Oral Administration of CBD Improves Cognitive and Histopathological Outcomes Following Traumatic Brain Injury

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Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability. Currently, there is a lack of treatment options to lessen the negative impact that injury-induced comorbidities have on long-term quality of life. Cannabidiol (CBD) is a nonpsychoactive, plant-derived compound that has beneficial outcomes in several nervous system disorders due to its anti-inflammatory and anti-apoptotic properties. In the present study, we sought to evaluate a clinically-relevant oral administration of CBD to investigate its potential to mitigate TBI-induced pathology in a preclinical model of TBI.

Methods

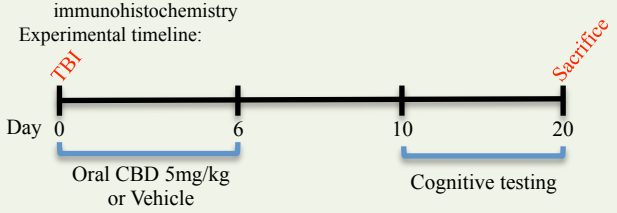
Surgery and treatment:

- Adult rats were exposed to a moderate fluid-percussion pulse over the right parietal cortex
- CBD (5 mg/kg) in 1 ml of peanut oil (or vehicle/peanut oil alone) was orally gavaged 1 hour post surgery, followed by 1x/day for 6 consecutive days

Outcome measures:

- Spatial memory – Morris Water Maze
- Cytoprotection – Volumetric analyses of contusion and cortical atrophy
- Neuroinflammation – Microglia reactivity using Iba1 immunohistochemistry

Experimental timeline:



Results

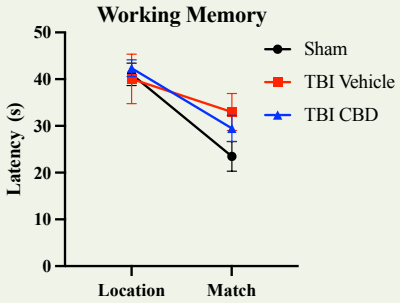


Fig 1. Short-term/working memory performance of TBI/CBD animals trended positively toward significance. Treated animals recalled match location more similarly to the Sham control group while TBI/Vehicle animals had worsened latencies

Results

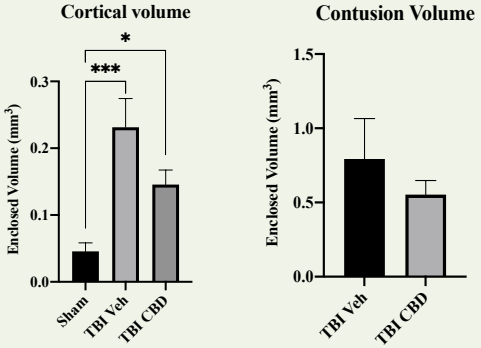


Fig 2. 3 weeks after injury, animals were sacrificed for histological assessment. Non-biased stereological volumetric analyses revealed that injured animals given CBD trended positively towards normalization of cortical volume atrophy (left panel) and exhibited reduced cortical contusions relative to injured vehicle-treated animals (right panel).

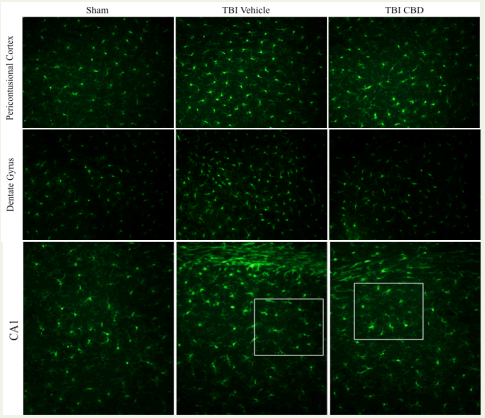


Fig 3. Immunohistochemical analyses showed normalization of injury-induced Iba+ microglia changes with CBD administration. In pericontusional cortex (top) there was a reduced density of Iba1+ cells after treatment. In the ipsilateral hippocampus, Iba1+ cells in dentate gyrus (middle) appeared significantly greater in number in control animals compared to CBD group. In CA1 (bottom), while no overt differences were observed in cell density, reactive morphological alterations were more pronounced in the injured-vehicle group. Boxes demarcate representative cells in which changes could be compared. TBI/Vehicle had cells with shorter thicker processes and compact cell bodies, while CBD-treatment seemed to reduce reactive microglia morphology, resembling sham animals to a greater degree.

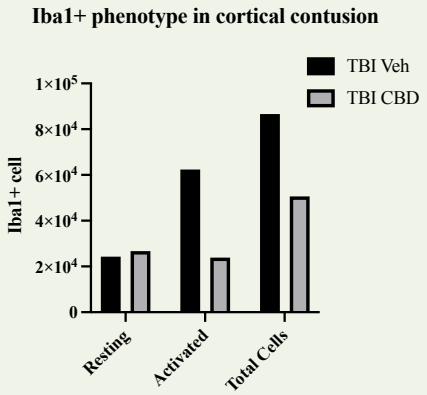


Fig 4. In the cortical penumbra, preliminary quantitative analyses showed CBD administration significantly decreased activated microglia phenotypes and reduced overall microglia numbers, two hallmark indicators of TBI-induced neuroinflammation

Conclusions

CBD has been shown to mediate neuroprotection and inflammatory pathways. We anticipated clinically-relevant oral administration would mitigate some of the behavioral deficits, degree of cytoarchitecture disruption, and reduce neuroinflammatory responses after moderate TBI. While positive trends were present, there was a lack of strong significance. However, because preliminary analyses showed reduction in microglial reactivity and overall numbers and positive trends in behavioral and histopathological outcomes, we propose that a higher oral dose may be more efficacious in reversing neuropathological sequelae. While the therapeutic potential of CBD after brain injury has yet to be fully elucidated, its neuroprotective, anti-apoptotic, and anti-inflammatory properties make it a promising therapeutic avenue to further pursue.

Future Directions

- Complete stereological analyses characterizing activated phenotypes and quantity of Iba1+ cells in cortical penumbra and in hippocampus
- Assess administration of higher doses of CBD
- Investigate alternative time points for behavioral testing and possible higher-sensitivity behavior paradigms

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