ORAL CANNABIDIOL PREVENTS ALLODYNIA AND NEUROLOGICAL DYSFUNCTIONS IN A MOUSE MODEL OF MILD TRAUMATIC BRAIN INJURY

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Introduction: Traumatic brain injury (TBI) is a complex injury with a number of symptoms accompanied by inflammatory process and cell death. It is characterized by an initial neuroinflammation, mediated by a rapid glia cells activation, peripheral immune cells recruitment and secretion of inflammatory cytokines, followed by the late appearance of psychologically debilitating symptoms and cognitive impairments. Despite recent advances in the knowledge of TBI pathophysiology, no adequate pharmacotherapies are currently available. A growing body of evidence suggests that the pharmacological manipulation of endocannabinoids (ECs) attenuate neuroinflammation and improve the recovery of neurobehavioral functions during the early weeks after TBI. To our knowledge, no studies have evaluated the effects of cannabidiol (CBD) on the neurological dysfunctions associated with the TBI. The phytocannabinoid CBD, the major non-psychoactive constituent of *Cannabis sativa*, exhibits a broad spectrum of potential therapeutic properties, including neuroprotective effects in Central Nervous System (CNS) disorders. CBD has very low affinity for cannabinoid receptors type 1(CB1) and type 2(CB2), whereas different mechanisms, such as inhibition of anandamide uptake and enzymatic hydrolysis, and decrease of adenosine reuptake, are believed to be responsible for its neuroprotective effects.

Materials and methods: Male C57BL/6mice (Charles River, Italy) weighing 18–20 g were housed three per cage under controlled illumination. CBD and vehicle were kindly provided by Enecta Group, Bologna (BO),Italy CBD was dissolved in hemp seed oil and natural tocopherols, used as vehicle. Time points of evaluations were based on our previous study. Behavioral tasks were performed at different time points and scheduled in order to avoid carry-over effects from prior testing experience. Precisely, was evaluated pain by Von Frey Test 7,14, 21and 34days after trauma; Motor coordination by Rotarod Test 7, 21and 60 days after trauma; Aggressiveness (Resident Intruder Test), depression (Tail Suspension Test), motor activity (Open Field Test) and anxiety was performed 14and 60 days after trauma. Moreover, we evaluated the neurotransmitter release by microdialysis/ HPLC analysis at 60 days after trauma, not only we also evaluated the social behaviour by Three Chambers Sociability 60 days after trauma.

Results: Oral CBD treatment, at the dose tested, does not change the normal attitude, in term of locomotion, nociception or emotional behavior, in not-injured animals. TBI mice developed chronic pain associated with anxious and aggressive behavior, followed by a late depressive-like behavior and impaired social interaction. Such behaviors were related with specific changes in neurotransmitters release at cortical levels. CBD oral treatment restored the behavioral alterations and partially normalized the cortical biochemicalchanges.

Discussion and conclusions: Neurological dysfunctions are the most impactful and persistent consequences of traumatic brain injury. In the present study, we demonstrated that the repeated treatment with commercially available 10% CBD oil exerts beneficial effects on the behavioral dysfunctions associated with TBI. mTBI mice presented a typical phenotype, characterized by chronic pain and an aggressive behavior followed by a depressive-like behavior. The impaired social activity was also observed in the three-chamber sociability task, suggesting a general illness, often reported in patients with TBI. CBD significantly prevented all these effects. Such behaviors were related with specific changes in neurotransmitters release at cortical levels. CBD oral treatment partially normalized the cortical biochemical changes. In conclusion, our data show some of the brain modifications probably responsible for the behavioral phenotype associated with TBI and suggest the CBD as a pharmacological tool to improve neurological dysfunctions caused by the trauma.