Brain, Behavior, & Immunity - Health 16 (2021) 100327

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Short review: The impact of sex on neuroimmune and cognitive outcomes after traumatic brain injury

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ARTICLE INFO

Keywords:
Traumatic brain injury
Sex-dimorphism
Neuroimmune
Cognition

ABSTRACT

Traumatic brain injury (TBI) is an ever growing health concern, with cases increasing in both the US and the world at large. With the improvement of emergency medicine in recent decades, survival from TBI has become more common place, and thus individuals are coping with long-term deleterious outcomes from trauma as a result. Such outcomes include altered cognitive (memory loss/executive function), social (isolation tendencies), and behavioral (risk-taking behavior/anxiety) function. Researchers use preclinical rodent models to investigate cellular and molecular underpinnings of adverse TBI outcomes. One leading mechanism of long-term cognitive changes include alterations of immune function in the brain (termed 'neuroimmune'). Studies have found that TBI can induce chronic maladaptive neuroimmune responses, which can in turn propagate long-term neurological deficits. Unfortunately, most of the molecular understanding of TBI-induced neuroimmune outcomes is derived from studies performed solely in males. This is especially problematic as sex-dimorphic neuroimmune changes have been identified in healthy individuals. If and how these basal neuroimmune differences influence TBI related outcomes is the focus of this short review. Importantly, understanding these differences could allow for improved therapeutic development for treating the long-term effects of TBI.

1. Sex-differences in traumatic brain injury

Traumatic brain injury (TBI) is defined as a bump, blow, or jolt to the head that leads to a disruption in normal brain function. The rising number of cases of TBI has resulted in it being the leading cause of neurological dysfunction and is often termed the "silent epidemic" (Hoffman and Harrison, 2009; Roozenbeek et al., 2013). Despite current estimates that ~5 million individuals are living with long-term consequences of TBI in the US alone (Wanget al., 2018), there are no FDA-approved therapeutics to prevent or reverse cognitive, social, and behavioral changes associated with TBI.

While there are a number of reasons why therapeutics have not been identified, one potential reason is that we lack an understanding of trauma-induced changes in both sexes. Both clinical trials and preclinical studies have focused solely on males; a recent review estimated that 93 % of preclinical studies precluded sex as a variable (Spani et al., 2018). While in young adults traumatic brain injury is more common in males (Faul and Coronado, 2015; Coronadoet al., 2010), there is a growing number of cases identified in females (Ledreuxet al., 2020; Gizaet al., 2013; Kutcher and Giza, 2014). Furthermore, female athletes report more concussions when playing the same sports as males (Covassin et al., 2016), In the elderly population, TBI is more prevalent in females (Maet al., 2019) as well, which makes the individual sex paradigm obsolete.

Traumatic brain injury can lead to a number of different long-term outcomes including memory loss, learning deficits, alterations in social behaviors, increased risk-taking behaviors, and depression (Wanget al., 2018; Smith et al., 2013; DeKosky et al., 2010; Engberg and Teasdale, 2004; Sullivan et al., 1987). While often analyzed individually, these outcomes can have comorbidities and overlapping mechanisms. There have been conflicting results as to how males and females respond to cognitive, behavior, and motor outcomes after trauma.

Neuroimmune mechanisms of trauma-induced cognitive and behavioral outcomes have focused on innate immune responses characterized by microglia reactivity and peripheral innate immune cell infiltration (monocytes and neutrophils), *reviewed in* (Morganti-Kossmann et al., 2019). In general, these studies have identified rapid cellular infiltration after physical head trauma followed by inflammatory responses

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https://doi.org/10.1016/j.bbih.2021.100327
Received 14 May 2021; Received in revised form 6 August 2021; Accepted 9 August 2021
Available online 13 August 2021

characterized by cytokine production, increased phagocytic activity, and reactive oxygen species release. The accumulation of these responses leads to an inflammatory milieu (often observed both in the brain and periphery) which can be neurotoxic, altering both neuronal function and structure. Again, the majority of studies that have investigated neuroimmune responses after trauma have been performed in male rodents, limiting our understanding of female responses and outcomes (Spani et al., 2018). This is especially problematic given the recent reports that have identified sex-dependent differences in microglia resting and injury states (Krukowskiet al., 2018a; Villaet al., 2018). In short, this study found that microglia isolated from young, naïve male mice had a significantly different transcriptome which was more reactive and inflammatory than matched female mice. If differences are observed at baseline or normal physiologic states, one would expect that trauma responses would also vary. Here we perform a literature analysis of preclinical studies investigating cognitive and behavioral outcomes to trauma in the context of sex-dimorphisms.

1.1. Mild TBI

We recently found a differential behavioral response to repetitive mild TBI (5 mild, midline impacts) in male and female mice. Multiple mild traumas resulted in significantly increased risk-taking behavior in males (Krukowskiet al., 2020). These behavioral responses to repetitive trauma had previously been reported in males (Mouzonet al., 2014; Petragliaet al., 2014; Kondoet al., 2015; Mouzonet al., 2018). Furthermore, trauma-induced alterations in risk-taking behavior were linked with cell-specific synaptic alterations in the type A subtype of layer V pyramidal neurons of the medial prefrontal cortex of male mice (Krukowskiet al., 2020). Conversely, female rodents were protected from this maladaptive behavioral response (Krukowskiet al., 2020). Unfortunately, we did not investigate if repetitive mild trauma altered pyramidal neuron dysfunction in females. Another group reported sex-differences in repetitive injury responses in rats (Wright et al., 2017). Following three mild injuries, male rats displayed short-term working memory deficits, whereas female rats did not. Female rats had increased depressive-like behaviors, whereas such responses were not observed in males. These changes were linked with neuronal atrophy, with females showing more loss in the prefrontal cortex and males with worsened white matter integrity in the corpus callosum. The prefrontal cortex and corpus callosum were the only brain regions investigated in this study. In a third study that investigated a model of five mild TBIs in adolescent male and female mice, investigators found impaired motor function, and recognition memory impairments in both sexes (Eyolfsonet al., 2020). Interestingly, the male rodents were significantly more impaired in motor function when compared with female mice following the repetitive, mild TBI. When investigating neuroimmune correlates of altered motor and cognitive performance, the investigators found differential leukocyte infiltration kinetics when comparing injured male and female animals. Specifically, injured male rodents had earlier macrophage infiltration and a more robust T cell infiltration when compared with injured female counterparts (Eyolfsonet al., 2020). When investigating the injury-induced microglia kinetics, there were decreased microglia numbers in the corpus callosum, thalamus and motor cortex in injured animals when compared with uninjured animals, with no differences between the sexes. No differences were observed in microglia cells in the hippocampus of injured animals.

SUMMARY: Sex-dimorphic behavioral and cognitive trauma responses have been reported in mild, repetitive trauma. Male rodents display increased risk-taking behavior, more impaired motor function, and deficits in spatial learning following repetitive mild trauma. Increased depressive behaviors were observed in female rodents. Recognition memory impairments were observed in both male and female adolescent mice. Mild trauma-induced neuroimmune outcomes are less well defined, with only one study investigating leukocyte infiltration and microglia responses in adolescent male and female mice. Nevertheless, sex differences were observed in this study, further highlighting the need for additional exploration.

1.2. Moderate to severe TBI

In moderate to severe injury models, we have not identified sex-dimorphic cognitive or behavioral alterations in either adult (Krukowski et al., 2021) or aged mice (Krukowskiet al., 2018b). When using the radial arm water maze, a tool for investigating spatial learning and memory, we found male and female adult rodents performed nearly identically following trauma—both showing deficits when compared with sex-matched uninjured animals (Krukowski et al., 2021). We linked these cognitive deficits with altered microglia responses (measured by increased phagocytic capacities) and altered neuronal structure and function (Krukowski et al., 2021). For this study analysis was focused on the injured hemibrain (microglia phagocytosis) or injured hippocampus (neuronal structure/function and microgliosis). While cognitive and neuronal changes were observed in both male and female rodents, our microglia analysis was only performed in male rodents. Interestingly, another group also investigated sex-dimorphic changes in microglia function using a nearly identical moderate trauma model (Doranet al., 2019). Doran et al. did not identify sex-dimorphic differences in microglia phagocytic function when comparing male and female mice. Other trauma-induced sex-dimorphic immune changes were analyzed, and differences in myeloid cell brain infiltration and microglia number were identified. Male adult TBI mice had significantly more myeloid cell infiltration (1 day post-injury) and microglia (3 days post-injury) when compared with the female adult TBI mice. Analysis for this study was performed on the injured hemibrain. Despite some sex-dimorphic immune responses, both male and female rodents displayed impaired motor function (with the rotarod) and spatial working memory deficits (in the Y-maze) following trauma. An additional report in a model of stab injury also found more microglia at the injury site in male mice when compared to female mice (Acaz-Fonseca et al., 2015). No sex differences were observed in astrocytes and cognitive outcomes were not investigated in this study. Another group found reduced neuronal cell loss (at the injury site), coupled with improved motor outcome in female mice following trauma when compared with their male counterparts (Clevengeret al., 2018). Interestingly, again these researchers did not observe differences in microgliosis or astrogliosis (in either the peri-injury cortex or the reticular thalamic nucleus) when comparing the male and female trauma animals. These authors did find that if female mice were ovariectomized the protective state was reduced, suggesting a link between hormonal levels and protection. In fact, ovariectomized female mice that underwent TBI surgery had the highest levels of microgliosis and astrogliosis (in the peri-injury cortex) in comparisons TBI males and females.

Manipulation of microglia has recently become a popular research topic with a few recent studies investigating this in TBI. Three of the studies investigated microglia depletion with CSF inhibitors (PLX3397 or PLX5622) solely in male rodents (Wanget al., 2020; Witcheret al., 2018; Henryet al., 2020) with one additional study performed solely in female rodents (Williset al., 2020). Different moderate injury models (controlled cortical impact, lateral fluid percussion), microglia depletion timeline (preventative versus therapeutic), and outcome measures (neuronal changes, microglia/astrocyte gene expression profiles, memory deficits) were used in each of the four studies, which makes direct comparisons problematic (reviewed in (Paladini et al., 2021)). Nevertheless, all of the studies revealed the therapeutic potential of modulating microglia in moderate to severe TBI models (Wanget al., 2020; Witcheret al., 2018; Henryet al., 2020; Williset al., 2020), demonstrating clear restorative effects on neuroimmune or memory outcomes. While additional studies are needed in order to determine how sex-dimorphic microglia responses impact TBI outcome, these initial studies lay the foundation for utilizing neuroimmune strategies in preventing and/or treating TBI.

SUMMARY: Trauma-induced behavioral and cognitive changes impact male and female rodents similarly following moderate to severe

injury models. However, trauma-induced microglia responses vary between sexes: Male TBI rodents have a more robust microglia and myeloid cell response as compared with female TBI rodents. Initial studies investigating microglia manipulation in TBI show promise in both sexes, while unfortunately lacking comparative analysis.

2. Links between sex-dimorphic changes in trauma and space radiation

Traumatic brain injury is not the only field that has failed to investigate sex-dimorphic responses. Fortunately, thanks to improved incentives from funding agencies more studies encompassing both sexes are underway. One field that has recently found sex-dimorphic cognitive and neuroimmune responses is the newly developing field of space radiation. Space radiation refers to galactic cosmic rays experienced by astronauts once outside of the Earth's magnetosphere (Cekanaviciute et al., 2018; Nelson, 2009, 2016). This exposure becomes especially detrimental as astronauts voyage further from the Earth's surface to the moon and onto Mars. Interestingly, similar to mild TBI models, exposure to space radiation can result in long-lasting cognitive and behavioral changes in the absence of gross neuronal loss (reviewed in (Rienecker et al., 2021)). As a result, comparisons between the two models could be useful for understanding mechanisms and potential therapeutic strategies.

We were the first to identify such findings in 2018, observing that male mice exposed to space radiation (galactic cosmic radiation) displayed diminished social interaction, increased anxiety-like phenotype, and impaired recognition memory (Krukowskiet al., 2018a). Mechanistically, the space radiation-induced responses corresponded with microgliosis and altered neuronal structures in the hippocampus. Cognitive, microglia, and neuronal changes were not observed in female mice exposed to identical space radiation paradigms, suggesting that space-radiation exposure impacts male and female rodents differently. Furthermore, as has been observed in TBI, microglia manipulation through CSF1R depletion antagonist can also mitigate or prevent the cognitive and behavioral effects of space radiation exposure (Krukowskiet al., 2018c; Allenet al., 2020), once again linking neuroimmune parameters with adverse cognitive outcomes. Unfortunately, similar to the initial TBI studies, the intervention strategies were performed solely in male rodents. Nevertheless, these two models (TBI and space radiation) demonstrate links between sex-dimorphic cognitive and neuroimmune responses with additional studies needed to further delineate mechanistic differences. It is possible that findings from one model could be used as a guideline for the other, as well as other neurodegenerative states.

3. Conclusions

Understanding of sex-dependent responses is emerging as an important variable in numerous disease and neurodegenerative states, including traumatic brain injury and space radiation. Initial preclinical TBI studies demonstrate clear differences in male and female response, including neuroimmune parameters and cognitive outcomes. Increased study numbers and improved understanding of such mechanisms are needed.

Study design for sex comparisons increases costs for investigators, which can be prohibitive for all labs, but especially smaller or newly emerging labs. One possible solution for this is to leverage data repositories such as the Open Data Commons for TBI (ODC-TBI.org) (ChouA.Hui et al., 2021), which implements FAIR (findable, accessible, interoperable, and reusable) data principles (Wilkinsonet al., 2016) and allows for a large data sharing network for preclinical TBI researchers. Shared resources and practices have been beneficial allowing for multidimensional analytics in clinical TBI research (Thompson et al., 2015; Nielsonet al., 2015; Yueet al., 2013; Steyerbergetal., 2019). If such practices are applied to preclinical research, it could allow for standardization of techniques and analysis across laboratories. Such resources could greatly expedite and enhance understanding of TBI-induced responses, specifically allowing for a focus on sex-dimorphic changes. This in turn could lead to improved therapeutic development for traumatic brain injury induced long-term consequences offering hope to the millions of individuals suffering from chronic maladaptive responses to trauma.

Declaration of competing interest

The author reports no conflict of interest.

Acknowledgements

KK is funded by the University of Denver, Department of Biological Science.

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Karen Krukowski. As a neuroimmunologist, my scientific career has focused on understanding complex, dynamic and bidirectional interactions between the immune and nervous systems. I investigate how disruptions in these interactions can underscore various pathological states including stress, neuropathy, traumatic brain injury and aging. Currently, my work focuses on understanding a role for the adaptive immune system in age- and trauma-related decline. Furthermore, I am exploring how sex-dimorphic changes can impact these responses. I went to the University of Miami Ohio for my undergraduate studies. I earned my doctorate at Loyola University Chicago under Dr. Herbert Mathews, after which I completed two post-doctoral research positions, the first at University of Texas MD Anderson Cancer Center (MDACC) with Dr. Annemieke Kavelaars and Dr. Cobi Heijnen, and most recently at University of California San Francisco (UCSF) with Dr. Susanna Rosi and Dr. Peter Walter. My laboratory opened in January 2021 at the University of Denver in the Knoebel Institute for Healthy Aging (https://www.krukowskilab.com/). Outside the lab, I love exploring Colorado with my daughters, Noelle and Hazel, my dog Cappie, and my partner Paul.