) and axons (Shlosberg et al., 2010; Johnson et al., 2013b). These secondary injury processes can occur within minutes to days after TBI, and may persist and contribute to chronic neurodegeneration (Blennow et al., 2012; Xiong et al., 2013). The exact nature of the secondary injury cascade may differ depending on factors such as type (e.g., focal versus diffuse) and severity (e.g., mild versus severe) of the TBI. For example, although BBB disruption has been reported in both diffuse and focal TBI models (Adelson et al., 1998), it is more common in focal TBI (Smith et al., 1995; Flierl et al., 2009; Shear et al., 2011). Consistent with the findings of worse BBB damage in focal TBI, neutrophil infiltration has also been reported to be more prominent following focal brain injury (Adelson et al., 1998). Nonetheless, there is optimism in the TBI field that secondary injury mechanisms could be therapeutically targeted to reduce additional injury regardless of TBI sub-type because of their delayed onset.

Amongst the different secondary injury mechanisms that can occur in TBI, neuroinflammation is perhaps the most common that is present across the various TBI sub-types. As detailed below, a number of inflammatory factors have been implicated in worse secondary injury after TBI. However, it is important to note that some extent of inflammation is beneficial post-TBI to clear cellular debris, isolate the injured tissue, and signal the up-regulation of growth factors and anti-inflammatory cytokines (Russo and McGavern, 2016). Both clinical and preclinical studies have reported that inflammatory cytokines, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, interferon-γ (IFNγ), and IL-6 are released acutely after TBI (Taupin et al., 1993; Shohami et al., 1994; Frugier et al., 2010). Microglia are innate macrophage-like cells in the central nervous system (CNS) and act as the primary immune cells in response to TBI, secreting high levels of inflammatory cytokines, chemokines, oxidative metabolites, and other toxic molecules (Loane and Kumar, 2016). These factors and cytokines can initiate a self-propagating cycle of damaging events that may cause chronic and dysregulated microglial activation (Block et al., 2007). Human and animal studies suggest that following TBI, microglia can be chronically activated for weeks and months (as reviewed in Loane and Byrnes, 2010; Ramlackhansingh et al., 2011; Shultz et al., 2012; Johnson et al., 2013a). For example, Johnson et al. (2013a) studied post-mortem brain samples from TBI patients and found a high frequency of densely packed reactive microglia in TBI cases that involved >3 months survival post-TBI. Reactive microglia were also present in 28% of TBI cases involving > 1-year survival, demonstrating the potential for chronic microglia activation after TBI. Notably, the presence of reactive microglia was associated with corpus callosum degeneration. However, microglia, macrophages, and other monocytes can also be beneficial after brain injury as they are able to phagocytose debris and aid in remyelination (Cherry et al., 2014; Natrajan et al., 2015; Russo and McGavern, 2016).

Astrocytes are another important glial cell that are involved in neuroinflammation. In a normal brain, astrocytes provide structural scaffold for neurons and blood vessels, and contribute to BBB formation, whereas during neuroinflammation after TBI, astrocytes are activated which results in astrogliosis (Laird et al., 2008; Shultz et al., 2014; Webster et al., 2015). Rodent studies suggest that astrocytic glutamate transporters are dysregulated after TBI (Raghavendra Rao et al., 1998), and therefore may contribute to post-TBI excitotoxicity. Furthermore, astrocytes are a main source of inflammatory mediators that may contribute to toxicity in the injured brain (Lau and Yu, 2001). However, other studies in mice have found that astrogliosis may be beneficial after TBI by promoting the formation of a glial scar, which isolates the lesion and prevents further cell loss (Bush et al., 1999; Laird et al., 2008).

Peripheral immune factors such as circulating leukocytes are recruited across the BBB into the injured brain in response to TBI. Human and preclinical studies have found that neutrophils are amongst the first wave of immune cells to infiltrate the brain, peaking within approximately 24 h, after which macrophages become the predominant infiltrating leukocytes (Soares et al., 1995; Hausmann et al., 1999; Jin et al., 2012; Shultz et al., 2013). Both neutrophils and macrophages may exacerbate the levels of cytokines and free radicals (Finnie, 2013). Free radicals (e.g., reactive oxygen species) can lead to oxidative stress (Awasthi et al., 1997), which is abundant in the brain within hours after TBI in rodents (Awasthi et al., 1997; Ansari et al., 2008). Lipid peroxidation is a common consequence and marker of oxidative stress (Del Rio et al., 2005), with levels of malondialdehyde (MDA; i.e., the end-product of lipid peroxidation) often found to be elevated after TBI (Bao et al., 2012; Shultz et al., 2013; Webster et al., 2015). Lipids are major structural components of cell membranes, and therefore their peroxidation can result in the lysis of membranes and the consequent release of various harmful molecules from the damaged membranes (Gutteridge, 1995).

Disruption to the BBB, a hallmark of TBI (see Shlosberg et al., 2010 for review), further facilitates access for peripheral factors

Please cite this article in press as: Sun, M., et al. The influence of immunological stressors on traumatic brain injury. Brain Behav. Immun. (2018), https://doi.org/10.1016/j.bbi.2018.01.007