Concussion and cannabinoids

Introduction

Concussion, commonly known as a mild traumatic brain injury (mTBI), is a prevalent form of TBI, accounting for 75–85% of all TBIs occurring in civilian[1] and military populations[2]. Short-term memory and attention impairments are typical symptoms of mTBI. Recent studies have revealed that repetitive concussions can lead to significant long-term emotional and cognitive disabilities and even early death[3], especially in vulnerable populations such as athletes involved in contact sports and military personnel. Despite the short-lived symptoms, physiological damage may persist beyond the point of clinical recovery[4], indicating physiological disruptions of neurological function induced by the trauma[5]. Currently, no pharmacological treatment options are available for those with an mTBI. However, research suggests that targeting the endocannabinoid system may provide a potential avenue for treatment.

Current knowledge suggests the endocannabinoid system comprises two well-characterised endogenous ligands, *N* -arachidonoylethanolamine (anandamide; AEA) and 2-AG, which can bind to at least two G-protein-coupled receptors, cannabinoid receptors CB_1 and CB_2[6]. The CB_1 receptor is abundant in the brain and is also present in other tissues and organs of the body. In contrast, CB_2 receptors are exclusively expressed in immune cells, including T and B lymphocytes and macrophages[8]. Cannabinoids are a family of compounds that can act on CB_1 and CB_2. There are three predominant categories of cannabinoids:

1. plant-derived phytocannabinoids[10];
2. synthetically produced cannabinoids used as research[11] or recreational drugs[12]; and
3. the endocannabinoids, which are endogenous CB_1 and CB_2 receptors, such as AEA[13] and 2-AG[14,15].

It is believed that the body's cannabinoid receptor system may play a part in protecting the nervous system following trauma. Recently reviewed (Pisani *et al.* [6]), cannabinoid CBD has neuroprotective, antiepileptic, hypoxia-ischemia, anxiolytic, antipsychotic, analgesic, anti-inflammatory, anti-asthmatic, and antitumor properties. Whilst there is no direct evidence of CBD offering therapeutic benefits following concussion, similar neuromolecular cascades have been observed in Alzheimer's disease and oxidative brain injury. mTBI induces inflammation, impairs oxidative metabolism, and induces an energy crisis, hinting at a target for CBD.

Studies of cannabinoids and head injury

Evidence for the role of the endogenous cannabinoid system in maintaining the balance of inflammation and CNS after an injury is growing[16-18]. 3 preclinical studies have been conducted on mTBI[17,19,20] whereby investigators treated mice with analogs of endogenous cannabinoids, anandamide and 2-AG (reviewed by Schurman & Lichtman, 2017[21]). The authors summarise that following a head injury, the brain levels of 2-AG and anandamide rapidly increase and decrease, suggesting a role for these cannabinoids in managing head injury. When these groups artificially increased the levels of 2-AG and anandamide following this injury, a type of 'topping up', mice were observed to recover more quickly than their controls[17,19,20].

In a model of hypoxia-ischemia (HI) brain injury, where restricted blood flow/oxygen causes this injury, Pazos *et al*.[22] found that "CBD administration after injury led to long-lasting neuroprotection." They found that dosing with CBD after the brain injury reduced the volume and extent of brain damage, inhibited excitotoxicity, and oxidative stress, reduced brain inflammation, and prevented neurological behaviour impairment in *in vitro* and *in vivo* models. The researchers observed that overall, rats with HI brain injury had long-lasting functional impairments, whereas the rats with CBD after the injury had functional results similar to control with no HI injury.

Finally, one phase II study examined the effect of administering dexanabinol, a synthetic, terpene-based cannabinoid derivative, to patients following a severe traumatic brain injury [23]. However, no differences in outcomes were observed when compared to the placebo.

The positive effect of CBD on the brain is compelling and could offer therapeutic options for those with an mTBI injury. Strong arguments are made for *whole plant extracts* due to synergism with the presence of other plant compounds such as terpenoids, flavonoids and other cannabinoids (i.e. "the entourage effect"[24]).

Summary notes/articles:

- Review of the endocannabinoid system to treat post-traumatic headaches[16]. This article has a good executive summary (at the end).
- A dense newer review of CBD and concussion[25], lead author is Singh *et al.* 2020 – article attached.
- Great summary of large research groups working in this space and a summary of science: https://www.concussionalliance.org/cannabis-research.
- Sports performance and CBD were reviewed by McCartney *et al.* 2020[26] and Ware *et al.* 2018[27].

Mouse studies attached:

- This study inhibited the enzyme that breaks down 2-AG. They argue this could be a form of treatment[17].
- A mouse study of TBI[19], the authors inhibited the breakdown of 2-AG and AEA.
    - Astrocyte and microglia activation was blocked, and BBB integrity was maintained following TBI using both 2-AG and AEA enzyme inhibitors
    - Improved neurological and behavioural function was observed with 2-AG enzyme inhibitors
    - No difference in measured interleukins, chemokines, TNFa, COX2 or NOX2 was observed between treatment groups
- Another mouse study of repetitive mTBI. 2-AG enzyme inhibitors promoted neurologic recovery
    - ↓ proinflammatory cytokines, astroglial reactivity, expression of amyloid precursor protein and enzymes that make Aβ and formation of Aβ
    - neurodegeneration, TDP-43 protein aggregation, and tau phosphorylation were suppressed following 2-AG enzyme inhibition

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