Short Chain Fatty Acid Supplementation After Traumatic Brain Injury Attenuates Neurologic Injury Via the Gut-Brain-Microgilia Axis

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Background

Tissue destruction caused by traumatic brain injury (TBI) is an underlying risk of 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, fecal microbiome transplantation (FMT) can reverse TBI-induced depletion of commensal bacteria, preserve white matter connectivity, protect cognition, and decrease brain lesion size in mice after TBI. The mechanisms that underly gut bacterial modulation remain unclear.

Research Objectives

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.

Methods

14-week-old (n=52) male C57BL/6J underwent TBI via controlled cortical impact vs sham injury. Post-TBI, each group was treated with acetate, butyrate, and propionate vs. a saline vehicle via free access to drinking water for four weeks post-TBI.

- Magnetic Resonance Imaging: White matter and cortical volume loss measured at 60 days post-injury (DP).
- Behavioral Analysis: Open field testing to measure anxiety levels (50 DP).
- Neuroinflammation: Brain microglia extracted to assess signs of neuroinflammation at (30 DP).
- Microbiome Analysis: Animal stool collected to assess microbial community structure via 16S RNA gene amplicon sequencing at (50 DP).

SCFA Treatment Decreases White Matter Loss and Behavioral Deficits

A) TBI is known to impair Fractional Anisotropy (white matter connectivity) in the brain. We used MRI scans of animals to measure FA through water diffusion (BDH). SCFA treated TBI mice were comparable sham (NS) and showed significant difference from untreated injured animals (p-value <0.05 (N=5)). B) Representative 3D contrast T2 weighted MR images. C) Representative renderings of white matter connectivity. D) Open Field test used to measure Levels of Anxiety/Seeking behavior. SCFA White matter connectivity protections correlated well with amelioration of behavioral deficits in TBI. While untreated animals showed an increase in aggressive/seeking behavior compared to Sham (p<0.001), SCFA treatment decreased TBI induced aggression by nearly 1/3 (p<0.001) compared to the TBI groups (p=0.012) (Two-way ANOVA).

Microglial Gene Expression Altered by Injury and Treatment

(A) Immune cells extracted & sorted. B) Immune cell proportions were revealed to be altered by injury and treatment. C) C57BL/6 mice (microglia) were grouped by gene expression according to function. C) Plot demonstrates clear clustering of different microglial phenotypes due to treatment/injury (2D genomics). D) Volcano plot revealed functional gene expression decrease neuropeptidergic heat shock genes and neuroregeneration-linked Us2s and Gapah in TBI mice compared to sham. E) volcano plot revealed functional gene expression increased neuroprotective heat shock genes and decreased neuroregeneration-linked Us2s and Gapah in treated TBI mice compared to untreated.

Limitations

- Limitations to CCI 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

- SCFA treatment improved white matter connectivity, protected normal behavior patterns, and maintained healthy gut microbial species, while reducing microglial inflammatory gene expression and increasing protective heat shock protein gene expression.
- These data suggest SCFA could mimic benefits of FMT for TBI treatment, offering a novel therapeutic approach for an injury with limited treatment options.

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