Post-TBI Administration of Short Chain Fatty Acids Supports Gut Microbial Structure and Attenuates Cognitive Deficits

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Background

Traumatic brain injury (TBI) is an underrecognized public health threat. There are limited therapeutic options for TBI, and supportive care remains the mainstay of treatment. Our previously published data demonstrate that post severe TBI fcal microbiome transplantation (FMT) can reverse TBI-induced depletion of commensal bacteria, preserve white matter connectivity, protects cognition, and decrease brain lesion size in mice after TBI.

Methods

14-week-old (n=52) male C57BL/6 underwent TBI via-controlled cortical impact vs. sham injury. Post-TBI, each group was treated with acetate, butyrate, and propionate vs. salt vehicle via free access to drinking water for four weeks post-TBI. We measured white matter connectivity using magnetic resonance at 60 days post injury(DPI), and measured for species-normal anxiety levels with open field testing at 50 DPI. We extracted at brain Microglia to assess signs of neuroinflammation at the 300FPI. Animal stool was collected at90 DPI to assess the gut microbial community structure via 16s RNA gene amplicon sequencing.

Research Objectives

To develop a basic understanding of the mechanisms within the Brain Gut Axis that impact TBI outcomes. We hypothesized that post-injury treatment with Short Chain Fatty Acids (SCFA), metabolites of commensal gut bacteria, would attenuate neurocognitive deficits after TBI in mice.

SCFA Treatment Decreases White Matter Loss and Behavioral Deficits

Microglial Gene Expression Altered by Injury and Treatment

(A) TBI is known to impede Fractional Anisotropy (white matter connectivity) in the brain. We used MRI scans of animals to measure FA through water diffusivity (GODPI). SCFA treated TBI mice were comparable sham (NS) and showed significant difference from untreated (p<0.0001 vs. control). SCFA white matter connectivity was improved compared to sham. (B) CSA White matter connectivity protections correlated well with amelioration of behavioral deficits in TBI. While untreated animals showed an increase in aggressive/seeking behaviors compared to Sham (p<0.0001), SCFA treatment decreased TBI induced aggression by nearly 2/3 compared to the TBI group (p<0.0001). (Two-way ANOVA)

Limitations

• Limitations to SCI include the need for craniotomy and the expense of acquiring the impactor and actuating device.
• There is a dearth of consistent foundational literature highlighting TBI in females. As sex is a confounding factor in TBI, female mice are being assessed in a separate study.

Conclusions

• In the context of a TBI, short chain fatty acid treatment improved white matter connectivity and protected species normal behavior patterns. SCFA administration also protected a limited number of healthy microbial species within the gut and attenuated microbial inflammatory gene expression, increasing the expression of protective heat shock protein gene within microglia.
• These data highlight the potential of SCFA to mimic some of the benefits of FMT as a novel therapeutic intervention for TBI. FMT is already an established, albeit non-traditional, therapy for other clinical disease entities; repurposing FMT and the addition of SCFA administration for TBI treatment may represent a novel treatment paradigm for an injury process that is notorious for having few treatment options other than supportive care.