Cannabidiol Reduces Inflammation: A Narrative Review

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Abstract

Cannabidiol (CBD) has become well-known for its variety of therapeutic benefits. Research shows antinociceptive, anticonvulsant, anxiolytic, neuroprotective, and anti-inflammatory properties of CBD. This narrative review will discuss the anti-inflammatory properties of CBD as found in research to date. First-line inflammatory response involves proinflammatory cytokine and chemokine production, nitric oxide production, vasodilation, leukocyte rolling, and release of endocannabinoids. If first-line inflammation becomes chronic, due to loss of immune homeostasis, inflammation can lead to debilitating and life-threatening diseases. CBD directly and indirectly interacts with multiple receptors and enzymes to reduce inflammation. This review describes CBD’s possible mechanisms of action that lead to inflammatory relief.

Introduction

Cannabidiol (CBD) is a non-psychoactive component of the cannabis plant, Cannabis sativa, that has become popular for its health benefits. After extraction from the cannabis plant, lipophilic CBD is often added to carrier oils that can be applied orally and creams that can be applied topically. While CBD-infused drinks and foods have become prevalent in stores and online, most research involves CBD in carrier oils and creams. Though derived from a plant, CBD is chemically similar to endogenous cannabinoids and can interact with the body’s endocannabinoid system. The interactions between CBD and the endocannabinoid system helps the body maintain immune and nervous homeostasis. CBD is considered a multitarget drug because it is able to interact with multiple endogenous receptors and enzymes to relay a variety of benefits. At low doses CBD exerts antinociceptive, anti-inflammatory, antioxidant and neuroprotective effects, and at high doses CBD has been shown to treat psychiatric disorders. Some studies suggest CBD may even be used to attenuate nausea and acne. This review will focus on the anti-inflammatory properties of CBD.

Studies suggest that CBD is effective at reducing inflammation associated with inflammatory bowel diseases, arthritis, atherosclerosis, and neurodegenerative diseases amongst others. This review will describe inflammatory processes that lead to inflammatory diseases and CBD’s role in attenuating inflammation.

First-Line Inflammation

Inflammation is a protective immunovascular response to stimulation by pathogens or endogenous signals such as damaged cells. Inflammation is largely regulated by cytokines and chemokines, which play a leading role in immunological responses, stem cell development, and cell-to-cell communication. A study by Netea et al. summarized the first-line inflammatory response to stimulation from pathogens or endogenous signals. They described that immune cells such as macrophages, neutrophils and dendritic
cells express germline-encoded pattern recognition receptors that receive the stimulation. Once stimulated, the immune cells release pro-inflammatory cytokines and chemokines, which induce the release of histamine from mast cells. Histamine will then travel through the interstitial fluid to capillary endothelial cells. When in contact with blood vessels, histamine causes vasodilation, allowing localized permeability across blood vessel walls. Proinflammatory cytokines and chemokines, as well as nitric oxide production, can then recruit leukocytes through the permeable blood vessels, a process called leukocyte rolling. These leukocytes such as macrophages and neutrophils are responsible for phagocytizing the cause of injury and clearing necrotic cells. During the first-line inflammatory response, proinflammatory cytokines and chemokines also mediate the production and release of endogenous cannabinoids, which can positively or negatively influence inflammation. 2-arachidonoyl-glycerol (2-AG) is an endogenous cannabinoid that activates CB2 receptor to further promote proinflammatory cytokines, nitric oxide production, and leukocyte rolling. On the other hand, N-arachidonoylethanolamine (AEA) reduces cytokine release and nitric oxide production, thereby reducing leukocyte rolling and the overall inflammatory response.

While this brief description gives a general overview of first-line inflammatory response, inflammation is an intricate immune response with many other influential factors. With such a plethora of influential factors, it is difficult for the body to maintain immune homeostasis. If this first-line inflammatory response becomes persistent, due to loss of immune homeostasis, inflammation may become chronic and lead to infiltration of inflammatory cells, overexpression of pro-inflammatory genes, and dysregulation of cellular signalling. Chronic inflammation is the driving factor in many serious diseases. Indeed, studies suggest inflammation is not only a major contributor in age-related conditions, but the driving factor in atherosclerosis, neurodegenerative diseases, hepatic inflammatory diseases, lung disease, chronic kidney disease, inflammatory bowel diseases, cancer, and autoimmunity.

**CBD as an Anti-Inflammatory Agent**

Because persistent first-line inflammation is the driving factor to many serious diseases, the need arises for safe anti-inflammatory agents. The World Health Organization stated that there is no evidence of public health-related problems associated with pure CBD treatment. Furthermore, they concluded from research to date that CBD exhibits no effects indicative of abuse or dependency. Studies repeatedly show anti-inflammatory properties of CBD, suggesting that CBD is a safe, effective anti-inflammatory agent.

CBD’s mechanisms of action to provide inflammatory relief are unclear, however preclinical trials have developed some possible direct and indirect mechanisms. The following will describe direct and indirect interactions with cannabinoid receptor 2 (CB2), transient vanilloid receptor subfamily group member 1 (TRPV1), adenosine A2 receptor (A2a), G protein-coupled receptor 55 (GPR55), and peroxisome proliferator-activated receptor γ (PPARγ). Because CBD is a multitarget drug, it may simultaneously interact with some or all of the listed receptors to relay anti-inflammatory benefits.

**Indirect Mechanisms of Action**

CBD can indirectly activate receptors and inhibit proinflammatory factors by increasing concentrations of AEA. CBD increases the concentration of AEA by inhibiting the degradation of AEA. Without the influence of CBD, AEA activates endocannabinoid receptors then is quickly degraded into arachidonic acid. Though a short duration of action, AEA can modulate nociception, inflammation, and oxidative stress by activating CB2 and TRPV1. In the degradation process, AEA is...
transported from endocannabinoid receptors to the endoplasmic reticulum by fatty acid binding protein transporters (FABPs) \(^{21}\). In the endoplasmic reticulum, fatty acid amide hydrolase (FAAH) is responsible for inactivating AEA via catabolism \(^{21}\). CBD binds to FABPs so that AEA is not delivered to FAAH. With the influence of CBD, AEA is not degraded or inactivated, which increases the levels of endogenous AEA and prolongs the duration of its therapeutic effects.

CBD has low affinity for CB2, meaning CBD shows agonism at CB2 at concentrations that are not pharmacologically relevant \(^{5}\). CB2 is expressed in areas of the brain and in myeloid, microglia, macrophage, lymphoid, and mast cells \(^{21,8,5}\). Studies show that deletion of CB2 receptor caused an inflammatory phenotype to worsen due to an upregulation of immune cell functions \(^{23,24}\). Though CBD has a low affinity for CB2, CBD may indirectly activate CB2 through elevation of AEA concentrations, which is a partial agonist at CB2 \(^{5,6}\). Studies show AEA bound to CB2 negatively regulates inflammatory responses like cytokine release, nitric oxide production, and leukocyte rolling in human and murine models \(^{14,13,15,16}\). A study by Sancho et al. showed elevated concentrations of AEA inhibiting tumor necrosis factor alpha (TNF-\(\alpha\))-induced NF-\(\kappa\)B activation \(^{25}\). This means, AEA inhibits the cytokine, TNF-\(\alpha\), that activates a proinflammatory transcription factor, ultimately reducing inflammation. Some studies even show increased production of the anti-inflammatory cytokine, IL-10, by cells treated with AEA \(^{22}\). Additionally, in-vivo studies by Krustev et al. showed elevation of AEA concentration by inhibition of FAAH attenuates inflammatory pain in murine models of osteoarthritis \(^{26}\).

With the influence of CBD, AEA is at high enough concentrations to agonize TRPV1 \(^{7}\). TRPV1 is a Ca\(^{2+}\) channel expressed on nociceptive neurons that changes the charge gradient across neuron membranes in response to injury \(^{27}\). The change in charge gradient allows release of glutamate, the main neurotransmitter involved in the sensation of pain. Not only does activation of TRPV1 induce pain signaling, but it promotes the release of vasodilating neuropeptides that enhance neurogenic inflammation and leukocyte rolling \(^{7}\). Based on these facts, agonism at TRPV1 would lead to increased pain and inflammation.

However, constant activation of TRPV1 will lead to desensitization of the Ca\(^{2+}\) channel, which decreases the release of glutamate and vasodilating neuropeptides \(^{1,6,7}\). Indeed, a literary review by Barrie et al. concluded FAAH inhibition mediates inflammation by down regulating cytokine production and desensitizing TRPV1, resulting in pain and inflammatory relief \(^{6}\).

**Direct Mechanisms of Action**

CBD can directly antagonize GPR55 to attenuate inflammation. GPR55 is frequently expressed in dorsal root ganglia that convey pain signals from muscles, joints, and skin and is expressed in the brain \(^{28}\). Like TRPV1, GPR55 exerts its effects by changing the charge gradient across neuron membrane \(^{29}\). Unlike TRPV1, GPR55 is not an ion channel, but modulates the activity of ion channels. Staton et al. showed that deletion of GPR55 in mice regulated proinflammatory cytokines \(^{30}\); moreover, activation of GPR55 aids in the recruitment of proinflammatory responses \(^{1,29,30}\). Because CBD is a full antagonist at GPR55, CBD inhibits the activation of GPR55. This means that anti-inflammatory effects of CBD may be performed through antagonism at GPR55. Hammell et al. observed reduced release of proinflammatory cytokines after CBD administration in vivo and in vitro; they attributed the anti-inflammatory effects to CBD’s interactions with TRPV1 and GPR55 \(^{1}\).

CBD directly interacts with PPAR\(\gamma\) to reverse vasodilation. PPAR\(\gamma\) is part of a transcription factor subfamily that controls the expression of genes involved in important functional processes like lipid, glucose and energy metabolism, adipogenesis, and inflammation \(^{31}\). CBD is an agonist at PPAR\(\gamma\), which relays a progressive vasorelaxant effect.
This action counterbalances the vasodilation associated with inflammation. Burstein et al. suggested that, through agonism at PPARγ, CBD also possesses inhibitory effects on reactive gliosis and neuronal damage that lead to inflammation. These data suggest CBD has proactive anti-inflammatory abilities through agonism at PPARγ.

A possible direct anti-inflammatory action of CBD is through agonism at A2a. A2a plays a large role in attenuating inflammation. In fact, Ohta et al. showed that genetically-modified mice without A2a are hypersensitive to inflammatory stimuli. Multiple studies report that CBD agonism at A2a reduces cytokine TNF-α production and leukocyte rolling in mice with inflammation; these effects were partially reversed by an A2a antagonist. The fact that CBD’s anti-inflammatory effects were only partially reversed by an A2a antagonist suggests that CBD interacts with more than one receptor to reduce inflammation.

Conclusions

Inflammation is an immensely intricate process that, if persistent, can lead to many serious diseases. CBD is a non-pharmaceutical treatment option for inflammation. Research repeatedly shows anti-inflammatory effects of CBD in preclinical studies. CBD directly interacts with GPR55, A2a, and PPARγ, while CBD indirectly interacts with TRPV1 and CB2 via inhibition of AEA degradation. Because CBD is a multitarget drug, it may interact with some or all of these receptors simultaneously to provide anti-inflammatory effects. Though CBD’s exact mechanisms of action are still unclear, preclinical data suggests that CBD treatment is an effective alternative to anti-inflammatory medications. While this narrative review discusses trials to 26 August 2019, exponential research on the therapeutic effects of CBD is expected. Further studies should involve long-term human use of CBD as an anti-inflammatory agent. The current data on the CBD as an anti-inflammatory agent suggests CBD is an effective treatment option for persistent inflammation.

Declarations

Availability of Data and Materials: The datasets analyzed during the current study are available in the University of Montevallo Carmichael Library or PubMed repositories, https://www.ncbi.nlm.nih.gov/pubmed/, http://libguides.montevallo.edu/index?group_id=15001

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References


