

Cannabis and Health

Module 11: Neurocognitive/Brain Disorders Part I

Lecture 6: Cannabis and Traumatic Brain Injury

Cannabis as a Treatment for Brain Injuries: Overview



- There is a small body of literature reporting neuroprotective effects of cannabinoid analogues in preclinical studies of head injuries
- There are also several observational studies in humans
- Currently there are no good- or fair-quality systematic reviews evaluating the efficacy of cannabinoids as a treatment or prevention for traumatic brain injury

Cannabis as a treatment for brain injuries

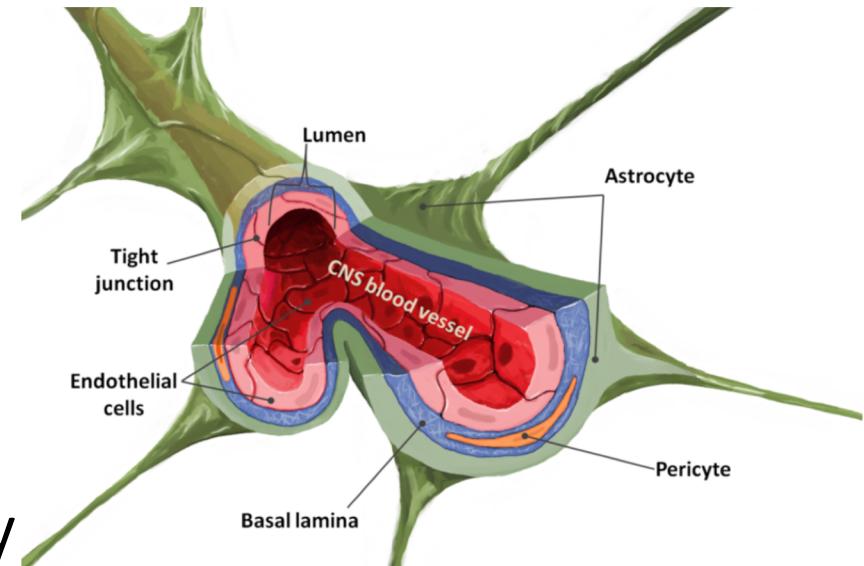
- **There is limited evidence of a statistical association between cannabinoids and better outcomes (i.e., mortality, disability) after a traumatic brain injury**
- However, there are only 2 existing high-quality studies
- Both are observational studies
 - Hard to draw meaningful conclusions about causality
 - more conclusive observational studies or randomized controlled trials are needed

TBI and the Endocannabinoid System

- Endocannabinoids appear to be neuroprotective against brain injury
- In response to traumatic brain injury, there is a local and transient accumulation of the endocannabinoid 2-AG at the site of injury
 - peaks at 4 h and can be sustained up to 24 h
- 2AG inhibits expression of pro-inflammatory cytokines and other mediators of inflammatory signaling in the brain
- 2AG suppresses formation of *reactive oxygen species* in head injury in mice
- Administration of 2AG associated with better function recovery after head injury in mice
- Most studies suggest that 2-AG effects on brain trauma are CB₁ dependent

TBI and the Endocannabinoid System— The Blood Brain Barrier

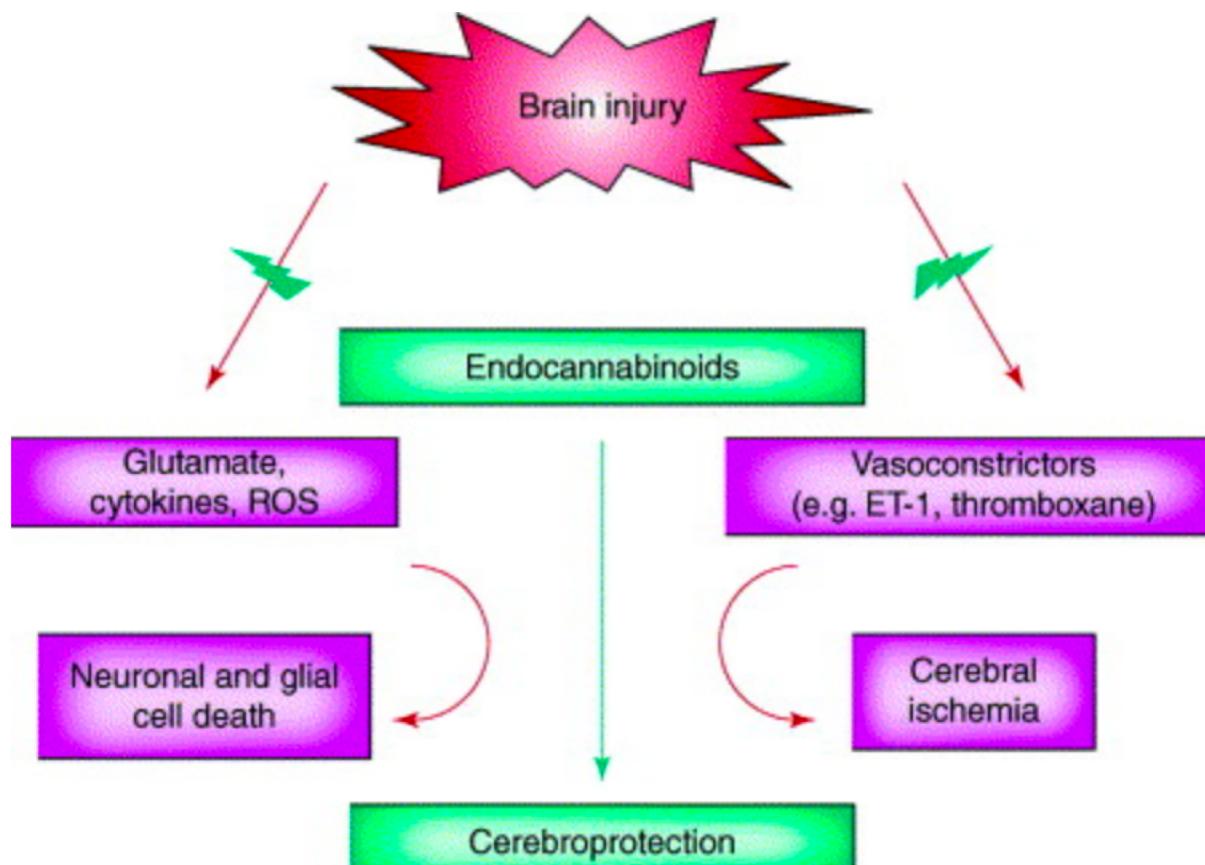
- One early harmful event in TBI is disruption of blood brain barrier (BBB)
 - allows infiltration of peripheral inflammatory mediators into brain tissue
- 2-AG has been shown to robustly reduce BBB disruption in animal models of head trauma
 - This may explain the ability of 2AG to aid in functional recovery and reduce edema in the brain after TBI
 - Important insight: 2AG acts EARLY in post-TBI response to decrease inflammation in brain



TBI and the Endocannabinoid System: Vasoconstriction

- Endothelin (ET) likely contributes to brain damage and cell death following TBI
- ET plays a significant role in cerebral circulation
 - produces vasoconstriction to reduce blood flow
- **Endocannabinoids (2-AG) can counteract the vasoconstrictory effects of ET-1**
- This one mechanism through which endocannabinoids are thought to exert cerebroprotection effects after brain injury

TBI and Endocannabinoids-- Overview



CBD and TBI: Preclinical Data

- Newborn rats underwent hypoxia-ischemia (oxygen deprivation) brain injury and then received vehicle (control) or CBD treatment
- CBD modulated brain excitotoxicity, oxidative stress and inflammation seven days after injury
- CBD reduced brain infarct volume by 17% and lessened the extent of tissue damage
- CBD decreased impairments in neurobehavioral function
- Overall conclusion= CBD administration after brain injury to newborn rats led to long-lasting neuroprotection

CBD and TBI: Preclinical Data

- Similar findings in study of newborn pigs
 - Newborn piglets exposed to acute hypoxia-ischemia received i.v. cannabidiol or vehicle
 - CBD group recovered brain function as measured by EEG
 - Neurobehavioral functioning was also normalized in CBD group
 - Tissue damage, such as increased inflammatory mediators, was suppressed in CBD group
 - Overall conclusion is post-injury administration of CBD protects neurons and astrocytes, leading to histological, functional, biochemical and neurobehavioral improvements.

THC and TBI

- Limited existing preclinical literature
 - THC protects against neuronal ouabain-induced excitotoxicity in neonatal rats (Van der Stelt, *et al.* 2001)
 - Ouabain is a toxic compound used to produce brain damage in animal models
 - The same research group showed similar effects of the endogenous cannabinoid anandamide
 - Thus, neuroprotective effects likely have to do with CB₁ activity
 - But many questions remain and future research is needed in humans and animals to better understand these effects!

Cannabis and TBI—Potential for Humans?

- **Two existing fair- to high-quality observational human studies found in the literature**
 - One study ($n = 446$) examined the TBI presentation and outcomes among patients with and without a positive THC blood test (Nguyen et al., 2014).
 - Patients who were positive for THC were more likely to survive the TBI than those who were negative for THC
 - These authors accounted for confounding variables (e.g., age, alcohol, Abbreviated Injury Score, Injury Severity Score, mechanism of injury, gender, and ethnicity).

Cannabis and TBI—Potential for Humans

- The other study was a study of intracranial hemorrhage (ICH) patients ($n = 725$) (Di Napoli et al., 2016)
- Found that individuals with a positive test of cannabis use demonstrated better primary outcome scores
- Authors adjusted for confounding variables known to be associated with worse ICH outcomes, including age, sex, Glasgow Coma Scale as continuous variables, and anticoagulant use

Research Challenges

- We can't randomly assign human subjects to get brain injuries
 - Difficult to draw meaningful conclusions from only observational studies
- TBI often co-occurs with other disorders such as PTSD and depression
 - Complicates treatment and research
- Limited amount of preclinical literature on cannabinoids and TBI
- Many questions remain regarding human translation!

Conclusions

- There is a lot that we do not know about cannabinoids and TBI
- Limited evidence that cannabinoids may be neuroprotective and helpful
- Difficult to do studies in humans
- More work in this area is needed!