MECHANISTIC REVIEW OF POTENTIAL ROLE FOR CANNABIDIOL IN ANEURYSMAL SUBARACHNOID HEMORRHAGE

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Subarachnoid hemorrhage (SAH) is a major health burden that affects roughly 9 out of 100,000 people worldwide and accounts for approximately 5% of strokes.\(^1\)

Delayed Cerebral Ischemia (DCI) is a major factor associated with patient mortality following SAH and is often a result of cerebral vasospasm (CV).\(^2\)

Cannabidiol (CBD) is emerging as a prominent drug for many therapeutic purposes including epilepsy, anxiety, and pain relief.\(^3\)

**Background**

- Subarachnoid hemorrhage (SAH) is a major health burden that affects roughly 9 out of 100,000 people worldwide and accounts for approximately 5% of strokes.\(^1\)
- Delayed Cerebral Ischemia (DCI) is a major factor associated with patient mortality following SAH and is often a result of cerebral vasospasm (CV).\(^2\)
- Cannabidiol (CBD) is emerging as a prominent drug for many therapeutic purposes including epilepsy, anxiety, and pain relief.\(^3\)

**Objectives**

- Review the known molecular mechanisms of SAH pathophysiology CBD pharmacology.
- Consider, based on the literature, the effects that each of these processes have on the physiologic environment.
- Address and describe mechanistic correlations found between CBD and SAH.
- Using these findings, evaluate the use of CBD as a potential therapeutic agent for post-SAH critically ill patients.
METHODS

- Using PubMed, the following terms were searched:

- Search results were manually reviewed. Article relevance was determined by the researcher’s discretion.

- Correlations between the molecular mechanisms of SAH pathophysiology and CBD pharmacology were categorized based on their physiologic effects.

- Conclusions were drawn based on the extent of literature on and the specificity of these correlations.

- PRISMA guidelines were followed.
The pharmacologic mechanisms of CBD were correlated with SAH pathophysiology into the following three major therapeutic categories. Each category depicts the physiologic outcomes associated with the specific molecules involved. These molecular mechanisms are listed below.

**Vascular Effects**
- In stressful molecular environments, CBD produces arterial vasodilation by inhibiting calcium channels.
- Through the allosteric actions with $5$-$HT_{1A}$, CBD has been shown to increase cerebral blood flow and attenuate ischemia-reperfusion in middle cerebral artery occlusion models.

**Anti-Inflammation**
- CBD down regulates the expression of adhesion molecules VCAM-1 and ICAM-1.
- CBD decreases expression of the pro-inflammatory cytokines IL-1β and TNF-α, among others.
- CBD decreases production of the transcription factor NF-κB.
- CBD inhibits other molecules important in pro-inflammatory cytokine regulation such as HMBG1.
- CBD reduces neutrophil infiltration & microglia proliferation after cerebral ischemia.

**Neuroprotection**
- CBD has antioxidant effects that reduce the expression of reactive oxygen species.
- By regulating the expression of glutamate, CBD reduces excitotoxicity.
- CBD induces neurogenesis & improves cognitive recovery after neurological injury.
- By inhibiting the activity of apoptotic molecules such as caspase-3, CBD reduces neuronal apoptosis & necrosis.
RESULTS CONT.

Figure 1: Potential Therapeutic Effects of Cannabidiol on Subarachnoid Hemorrhage Pathophysiology
DISCUSSION

- Anti-inflammation has the most evidence of being the major therapeutic effect of CBD in SAH based on the number of molecular correlations found and the extent by which these were described in the literature.
- By reducing infarct following ischemia, decreasing immune-mediated inflammation, and inducing vasodilation, CBD may be protective by lowering the incidence and/or degree of DCI as a result of cerebral vasospasm following SAH.
- The excitotoxicity and oxidative stress that occur in the acute phase of SAH pathology may be attenuated by CBD.
- CBD has been shown to have neuroprotective effects that may provide positive therapeutic outcomes following SAH and DCI by attenuating ischemia/reperfusion infarction, reducing neuronal apoptosis, and inducing both neurogenesis and cognitive recovery.
CBD’s main pharmacologic mechanisms that have potential therapeutic effects involve antagonizing or attenuating several known molecules or molecular changes important in SAH pathophysiology.

Anti-inflammation was found to be the most significant and promising therapeutic effect CBD may have if administered following SAH.

The anti-inflammatory, vascular, and neuroprotective effects of CBD provide plausible mechanisms by which CBD has potential as being a secondary treatment for post-SAH critically ill patients.
REFERENCES

