The gastrointestinal track is inhabited by tens of trillions of microorganisms. The gut microbiota is involved in gut motility, nutrient absorption and synthesis of metabolites that influence hormone axis, metabolism, and immune function. Given the influence gut microbiota has on health, there is a growing body of literature describing the gut microbiota’s impact on brain and behavior. The bidirectional nature of the gut-brain axis involves neurological, immunological and hormonal mechanisms that can induce perturbations in gut or brain homeostasis. Studies using different but complementary approaches, such as germ free mice, antibiotics, probiotics, gut microbiota transplant, have shown that the gut microbiota acting via the gut-brain axis contribute to the regulation of brain and behavior, impacting depression, stress and cognition. Moreover, gut microbiota disruption has been associated with neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease and implicated in modulating disease severity in stroke. Traumatic brain injury (TBI) is a complex, acute neurological insult that can lead to chronic neurodegeneration. Understanding the influence of the gut-brain axis in the setting of TBI may create new avenues of therapeutic approaches for TBI survivors.

Preclinical investigations provide evidence that TBI can impact intestinal function and the gut microbiota. In a moderate TBI rat model utilizing 16S RNA sequencing of stool, changes in gut microbiota were detected as early as 2 days after injury (Nicholson et al., 2019). TBI’s impact on gut microbiota may be long-lasting with significant changes in gut bacterial populations for up to 28 days after injury (Opeyemi et al., 2021). Larger lesion volume was associated with alterations of gut microbiota that may influence functional outcome. In another preclinical study of diffuse brain injury, TBI-induced microbial dysbiosis with gastrointestinal dysfunction and alteration of bile acid was an important mediator of chronic neurodegeneration (You et al., 2021). Gut microbial dysbiosis was associated with decreased levels of bile acid in feces and plasma. This study supported the hypothesis that TBI-induced gut microbial dysbiosis contributed to intestinal inflammation by decreasing bile acid (You et al., 2021). Fecal microbiota transplant for 7 days after TBI in rats restored gut microbiota, improving neurological outcomes and exerting an anti-inflammatory effect via decreasing TBI-induced trimethylamine N-oxide, a gut microbiota metabolism, and inducing short-chain fatty acids enzyme methanocorpuscle sulfoxide reductase A expression in the hippocampus (Du et al., 2021). This data supports the concept that the gut-brain axis is bidirectional and TBI can induce alterations in the gut microbiome.

The composition of the gut microbiota is shaped significantly by the immune system and resident microbes provide signals for normal immune system development. Disruption of the gut-immune axis induces profound consequences in host health. However, there are still major gaps in our understanding of how the immune system can regulate microbiota and how the microbiota shape host immunity. Utilizing germ free mice and transient alteration of gut microbiota by antibiotic treatment, Erny et al. (2015) demonstrated that gut microbiota control microglia maturation and homeostasis. Microglia dysfunction in germ free mice was rescued by exercise, probiotics and adoptive transfer of Ly6C+ monocytes (Mohle et al., 2016). Hippocampal neurogenesis was reduced in antibiotic-treated mice but was rescued by exercise, probiotics and adoptive transfer of Ly6C+ monocytes (Mohle et al., 2016). Gut microbiota have been also described as influencing the brain’s response to injury. In an ischemic stroke model, antibiotic-induced alteration of the gut microbiota modulated the trafficking of effector T cells from the gut to the leptomeninges impacting stroke severity (Benakis et al., 2016). They demonstrated that intestinal dysbiosis alters immune homeostasis in the small intestine, leading to an increase in regulatory T cells and a reduction in interleukin-17-positive T cells inducing a neuroprotective effect after stroke (Benakis et al., 2016). Hence, a deeper understanding of the gut microbiome’s influence on neuroinflammation in the setting of TBI may provide new approaches to neuroprotection (Figure 1).

The gut microbiota’s influence on TBI is of paramount clinical significance as TBI patients are highly susceptible to developing gut microbial dysbiosis due to frequent antibiotic administration, prolonged hospitalization, and autonomic dysfunction. In our most recent published preclinical study (Celorio et al., 2021), we hypothesized that microbial dysbiosis leads to worsened outcomes after TBI, and this effect is mediated by microbial-host immune interactions, which are dependent on changes induced by the peripheral or resident immune cells such as microglia. To test this hypothesis, adult male C57Bl/6J mice experienced moderate controlled cortical impact (2 mm depth) or sham surgery and were randomized to a control group or broad-spectrum antibiotics (vancomycin, neomycin, ampicillin, and metronidazole) or Kool-Aid as a control in drinking water for 7 days after injury. All mice resumed regular drinking water after 7 days. We performed flow cytometry, histological assessments, and behavior testing at various time points after injury.

16S RNA sequencing of stool samples confirmed dramatically altered gut bacterial populations after 7 days of antibiotic exposure, with persistent changes still detected at 1 month after injury. Microglia showed time-dependent lasting changes after TBI that were reduced neurogenesis, increased hippocampal neurogenesis and neuronal degeneration in the CA3 region of the injured hippocampus was exacerbated in antibiotic-treated animals despite discontinuation of antibiotics 1 week after injury and normalization of hippocampal neurogenesis by 3 months. Chronic neuronal degeneration was accompanied by altered fear memory response in antibiotic-injured mice. Nevertheless, other studies have shown a neuroprotective effect of broad-spectrum antibiotics prior to brain injury in TBI model (Simon et al., 2020). Simon et al. (2020) demonstrated antibiotic exposure immediately after TBI reduced hippocampal cell loss, decreased microglia density, and increased fear conditioning response. The opposing results of our data could be related to the timing of antibiotic administration (pre-injury versus post-injury), injury severity, timing, and region of histologic and behavioral assessments. In summary, induction of gut microbial dysbiosis immediately after injury altered microglia homeostasis, suppressed monocyte and lymphocyte infiltration and was associated with reduced neurogenesis, increased hippocampal neurodegeneration, and fear memory changes long after antibiotic exposure.

Bacteria metabolites, specifically SCFAs, have been shown to reverse gut microbial dysbiosis induced microglia dysfunction (Enry et al., 2015). In addition, supplementation of soluble SCFAs prior to and after TBI improved spatial learning in mice (Opeyemi et al., 2021). However, how these mediators overcome the blood-brain barrier and dilutional challenges is currently unknown. Recently, it has been shown that brain resident CD4+ T cells are required for microglia maturation, and their absence results in delayed neuroinflammation and behavior deficits (Pasciutto et al., 2020). Furthermore, brain-resident T cells derived from activated circulatory T cells were influenced by the gut microbiota, supporting a possible mechanistic link for gut microbiota control of microglia maturation and homeostasis. This link is further supported by activation surface markers (toll-like receptor 4, and major histocompatibility complex II) that were associated with microglial morphology changes toward amoeboid microglia. At 3 months, we found evidence of chronic microbial activation with increased histological neuronal loss in antibiotic-exposed injured mice. Microglia play an important role in TBI-induced neurogenesis (Willis et al., 2020). Utilizing 5-bromodeoxyuridine injections on post-injury days 3–6, we observed reduced neurogenesis in the dentate gyrus of antibiotic-exposed injured mice. We also found that gut microbial dysbiosis induced an acute suppression of monocyte circulation in the peripheral blood and infiltration into the brain parenchyma with no associated changes in T cell infiltration 3 days after injury. However, by 7 days after injury, TBI-induced recruitment of lymphocytes (CD4+, CD8+, and CD4+CD25+ cells) and monocytes (Ly6C+Ly6G-) into the hippocampus was suppressed in antibiotic-injured mice, an effect that persisted for up to 1 month. Our initial characterization of reduced T cell infiltration associated with changes in microbial morphology and neurodegeneration in antibiotic-injured mice suggest that T cell-microglia crosstalk may be an important mechanistic link of gut microbiota modulation of TBI.

These changes in neuroinflammation following antibiotic-induced gut microbial dysbiosis after TBI impacted long-term neurobehavioral outcome. Neuronal degeneration in the CA3 region of the injured hippocampus was exacerbated in antibiotic-treated animals despite discontinuation of antibiotics 1 week after injury and normalization of hippocampal neurogenesis by 3 months. Chronic neuronal degeneration was accompanied by altered fear memory response in antibiotic-injured mice. Nevertheless, other studies have shown a neuroprotective effect of broad-spectrum antibiotics prior to brain injury in TBI model (Simon et al., 2020). Simon et al. (2020) demonstrated antibiotic exposure immediately after TBI reduced hippocampal cell loss, decreased microglia density, and increased fear conditioning response. The opposing results of our data could be related to the timing of antibiotic administration (pre-injury versus post-injury), injury severity, timing, and region of histologic and behavioral assessments. In summary, induction of gut microbial dysbiosis immediately after injury altered microglia homeostasis, suppressed monocyte and lymphocyte infiltration and was associated with reduced neurogenesis, increased hippocampal neurodegeneration, and fear memory changes long after antibiotic exposure.
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