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Free Radic Biol Med. Author manuscript; available in PMC 2012 September 1.

Published in final edited form as:
Free Radic Biol Med. 2011 September 1; 51(5): 1054–1061. doi:10.1016/j.freeradbiomed.2011.01.007.

Cannabidiol as an Emergent Therapeutic Strategy for Lessening the Impact of Inflammation on Oxidative Stress

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Abstract

Oxidative stress with reactive oxygen species generation is a key weapon in the arsenal of the immune system for fighting invading pathogens and to initiate tissue repair. If excessive or unresolved, however, immune-related oxidative stress can initiate further increasing levels of oxidative stress that cause organ damage and dysfunction. Targeting oxidative stress in these various diseases therapeutically has proven more problematic than first anticipated given the complexities and perversity of both the underlying disease and the immune response. However, growing evidence suggests that the endocannabinoid system, which includes the CB_1 and CB_2 G protein-coupled receptors and their endogenous lipid ligands, may be an area that is ripe for therapeutic exploitation. In this context, the related nonpsychotropic cannabinoid cannabidiol, which may interact with the endocannabinoid system, but has actions that are distinct, offers promise as a prototype for anti-inflammatory drug development. This review discusses recent studies suggesting that cannabidiol may have utility in treating a number of human diseases and disorders now known to involve activation of the immune system and associated oxidative stress, as a contributor to their etiology and progression. These include rheumatoid arthritis, types I and II diabetes, atherosclerosis, Alzheimer's disease, hypertension, the metabolic syndrome, ischemia-reperfusion injury, depression, and neuropathic pain.

Keywords

Inflammation; Oxidative Stress; Immune System; Metabolic Syndrome; Endocannabinoid

Introduction

(−)-Cannabidiol (CBD) is the major nonpsychotropic cannabinoid compound derived from the plant *Cannabis sativa*, commonly known as marijuana. CBD was first isolated in 1940 and its structure and stereochemistry determined in 1963 [1,2]. Interest in exploiting CBD therapeutically was initially focused on its interactions with the primary psychotropic ingredient of *Cannabis*, Δ^9-THC and its sedative and antiepileptic effects, and later its antipsychotic and anxiolytic actions and utility in treating movement disorders [3]. As

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chronicled elsewhere [3], the last several years have seen a renewed interest in CBD due to the discovery of its antioxidative, anti-inflammatory, and neuroprotective effects, actions that occur for the most part independently of the canonical cannabinoid CB_1 and CB_2 receptors [1,4]. CBD may prove to have therapeutic utility in a number of conditions involving both inflammation and oxidative stress, including Parkinson's disease, diabetes, rheumatoid arthritis, Alzheimer's disease, and ischemia-reperfusion injury.

The contribution of the endocannabinoid system to inflammation and regulation of the immune system is an area of intense study that is beyond the scope of this article, and the reader is referred to several recent excellent reviews [5–8]. However, a brief overview of the system is helpful in discussing CBD. The endocannabinoid system comprises the following: (1) the G protein-coupled cannabinoid receptors CB_1 and CB_2, which are located in both the central nervous system and periphery; (2) their arachidonate-based lipid ligands, e.g., 2-arachidonoylglycerol (2-AG) and anandamide (N-arachidonoylethanolamine, AEA) and (3) the enzymes that synthesize and degrade these ligands. The endocannabinoid system plays a role in a variety of physiological processes including appetite, pain sensation, and mood. Evidence indicates that both CB_1 and CB_2 are expressed by cells of the immune system and are upregulated in the activation state. Levels of CB_2 appear to be higher than those of CB_1 with decreasing amounts of CB_2 in human B cells, NK cells, monocytes, polymorphonuclear neutrophils and T cells [6]. Macrophages and related cells, microglia and osteoclasts, express both cannabinoid receptors. CB_2 activation of immune cells is associated with changes in cytokine release and migration [6].

Biochemistry of Cannabidiol

CBD (Fig. 1) is a resorcinol-based compound that was shown to have direct, potent antioxidant properties by cyclic voltammetery and a spectrophotometric assay of oxidation in a Fenton reaction [9]. In an *in vitro* glutamate neuronal toxicity model, CBD was shown to be more protective than either α-tocopherol or vitamin C and comparable to butylated hydroxytoluene (BHT); although as noted by the authors, CBD unlike BHT does not seem to promote tumors [9]. CBD was also reported to act as an antioxidant at submicromolar concentrations in preventing serum-deprived cell death of cultured human B lymphoblastoid and mouse fibroblasts cells [10]. The antioxidant chemistry of CBD may have utility *in vivo* as well. The protective effects of CBD in a rat binge ethanol-induced brain injury model [11] and a rat model of Parkinson's disease [12] were ascribed to its antioxidant properties. As will become clear from this review, however, the anti-oxidant actions ascribed to CBD in various *in vivo* models of human diseases likely exceed those attributable to its chemistry alone. Rather, the therapeutic anti-oxidant properties of CBD would seem to result in no small measure from its modulation of cell signaling events that underlie the self-sustaining cycle of inflammation and oxidative stress.

Mechanisms of Action

Several interactions with relevance to the immune system and oxidative stress are discussed here. First, despite having low affinity for CB_1 and CB_2 receptors, CBD has been shown to antagonize the actions of cannabinoid CB_1/CB_2 receptor agonists in the low nanomolar range, consistent with non-competitive inhibition [13]. At 1–10 μM, CBD appears to function as an inverse agonist at both CB_1 and CB_2 receptors [13]. Second, CBD acts as an inhibitor (IC_{50} = 28 μM) of fatty acid amide hydrolase (FAAH), the major enzyme for endocannabinoid breakdown. Because FAAH activity correlates with gastrointestinal mobility, CBD may have utility in treating intestinal hypermotility associated with certain inflammatory diseases of the bowel [14].

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Third, CBD is a competitive inhibitor with an IC_{50} in the nanomolar range of adenosine uptake by the equilibrative nucleoside transporter 1 (ENT1) of macrophages and microglial cells, the resident macrophage-like immune cells of the brain. By increasing exogenous adenosine, which in turn activates the A_{2A} adenosine receptor, CBD exerts immunosuppressive actions on macrophages and microglial cells as evidenced by decreased TNFα production after treatment with lipopolysaccharide (LPS) [15,16]. CBD may thus be of benefit in treating neueodegenerative diseases associated with hyperactivation of microglial, as well as retinal neuroinflammation seen in such conditions as uveitis, diabetic retinopathy, age-related macular degeneration, and glaucoma. Note, however, that adenosine activates other receptors besides A_{2A} that often have opposing consequences on immune regulation and inflammation [17,18]. In several *in vivo* models of neurodegeneration or inflammation, moreover, the beneficial effects of CBD were demonstrated not to involve adenosine receptors.

Fourth, CBD has been shown to have potent actions in attenuating oxidative and nitrosative stress in several human disease models, although the exact mechanism is unclear. For instance, CBD pretreatment was found to attenuate high glucose-induced mitochondrial superoxide generation and NF-κB activation in human coronary artery endothelial cells, along with nitrotyrosine formation and expression of inducible nitric oxide synthase (iNOS) and adhesion molecules ICAM-1 and VCAM-1 [19]. Notably, high glucose-induced transendothelial migration of monocytes, monocyte-endothelial adhesion, and barrier disruption were attenuated as well. These findings lend support to the conclusion that that CBD may have therapeutic utility in treating diabetic complications and atherosclerosis. In another study, CBD was reported to reduce expression of reactive oxygen species (ROS) generating NADPH oxidases, as well as iNOS and nitrotyrosine generation in a cisplatin nephropathy model *in vivo*, consequently lessening cell death in the kidney and improving renal function [20]. From these studies, it is tempting to speculate that CBD may act directly at the level of the mitochondrion or nucleus to oppose oxidative/nitrosative stress.

Fifth, at low micromolar concentrations, CBD was found to inhibit indoleamine-2,3-dioxygenase activity thereby suppressing tryptophan degradation by mitogen-stimulated peripheral blood mononuclear cells and LPS-stimulated myelomonocytic THP-1 cells *in vitro* [21]. Based on this finding, CBD might be useful therapeutically to counter the increased risk of depression in diseases associated with immune activation and inflammation, which often lead to decreased tryptophan, the precursor of serotonin. Finally, CBD has been shown to act as an antagonist at G protein-coupled receptor 55 (GPR55) and as an antagonist or agonist at several transient receptor potential (TRP) channels; however, these observations are controversial and the pharmacophysiological significance of these interactions is not known [1,4].

Actions on Immune Cells

CBD has been shown to modulate the function of the immune system. Overall these actions may be nuanced and concentration-dependent, but in general include suppression of both cell-mediated and humoral immunity and involve inhibition of proliferation, maturation, and migration of immune cells, antigen presentation, and humoral response [1,13]. Key aspects are discussed here. In most *in vivo* models of inflammation, CBD attenuates inflammatory cell migration/infiltration (e.g. neutrophils) [22]. During neuroinflammation, activated microglial cells migrate towards the site of injury where they release pro-inflammatory cytokines and cytotoxic agents, including ROS. Although important in removal of cellular debris and fighting infection, activated microglial cells often exacerbate local cell damage. CBD was shown to inhibit activated microglial cell migration by antagonizing the abnormal-cannabidiol (Abn-CBD)-sensitive receptor at concentrations < 1 μM [23]. Evidence that the

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Abn-CBD receptor is the orphan G protein-coupled receptor GPR18 was recently reported [24]. CBD was also shown to block endotoxin-induced oxidative stress resulting from retinal microglial cell activation in uveitis [25]. CBD blocked the immediate activation of NADPH oxidase as well as a second wave of ROS formation and the associated TNFα secretion and p38 MAPK activation. The direct antioxidant property of CBD is unlikely to be the entire explanation for these actions as they occurred at a concentration of 1 μM. Inhibition of adenosine uptake as discussed previously may have been involved. However, a complete understanding of the anti-inflammatory actions of CBD on microglial cells is not yet available. Recently, through an unidentified mechanism, CBD was reported to suppress LPS-induced pro-inflammatory signaling in cultured microglial cells, including NF-κB and STAT1 activation, while enhancing STAT3-related anti-inflammatory signaling [26].

CBD induces apoptosis of monocytes and certain normal and transformed lymphocytes, including thymocytes and splenocytes, through oxidative stress and increased ROS levels [27–31]. The basis for this action appears to be glutathione depletion due to adduct formation with the reactive metabolite of CBD, cannabidiol hydroxyquinone, thereby triggering cell death through caspase 8 activation and/or the intrinsic apoptotic pathway. Increased ROS from the upregulation of NADPH oxidases via an undefined mechanism may contribute to cell death as well [31]. A recent study assessed the impact of repeated administration of relatively low levels of CBD to adult male Wistar rats on peripheral blood lymphocyte subset distribution [32]. At 2.5 mg/kg/day for 14 days, CBD did not produce lymphopenia, but increased the total number of natural killer T (NKT) cells and percentage numbers of NKT and natural killer (NK) cells. A dose of 5 mg/kg/day did have a lymphopenic effect, but by reducing B, T, Tc and Th lymphocytes. Thus, CBD would appear to suppress specific immunity, while enhancing nonspecific antitumor and antiviral immune response. As discussed by the authors [32], the lymphopenic effect of CBD was observed at a concentration shown to be efficacious in a number of animal models of neurodegenerative and inflammatory diseases, including blocking the progression of collagen-induced arthritis in a murine model of rheumatoid arthritis, decreasing damage to pancreatic islets in the NOD mouse model of type 1 diabetes, lessening hyperalgesia in rat models of neuropathic and inflammatory pain, and preventing cerebral ischemia in gerbils.

Pain

Neuropathic pain is associated with microglia activation in the spinal cord and brain and their subsequent release of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNFα) [33]. The etiology of neuropathic pain, which is common in cancer, diabetes, multiple sclerosis, and peripheral nerve injury, is poorly understood, but recent evidence indicates that increased ROS generation by microglial cells is the critical initiating factor [34]. The drug Sativex, which consists of Δ^9-THC and CBD, is approved in several countries for treatment of central and peripheral neuropathic pain and for spasticity associated with multiple sclerosis [35]. In a mouse model of type I diabetic peripheral neuropathic pain, intranasal or intraperitoneal administration of a moderate-high dose of CBD attenuated tactile allodynia and thermal hypersensitivity without affecting the diabetic state [36]. The antinociceptive effects of CBD were associated with less of an increase in microglial density and p38 MAPK activity in the dorsal spinal cord. Finally, the anti-inflammatory and immunosuppressive actions of CBD may be of use in treating rheumatoid arthritis and the associated pain [37,38].

Diabetes and Diabetic Complications

CBD was shown to reduce either the initiation of diabetes or the development of overt or latent diabetes in non-obese diabetes-prone (NOD) mice by reducing insulitis [39,40]. This

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action was accompanied by a shift in the immune response from a dominant Th1 pattern with pro-inflammatory cytokines to a Th2 pattern with increased levels of the anti-inflammatory cytokine IL-10. Major effectors of β-cell death in type 1 diabetes are various free radicals and oxidant species, including NO, and infiltrating macrophages are one source of high concentrations of NO and inflammatory cytokines that further enhance NO and ROS formation [41]. CBD was also shown to be effective in blocking ROS-induced up-regulation of surface adhesion molecules on endothelial cells due to high glucose and in preserving endothelial barrier function [19,42]. Adhesion of monocytes followed by their transmigration into the subendothelial space is an early event in atherosclerosis, the most common macrovascular complication of diabetes, and may contribute as well to diabetic retinopathy [19,42,43]. The anti-inflammatory actions of CBD may also protect retinal neurons in diabetes by attenuating activation and ROS generation by Müller glia, thus preventing tyrosine nitration and inhibition of Müller cell glutamine synthetase and the consequent accumulation of glutamate, which in turn leads to oxidative stress-induced death of retinal neuronal cells [44].

In a mouse model of type I diabetic cardiomyopathy, both pre- and post-treatment with CBD attenuated cardiac fibrosis and cell death, myocardial dysfunction, inflammation, oxidative/nitrosative stress, and the activation of related signaling pathways [45]. CBD attenuated diabetes-induced activation in the heart of the key pro-inflammatory transcription factor, NF-κB and its consequences, e.g. expression of ICAM-1, iNOS, VCAM-1, and TNFα. These observations underscore the point that CBD likely attenuates inflammation far beyond its antioxidant properties *per se*. CBD also reduced high glucose-induced increases in both cytosolic and mitochondrial reactive oxygen and nitrogen species generation in primary human cardiac myocytes, which was accompanied by reduced NF-κB activation and cell death. These findings indicate that CBD may have great therapeutic potential in alleviating cardiac complications of diabetes.

Hypertension

Although CBD has not been considered for treating hypertension, a parallel between the role of microglia in diabetes and hypertension deserves mention. Activation of microglia within the paraventricular nucleus (PVN) was recently shown to contribute to neurogenic hypertension resulting from chronic angiotensin II infusion in the rat [46]. Microglia activation was associated with enhanced expression of pro-inflammatory cytokines, the acute administration of which into the left ventricle or PVN resulted in increased blood pressure. The hypertensive action of angiotensin II infusion could be blocked by overexpression of IL-10 in the PVN or intracerebroventricular infusion of minocycline, supporting the involvement of ROS.

The immune system contributes as well to systemic endothelial dysfunction observed in hypertension [47]. Local production of angiotensin II by activated leukocytes within the vessel wall is thought to reduce endothelial function and NO production, leading to attenuated vasodilation and increased blood pressure, through the production of inflammatory cytokines and ROS [48,49]. Interestingly, recent evidence has shown that the initial stimulus for peripheral leukocyte activation in angiogensin II-induced hypertension is the increase in blood pressure that results from stimulation of cells within the anteroventral third ventricle (AV3V) of the brain by angiotensin II [50].

Ischemia Reperfusion Injury

Redox stress and ROS produced by ischemia-reperfusion of organs activates the immune system, which aids in repair by removing debris and stimulating remodeling. An excessive or prolonged inflammatory response, however, may prove detrimental to organ function by

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exacerbating ROS production and causing death of the parenchyma. Several hours after ischemia-reperfusion in the heart, a model of myocardial infarction, neutrophils accumulate in the myocardium [51]. Several lines of evidence suggest that this accumulation of neutrophils worsens injury to the myocardium [51]. In rats, treatment with CBD for 7 days following a 30 minute occlusion of the left anterior descending coronary artery markedly reduced infarct size, myocardial inflammation and IL-6 levels and preserved cardiac function [52]. In addition, the number of leukocytes infiltrating the border of the infarcted area was dramatically reduced. CBD has been shown to inhibit stimulated migration of neutrophils [22]. CBD treatment was also recently shown to reduce neutrophil migration in a rat model of periodontitis [53]. Hyperactive neutrophils exacerbate periodontal tissue injury and lead to tooth loss in part by excessive ROS formation in individuals with refractory periodontitis [54]. Finally, pre- or post-ischemic treatment with CBD was shown to have a prolonged and potent protective action in cerebral ischemia. The neuroprotective actions of CBD were attributed to reduced neutrophil accumulation and myeloperoxidase activity [55], as well as decreased high mobility group box 1 (HMGB1) expression by microglia [56].

Depression

CBD is reported to have anti-depressive actions, the basis for which is not established although activation of 5-HT_{1A} receptors may be involved at least at higher concentrations [13,57,58]. Growing evidence in recent years has implicated pro-inflammatory cytokines, free radical species, and oxidants in the etiology of depression [59,60]. One explanation is that the resultant oxidative stress adversely affects glial cell function and leads to neuron damage in the brain.

Neurodegenerative Diseases

Microglial hyperactivation is a common feature of a number of neurodegenerative diseases, including Parkinson's, Alzheimer's, Huntington's, amyotrophic lateral sclerosis (ALS) and multiple sclerosis(MS) [61,62]. Activated microglia produce a number of pro- and anti-inflammatory cytokines, chemokines, glutamate, neurotrophic factors, prostanoids, and a variety of free radicals that together create a state of oxidative stress. Alzheimer's disease, which is the most common form of dementia, is characterized by the deposition of "senile" plaques that are sites of microglia activation and inflammation. The resultant oxidative stress is a critical factor in the pathophysiology of Alzheimer's [63]. The plaques are composed of insoluble aggregates of the beta-amyloid peptide (Aβ), which self-assembles as monomers, oligomers and finally fibrils. Recent evidence shows that the oligomeric form of beta-amyloid is the most neurotoxic species and is most effective as a chemotactic agent for microglia and stimulator of microglial oxidative stress [61,64]. Activated microglia are a major contributor of inflammatory factors in Alzheimer's and secret a number of pro-inflammatory cytokines, which ironically further enhance Aβ production by neuronal cells [65]. In addition, an inflammatory state was shown to block the ability of microglia to phagocytize fibrillar Aβ [66]. Aging was also shown to negatively impact on the ability of microglia to internalize Aβ [67]. Microglia from aged mice were also shown to be less responsive to stimulation and to secrete greater amounts of IL-6 and TNFα compared to microglia of younger mice. Aged microglia also had lower levels of glutathione, suggesting an increased susceptibility to the harmful effects of oxidative stress. Finally, although controversial, evidence has been put forward suggesting that bone marrow-derived monocytic cells may somehow gain access to the diseased brain in Alzheimer's and be better at phagocytosing amalyoid plaques than resident microglia [65,68].

Based on rather scant evidence, some have proposed that CBD might have utility in treating neurodegenerative diseases [1,3,69–71]. CBD was shown to have a protective effect on

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cultured rat pheocromocytoma PC12 cells exposed to Aβ [72,73]. In a concentration-dependent manner, CBD increased cell survival, while decreasing ROS and nitrite production, lipid peroxidation, and iNOS protein expression. CBD was shown to have anti-inflammatory actions *in vivo* in a mouse model of Alzheimer's neuroinflammation induced by injection of human Aβ into the hippocampus. CBD dose-dependently attenuated Aβ-induced glial fibrillary acidic protein (GFAP) mRNA, iNOS and IL-1β protein expression, and NO and IL-1β release [74]. In a recent study, CBD was found to protect against amphetamine-induced oxidative protein damage in a rat model of mania and to increase brain-derived neurotrophic factor (BDNF) expression levels in the reversal protocol [75]. Results of these preclinical studies are persuasive and support the need for double-blind placebo controlled trials to assess the therapeutic utility of CBD in patients with neurodegenerative diseases.

Obesity and the Metabolic Syndrome

Metabolic syndrome is a combination of medical disturbances including central obesity, glucose intolerance, hypertension, and dyslipidemia that increases the risk for developing cardiovascular diseases and type 2 diabetes. Adipocyte dysfunction leading to a low-grade chronic inflammatory state is thought to underpin the etiology of the metabolic syndrome [76]. Metabolic overload of adipocytes causes production of ROS, pro-inflammatory cytokines, and adipokines that activate inflammatory genes and stress kinases and interfere with insulin signaling [76,77]. Saturated fatty acids also activate toll-like receptors on adipocytes and macrophages, components of the innate immune system, to induce production of proinflammatory cytokines and chemokines. Enhanced mitochondrial flux together with relative hypoxia due to adipocyte tissue hypertrophy, endothelial cell apoptosis, and inflammation-impaired angiogenesis further enhances ROS generation. Enhanced rupture of adipocytes due to excessive hypertrophy attracts and activates macrophages that further exacerbate the inflammatory state through the production of inflammatory cytokines and ROS. The chronic inflammatory state compromises the ability of adipose tissue to absorb incoming fat leading to fat build up in other organs, including liver, heart, and skeletal muscle, and creating a local inflammatory state that progresses to insulin resistance in those organs as well. Increased ROS levels are thought to be the major contributing factor to insulin resistance [78,79].

Macrophages, both resident and to a greater extent bone marrow-derived, play a critical role in initiating adipose tissue dysregulation and inflammation in the metabolic syndrome and together with adipocytes constitute a paracrine loop that sustains the chronic inflammatory state [80]. Macrophages secrete TNFα which acts on hypertrophied adipocytes to downregulate adiponectin and induce pro-inflammatory cytokines and lipolysis. The released free fatty acids act in turn on the toll-like receptor 4 (TLR4) of macrophages to induce production of pro-inflammatory cytokines, including TNFα. Both macrophages and adipocytes secrete monocyte chemotactic protein 1 (MCP1), which serves to recruit more macrophages to the adipose tissue.

Recent evidence has revealed that most macrophages in obese adipose tissue are polarized towards the M1 or classically activated, pro-inflammatory state, as opposed to the M2 or alternatively activated, anti-inflammatory state [80,81]. Th1 cytokine interferon gamma (IFNγ), microbial byproducts (e.g., LPS), and free fatty acids from visceral adipose tissue promote polarization towards the M1 state, whereas Th2 cytokines IL-4 and IL-13 promote polarization towards the M2 phenotype. Ligand-dependent transcription factors peroxisome proliferator activated receptors (PPARs) play a key role in determining the M1/M2 phenotype [81,82]. Activation of PPARγ or PPARδ promotes differentiation towards the M2 phenotype, while PPARγ activation inhibits M2 to M1 phenotype switch and represses the

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M1 pro-inflammatory gene expression profile. Of interest, CBD as well as some other cannabinoids, has been shown to activate PPARγ, possibly through direct binding [83,84]. Although tonic activation of CB_1 receptors by endocannabinoids is implicated in the development of abdominal obesity and CB_1 antagonists and inverse agonist reduce obesity, their clinical use is problematic due to serious neuropsychiatric effects [85]. Given its anti-inflammatory actions and PPARγ agonism, CBD might serve as the basis for design of a new anti-obesity drug [1]. In this regard, a cautionary note regarding the PPARγ agonism associated with CBD should be sounded, although this was observed only in very high concentrations and only *in vitro*, which is that several PPARγ agonists have been retracted because of various problems [86,87].

Atherosclerosis

Atherosclerosis is an inflammatory disease in which monocytes/macrophages play a critical role in the initiation and progression, as well as rapture, of the atherosclerotic plaque [88]. Plaques form in the arterial wall at areas of disturbed flow and endothelial dysfunction (Fig. 2). The initiating event is the transcytosis of low density lipoprotein (LDL) into the subendothelial space where it is trapped by binding to proteoglycans of the extracellular matrix [88,89]. LDL is oxidized by various cells including macrophages, first to minimally modified LDL (mmLDL) and then extensively oxidized LDL (oxLDL). The former activates endothelial cells to secrete various factors that attract monocytes and to express adhesion molecules that support the binding and transmigration of monocytes into the subendothelial space. Once there, monocytes differentiate into macrophages under the influence of cytokines and oxLDL. Macrophages take up oxLDL and differentiate into foam cells that secrete a number of cytokines and growth factors that sustain the inflammatory response and stimulate migration of smooth muscle and endothelial cells into the intima. Continued oxLDL uptake by foam cells combined with impaired cholesterol efflux results in their apoptosis and exposure of thrombogenic lipids [88,89]. A number of events in monocyte/macrophage physiology may be potential therapeutic targets for dealing with atherosclerosis and are discussed in detail elsewhere [88,89].

ROS play a pivotal role in atheroma development and macrophages are the major source for ROS with NADPH oxidase, cyclooxygenases (COX), lipooxygenases (LOX), iNOS, and myeloperoxidase contributing [88,89]. ROS participate in atherosclerosis in part by causing LDL oxidation, activating stress signaling pathways, inducing apoptosis, and facilitating plaque rupture [88]. Based on their ability to inhibit 15-LOX, CBD and its mono- and dimethylated derivatives have been proposed as potentially useful in treating atherosclerosis [90]; however, the question of whether 15-LOX has a detrimental or beneficial role in atherosclerosis is unsettled [91]. Nevertheless, a growing body of evidence supports the utility of targeting endocannabinoid signaling, particularly that of macrophages, in the treatment of atherosclerosis [92]. Differentiation of human monocytes, including that induced by oxLDL, results in a change in their CB_1 and CB_2 expression profile such that CB_1 becomes more prominent [93]. Activation of macrophage CB_1 receptor was shown to upregulate the CD36 scavenger receptor and cholesterol accumulation by macrophages/foam cells [94]. CB_1 receptor activation of human macrophages was linked to ROS generation via p38 MAPK activation, as well as production of TNFα and MCP1 [93]. In contrast, activation of the CB_2 receptor was shown to attenuate the pro-inflammatory actions of the CB_1 receptor through activation of the Ras family small G protein, Rap1 [93]. Consistent with these findings, a nonselective CB_1/CB_2 receptor agonist reduced oxLDL-induced ROS generation and TNFα secretion via the CB_2 receptor of murine macrophage, which in contrast to human macrophages do not express much CB_1 receptor [93,95]. Such tantalizing findings have fueled the idea that the endocannabinoid system may be a avenue for further

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drug development in dealing with atherosclerosis, likely involving a role for CBD as well [7].

Opposing regulatory effects of CB_1 and CB_2 receptors on inflammation and oxidative/nitrative stress is a general theme that has significance in atherosclerosis, as well as other human maladies. CB_2 activation in endothelial cells, which play a key role in development of early atherosclerosis and any inflammatory response, decreases activation and the inflammatory response [96], while CB_1 activation in human coronary artery endothelial cells was reported to induce ROS-dependent and -independent MAPK activation and cell death [97]. CB_1 cannabinoid receptors promote oxidative stress and cell death in murine models of doxorubicin-induced cardiomyopathy and in human cardiac myocytes [98]. In contrast, CB_2 activation was found to reduce oxidative stress and neutrophil infiltration in the infracted mouse myocardium [99]. In nephropathy, CB_2 limits oxidative/nitrosative stress, inflammation, and cell death [100], while activation of CB_1 cannabinoid receptors promote oxidative/nitrosative stress, inflammation, and cell death [101].

Conclusions

Inflammation and oxidative stress are intimately involved in the genesis of many human diseases. Unraveling that relationship therapeutically has proven challenging, in part because inflammation and oxidative stress “feed off” each other. However, CBD would seem to be a promising starting point for further drug development given its anti-oxidant (although relatively modest) and anti-inflammatory actions on immune cells, such as macrophages and microglia. CBD also has the advantage of not having psychotropic side effects. Studies on models of human diseases support the idea that CBD attenuates inflammation far beyond its antioxidant properties, for example, by targeting inflammation-related intracellular signaling events. The details on how CBD targets inflammatory signaling remain to be defined. The therapeutic utility of CBD is a relatively new area of investigation that portends new discoveries on the interplay between inflammation and oxidative stress, a relationship that underlies tissue and organ damage in many human diseases.

Acknowledgments

This work was supported by grants from the National Heart, Lung, and Blood Institute (R01HL088101-04 and R01HL088101-02S1).

List of Abbreviations

2-AG	2-arachidonoylglycerol
5-HT$_{1A}$ receptor	5-hydroxytryptamine (serotonin) receptor subtype 1A
A_{2A}	adenosine A_{2A} receptor (ADORA2A)
Abn-CBD	abnormal-cannabidiol
AEA	N-arachidonoylethanolamine (anandamide)
ALS	amyotrophic lateral sclerosis
AV3V	anteroventral third ventricle
Aβ	beta-amyloid peptide
BDNF	brain-derived neurotrophic factor
BHT	butylated hydroxytoluene

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CB_1	cannabinoid receptor type 1
CB_2	cannabinoid receptor type 2
CBD	cannabidiol
CD36	Cluster of Differentiation 36
COX	cyclooxygenases
ENT1	equilibrative nucleoside transporter 1
FAAH	fatty acid amide hydrolase
GFAP	glial fibrillary acidic protein
GPR55	G protein-coupled receptor 55
HMGB1	high mobility group box 1
ICAM-1	intercellular adhesion molecule 1
IFNγ	interferon gamma
IL	interleukin
iNOS (or NOS2)	inducible NOS
LDL	low density lipoprotein
LOX	lipooxygenases
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
MCP1	monocyte chemotactic protein 1
mmLDL	minimally modified LDL
MS	multiple sclerosis
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NK	natural killer
NKT	natural killer T
NO	nitric oxide
NOD mouse	non-obese diabetic mouse
oxLDL	oxidized LDL
PPARs	peroxisome proliferator activated receptors
PVN	paraventricular nucleus
Rap1	ras-related protein 1
ROS	reactive oxygen species
STAT1/STAT3	single transducers and activators of transcription 1/3
Tc cell	cytotoxic T cell
Th cell	T helper cells
TLR4	toll-like receptor 4
TNFα	tumor necrosis factor-α

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TRP	transient receptor potential
VCAM-1	vascular cell adhesion molecule 1
Δ^9-THC	delta9-tetrahydrocannabinol

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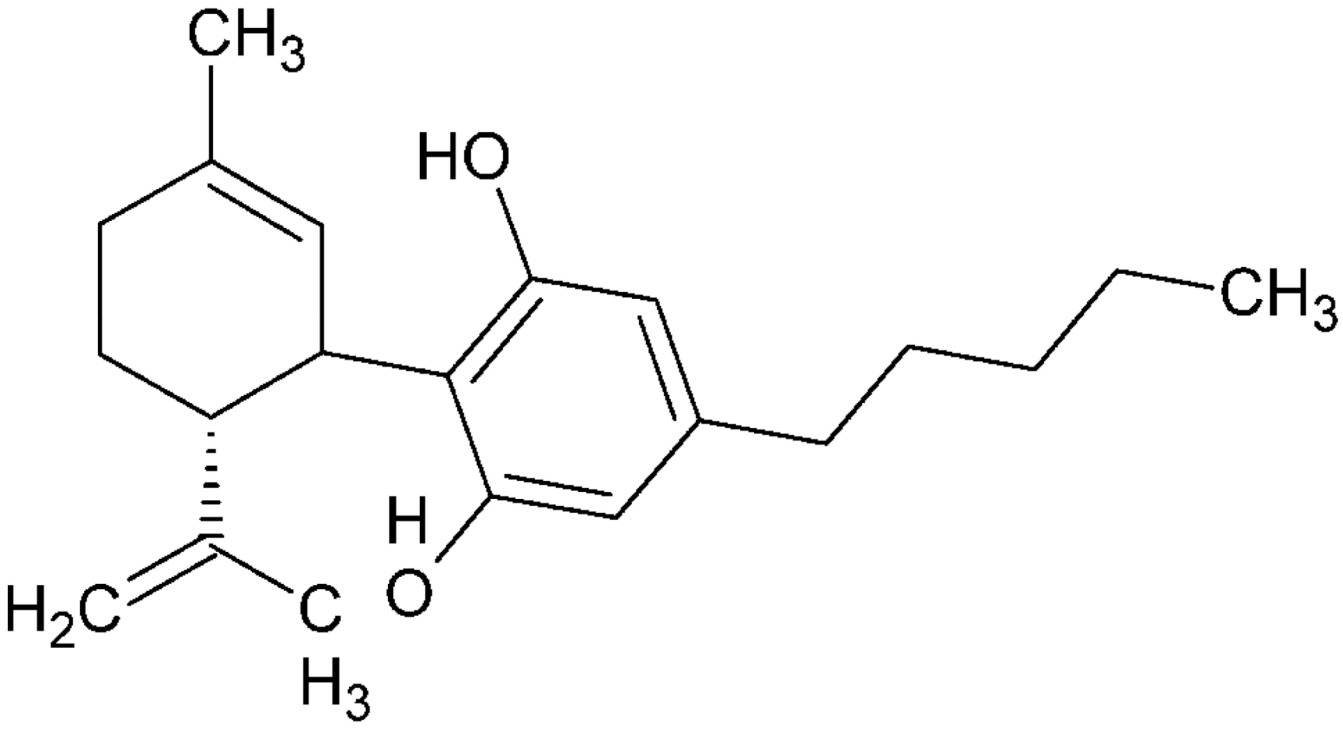

Figure 1.
Chemical structure of cannabidiol (CBD).

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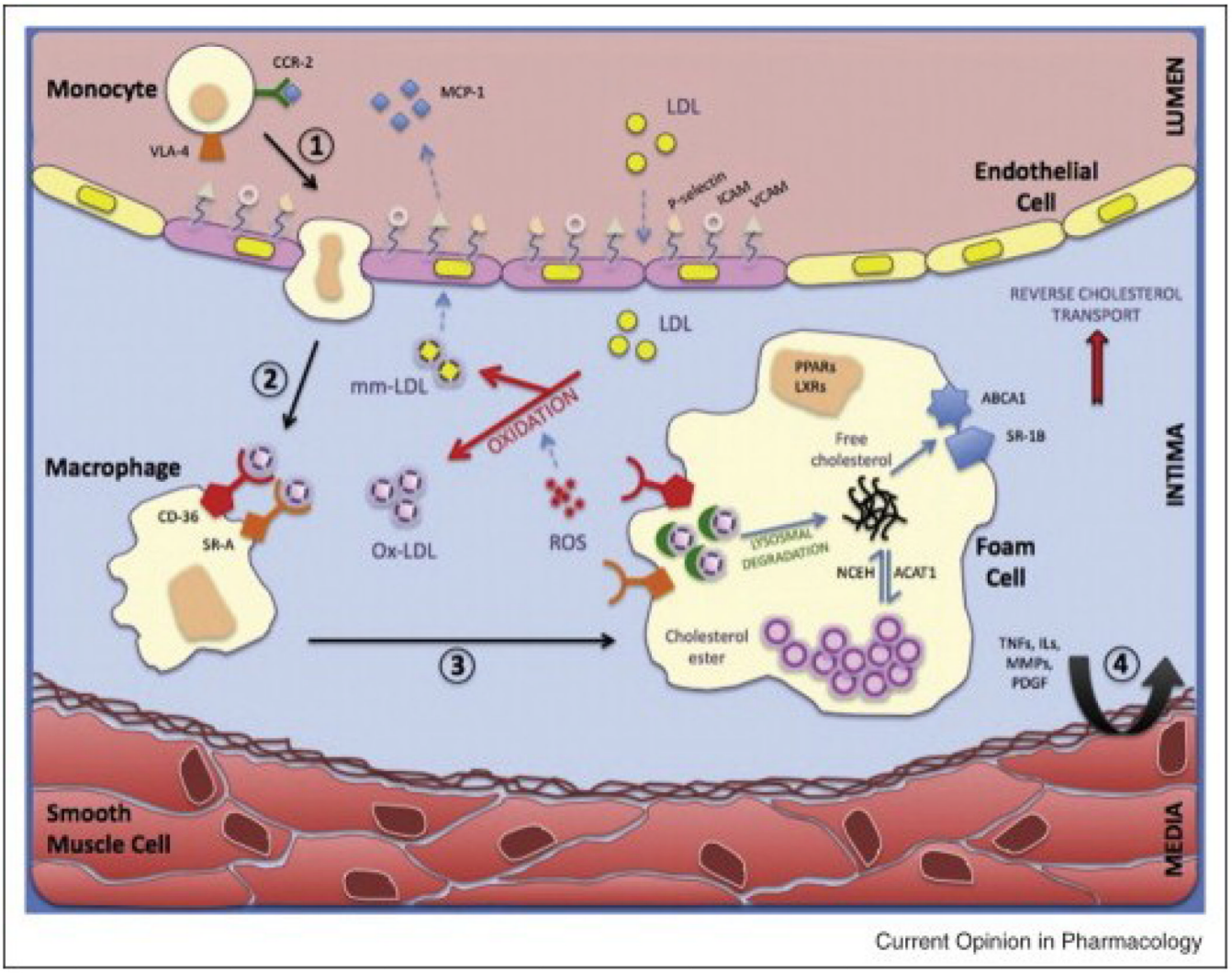

Figure 2.

Inflammation and oxidative stress in atherosclerotic plaque formation. Endothelial dysfunction causes monocyte activation and their binding to endothelial cells, via the production of MCP-1, its binding to CCR2 receptors, and the upregulation of adhesion molecules on endothelial cells (1). Monocytes cross the endothelium and differentiate into macrophages (2). Due to ROS, LDL that traverses the endothelium is converted to mmLDL and oxLDL. Macrophages accumulate oxLDL through scavenger receptors and are turned into foam cells (3). Along with T cells, foam cells produce inflammatory mediators that stimulate migration of smooth muscle and endothelial cells into the intima (4). Figure taken with permission from Reference 88.