


- 
- [NCBI](#) 
  - [Skip to main content](#)
  - [Skip to navigation](#)
  - [Resources](#)
  - [How To](#)
  - [About NCBI Accesskeys](#)

[Sign in to NCBI](#)

## [PMC](#)

[US National Library of Medicine](#)  
[National Institutes of Health](#)

- [Advanced](#)
- [Journal list](#)
- [Help](#)
  
- [Journal List](#)
- [Mediators Inflamm](#)
- [v.2016; 2016](#)
- [PMC4997072](#)



[Mediators Inflamm.](#) 2016; 2016: 5831315.

Published online 2016 Aug 11. doi: [10.1155/2016/5831315](https://doi.org/10.1155/2016/5831315)

PMCID: PMC4997072

# Interaction between Cannabinoid System and Toll-Like Receptors Controls Inflammation

[Kathleen L. McCoy](#) \*

[Author information](#) ► [Article notes](#) ► [Copyright and License information](#) ►

This article has been [cited by](#) other articles in PMC.

[Go to:](#)

## Abstract

Since the discovery of the endocannabinoid system consisting of cannabinoid receptors, endogenous ligands, and biosynthetic and metabolizing enzymes, interest has been renewed in investigating the promise of cannabinoids as therapeutic agents. Abundant evidence indicates that cannabinoids modulate immune responses. An inflammatory response is triggered when innate immune cells receive a danger signal provided by pathogen- or damage-associated molecular patterns engaging pattern-recognition receptors. Toll-like receptor family members are prominent pattern-recognition receptors expressed on innate immune cells. Cannabinoids suppress Toll-like receptor-mediated inflammatory responses. However, the relationship between the endocannabinoid system and innate immune system may not be one-sided. Innate immune cells express cannabinoid receptors and produce endogenous cannabinoids. Hence, innate immune cells may play a role in regulating endocannabinoid homeostasis, and, in turn, the endocannabinoid system modulates local inflammatory responses. Studies designed to probe the interaction between the innate immune system and the endocannabinoid system may identify new potential molecular targets in developing therapeutic strategies for chronic inflammatory diseases. This review discusses the endocannabinoid system and Toll-like receptor family and evaluates the interaction between them.

[Go to:](#)

## 1. Introduction

*Cannabis sativa*, better known as marijuana, has been used in traditional medicine for millennia to treat various ailments [1–4]. Development of cannabinoids from the cannabis plant as therapeutic agents has been hindered by their recreational abuse and addictive properties [5, 6]. Legalization of medical marijuana is a growing trend during the past few years. Medical marijuana is primarily used to treat glaucoma and to stimulate appetite and prevent weight loss in AIDS and cancer patients [1–4]. At present, the Food and Drug Administration has approved two cannabinoid medications, Marinol® containing a psychoactive phytocannabinoid and Cesamet® consisting of a synthetic cannabinoid, for the treatment of nausea, emesis, and cachexia [6–8]. In several other countries, Sativex® has been approved to treat spasticity and neuropathic pain in multiple sclerosis patients and pain in patients with advanced cancer [1, 9]. It contains an equimolar combination of psychoactive  $\Delta^9$ -tetrahydrocannabinol and nonpsychoactive cannabidiol, which are phytocannabinoids [1, 9]. Nevertheless, the beneficial health effects of cannabinoids, for the most part, remain empirical and anecdotal. However, discovery of two major cannabinoid receptors and endogenous cannabinoids in humans provides the opportunity to understand the mechanisms of action and to develop approaches for manipulating the cannabinoid system as effective treatment for particular human diseases.

Familiar effects of marijuana result from phytocannabinoids acting as neurotransmitters or modulating neurotransmitter release that, in turn, causes euphoria, diminished pain, altered sensory perception, impaired memory, and enhanced appetite [6, 7]. Neurological consequences of cannabinoid exposure can be attributed to cannabinoid receptors within the brain. Moreover, cannabinoids impact other biological systems besides the central nervous system. Numerous studies report that cannabinoids suppress *in vitro* functions of human and animal immune cells, and animals exposed to cannabinoids have decreased host resistance to various pathogens and tumors (reviewed in [10–12]). Chronic cannabis use is associated with increased incidence of rhinitis, pharyngitis, asthma, bronchitis, and sexually transmitted diseases [5, 9, 13, 14]. Besides social behavior contributing to an increased rate of sexually transmitted diseases, depressed immune functions could enhance susceptibility of marijuana users to infections [5].

Because all immune cells examined so far express cannabinoid receptors regardless of their cell lineage, all types of immunity are sensitive to cannabinoid modulation [10–12]. The importance of the cannabinoid system in regulating immune competency is revealed by altered immune status in mice genetically deficient in cannabinoid receptors [15]. In terms of adaptive immunity, cannabinoids usually suppress primary antibody responses to T cell-dependent antigens, induction of cytotoxic CD8<sup>+</sup> T cells, and cytokine production by helper CD4<sup>+</sup> T cells, whereas other adaptive immune responses are unaffected or enhanced [10–12]. The current view is that cannabinoid exposure skews T cell responses leading to suppression of cell-mediated immunity and inflammatory reactions [10–12]. Furthermore, cannabinoids impact innate immunity that mediates inflammatory responses and promotes initiation of adaptive immune responses. For example, alveolar macrophages isolated from chronic marijuana users have compromised phagocytosis of microorganisms, ability to kill bacteria, and production of proinflammatory cytokines [16, 17]. These consequences of drug use parallel *in vitro* cannabinoid suppression of immune functions by monocytes, macrophages, and macrophage cell lines of human and rodent origins [10–12]. My laboratory reported that cannabinoids impair the ability of murine macrophages to function as antigen-presenting cells resulting in depressed helper CD4<sup>+</sup> T cell responses [18–20]. Furthermore, macrophages from mice lacking cannabinoid receptor expression are refractory to cannabinoid suppression of antigen-presenting cell function [21, 22]. Therefore, cannabinoids can exert their influence on an immune response before helper CD4<sup>+</sup> T cell activation.

The endocannabinoid system consists not only of cannabinoid receptors, but also of endogenous cannabinoids and their biosynthetic and metabolizing enzymes. Macrophages are major producers of endogenous cannabinoids [23], which may not be a coincidence. Both exogenous and endogenous cannabinoids inhibit proinflammatory cytokine production by macrophages stimulated through Toll-like receptors (TLRs). TLRs play a crucial role in macrophages sensing danger to trigger inflammatory responses. Conversely, activation of macrophages via TLRs alters their expression of cannabinoid receptors and levels of endogenous cannabinoids. This review discusses the endocannabinoid system and TLR family and evaluates the interaction between them with emphasis on the innate immune system.

[Go to:](#)

## 2. Endocannabinoid System

### 2.1. Cannabinoid Receptors

Cannabinoid receptors encompass multiple subtypes (reviewed in [24–26]). Central cannabinoid receptor type 1 (CB1) and peripheral cannabinoid receptor type 2 (CB2) are the predominant receptors and share approximately 44% homology [27–30]. Endogenous cannabinoids also bind Transient Receptor Potential Vanilloid 1 receptor, a capsaicin receptor, which is structurally different from CB1 and CB2 receptors [24–26]. The orphan receptor GPR55 may be another receptor subtype, although it has low homology to the other cannabinoid receptors [24–26]. Other candidate receptors have been implicated by pharmacological and functional studies [24–26]. CB1 and CB2 receptors greatly differ in their tissue distribution. CB1 receptor, originally identified in rat cerebral cortex, is primarily expressed in the central nervous system [27, 28]. This receptor subtype is also expressed in various peripheral tissues, such as testis, vascular endothelium, and small intestine [27, 28]. Its expression is heterogeneous within the nervous system and is mainly responsible for cannabinoid psychoactive properties. In contrast, CB2 receptor was originally identified in the promyelocytic leukemic cell line HL60 and is prevalent within the immune system [29, 30]. All lineages of immune cells express the CB2 receptor, although its expression level varies among the cell types. In rank order, B cells express the highest level followed by natural killer cells, macrophages, monocytes, polymorphonuclear cells, and T cells [31]. CB2 receptor expression in healthy brains is limited to a few neurons in the brain stem [32, 33]. However, during neurological diseases, such as multiple sclerosis and Alzheimer's disease, microglial cells, which are brain macrophages, express a high level of CB2 receptor [33, 34]. Some immune cells, including

monocytes, also express the CB1 receptor [35–37]. When both receptor subtypes are present in immune cells, the CB2 receptor is usually expressed at a significantly higher level than the CB1 receptor [35–37]. Unlike CB1 receptor-mediated cell activation, signal transduction through the CB2 receptor lacks psychotropic effects [38, 39] making it an attractive target for immunotherapy.

## 2.2. Exogenous and Endogenous Cannabinoids

Cannabis is a complex mixture of over 100 cannabinoids along with other classes of compounds that have pharmacological and biological activities. Numerous synthetic analogues have been produced based on structure-activity relationship studies [24, 25]. Many synthetic cannabinoid analogues have biological effects similar to their natural counterparts [40, 41]. Cannabimimetic compounds are lipophilic molecules and are classified into four main groups based on their chemical structure [24, 25].

The classical group consists of dibenzopyran derivatives, and the phytocannabinoids fall into this group [24, 25].  $\Delta^9$ -Tetrahydrocannabinol is the major psychoactive compound in marijuana and the best-studied cannabinoid. It is a partial agonist binding both CB1 and CB2 receptors and is an ingredient of Marinol and Sativex. Another notable member is cannabidiol that is a nonpsychoactive ingredient of Sativex. Cannabidiol does not activate cannabinoid receptors and yet has biological activity, including immune suppression. Instead, cannabidiol appears to behave as a potent antagonist or inverse agonist [24, 25]. Cannabigerol is the common biosynthetic precursor of  $\Delta^9$ -tetrahydrocannabinol and cannabidiol [26]. Major homologues of  $\Delta^9$ -tetrahydrocannabinol and cannabidiol are  $\Delta^9$ -tetrahydrocannabivarin and cannabidivarin, respectively, with propyl side chains rather than pentyl side chains [26]. Other members are synthetic analogues of phytocannabinoids, and some synthetic compounds are selective receptor agonists with higher affinity for one or other cannabinoid receptor subtype.

Nonclassical cannabinoids are bicyclic and tricyclic analogues of  $\Delta^9$ -tetrahydrocannabinol [24, 25]. These synthetic compounds lack a pyran ring. Several are selective cannabinoid receptor agonists. The best-studied member is (-)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl) cyclohexanol referred to as CP55,940, which is a full nonselective agonist with higher potency than  $\Delta^9$ -tetrahydrocannabinol.

Cannabinoids belonging to the aminoalkylindole group are very structurally different from classical and nonclassical compounds [24, 25]. They were initially developed as potential analogues of nonsteroidal anti-inflammatory drugs [42]. The most widely studied member is (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo [1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone called WIN 55,212-2 with slightly higher CB2 than CB1 receptor affinity.

Eicosanoids are the endogenous compounds and are oxidized derivatives of 20-carbon fatty acids [24, 25]. Arachidonoyl-ethanolamide also called anandamide was the first one isolated from porcine brain and was found to have cannabimimetic activity [43]. Anandamide is an arachidonic acid derivative that is highly sensitive to oxidation and hydrolysis. It behaves as a partial agonist and has lower intrinsic activity for CB2 than for CB1 receptor. Another prominent member is 2-arachionoyl glycerol, a monoglyceride, which is more potent than anandamide. Initially, 2-arachionoyl glycerol was isolated from intestine and brain [44, 45], and its concentration in the brain is approximately 170-fold higher than that of anandamide [46]. Because 2-arachionoyl glycerol favors the CB2 receptor, it is viewed as the main endocannabinoid to modulate immune functions. Several synthetic analogues of anandamide have been produced to achieve higher potency and efficacy.

Most cannabinoids exhibit stereoselectivity in pharmacological assays due to chiral centers in the molecules. Frequently, stereoselectivity is also observed in biological assays. Classical and nonclassical cannabinoids and aminoalkylindoles are far more active than their corresponding enantiomer or stereoisomer [24, 25]. Stereoselectivity is one criterion for receptor-mediated actions.

## 2.3. Cannabinoid Signal Transduction Pathways

Cannabinoid receptors are seven-transmembrane-spanning G protein-coupled receptors [27–30]. The first evidence that cannabinoid receptors are  $G_{i/o}$  protein-coupled receptors was cannabinoid-induced inhibition of adenylate cyclase leading to decreased intracellular cAMP level [47]. Pertussis toxin inhibition of a cannabinoid effect confirms  $G_{i/o}$  protein-mediated signal transduction [48]. G proteins are heterotrimers, and upon activation the  $\alpha$  subunit dissociates from the  $\beta\gamma$  dimer (Figure 1). The  $G_{i/o}$   $\alpha$  subunit inhibits adenylate cyclase decreasing intracellular cAMP levels [40, 41]. In turn, cAMP-dependent protein kinase A activity diminishes leading to less active transcription factor cAMP response element-binding protein affecting gene expression [40, 41]. The G protein  $\beta\gamma$  dimer eventually leads to activation of the mitogen-activated protein kinase (MAPK) pathways and phosphatidylinositol-3 kinase (PI-3K) [49, 50].



Figure 1

Cannabinoid receptor signal transduction pathway. Upon cannabinoid receptor engagement by a cannabinoid, the activated  $G_{i/o}$   $\alpha$  subunit inhibits adenylate cyclase activity causing a decrease in cAMP, which, in turn, decreases PKA activity. The ...

MAPK and Akt regulation by cannabinoid receptor signaling pathways is not well understood (Figure 1). PI-3K inhibitors attenuate cannabinoid-induced activation of MAPK in Chinese hamster ovary cells transfected with human CB1 receptor cDNA [50]. This finding indicates that PI-3K leads to Akt activation eventually causing p42/44 and p38 MAPK activation. Similarly,  $\Delta^9$ -tetrahydrocannabinol

activates the PI-3K/Akt pathway in epithelial cells leading to Raf-1-mediated activation of p42/p44 MAPK [41]. In contrast, stimulation of rat microglial cells with 2-arachionoyl glycerol causes MAPK activation that is dependent on protein kinase C, not PI-3K [51]. Conversely, WIN 55,212-2 has the opposite effect and inhibits p42/p44 MAPK activation in murine splenic immune cells [52]. Akt may activate mammalian target of rapamycin (mTOR) present in complex 1 (mTORC1), and, in turn, mTORC1 regulates protein synthesis, glucose metabolism, and autophagy. Rapamycin, a mTOR inhibitor, blocks cannabinoid-induced neural progenitor cell proliferation and cannabinoid-enhanced oligodendrocyte differentiation [53, 54]. On the other hand, WIN 55,212-2 decreases mTORC1 activation in prostate cancer cells [55]. Furthermore, stimulation of promyelocytic HL60 cells with 2-arachionoyl glycerol or other cannabinoid agonists does not activate Akt or mTOR [40]. Thus, cannabinoids may or may not activate Akt, MAPKs, and mTOR depending on the cannabinoid group type, cannabinoid concentration, and/or cell type with differential cannabinoid receptor expression.

While CB1 and CB2 receptors share many signaling steps, distinct differences have been identified in the signaling pathways of these receptors. CB1 receptor signaling can cause increased intracellular  $Ca^{+2}$  level, which may result from phospholipase C activation [40]. Stimulation through the CB1 receptor also activates A-type and inwardly rectifying potassium channels and inhibits N- and P/Q-type calcium currents in neural cells [40, 41, 49]. Most notably, CB1 receptor signaling may increase intracellular cAMP levels and cAMP-dependent protein kinase A activity due to the receptor associating with  $G_s$  proteins [40]. Furthermore, the CB1 receptor may associate with  $G_q$  proteins leading to phospholipase D activation [40]. While the CB1 receptor may couple to  $G_s$  or  $G_q$  proteins, the CB2 receptor does not [41].

## 2.4. Endocannabinoid Biosynthesis and Metabolism

Within the central nervous system, anandamide and 2-arachionoyl glycerol are not preformed molecules stored in vesicles but rather are synthesized when cells are stimulated, such as depolarization of neurons [56, 57]. Their synthesis depends on increased intracellular  $Ca^{+2}$  concentration mainly due to  $Ca^{+2}$  dependency of the biosynthetic enzymes [58–61]. Anandamide is predominantly produced in a two-step enzymatic process starting with phosphatidylethanolamine that is catalyzed by  $Ca^{+2}$ -dependent N-acyltransferase followed by N-acylphosphatidylethanolamine-hydrolyzing phospholipase D (reviewed in [62–65]). The critical precursors of 2-arachionoyl glycerol are *sn*-1-acyl-2-arachidonoylglycerols, and multiple enzymatic pathways generate 2-arachionoyl precursors [63]. The main pathway involves phosphoinositide-selective phospholipase C or similar phospholipases followed by two *sn*-1-selective diacylglycerol lipase isoenzymes (reviewed in [62–65]). In contrast to anandamide, various stimuli in addition to  $Ca^{+2}$ -mobilization trigger 2-arachionoyl glycerol synthesis in neural cells, epithelial cells, and macrophages [56, 64]. Unlike anandamide, 2-arachionoyl glycerol is an important precursor of other molecules [63], which may explain their differential resting levels. In most cases, enhanced anandamide and 2-arachionoyl glycerol biosynthesis is limited in time and location, and, thus, their release affects only cells in the nearby vicinity.

After release, endocannabinoids are rapidly internalized into cells by an undefined mechanism, and a proposed transporter has not been definitely identified. Intracellular anandamide is principally hydrolyzed by fatty acid amide hydrolase, an integral plasma membrane protein [66]. Similarly, internalized 2-arachionoyl glycerol is primarily hydrolyzed by monoacylglycerol lipase associated with the plasma membrane [67]. Reaction products do not activate cannabinoid receptors and may recycle back into their respective biosynthetic pathways [63]. One hydrolysis product, arachidonic acid, may be metabolized by various enzymes to produce prostaglandins, thromboxanes, leukotrienes, and other biologically active compounds, which are potent inflammatory mediators or immune suppressors. Anandamide and 2-arachionoyl glycerol themselves may be oxidized by cytochrome P450, cyclooxygenase-2, and 5- and 12-lipoxygenases [63, 65]. Some lipoxygenase products bind both CB1 and CB2 receptors [25, 56, 57]. Hence, results from metabolic enzyme inhibitors or enzyme deficient mice should not presume to be caused by only increased endocannabinoid levels.

[Go to:](#)

## 3. Toll-Like Receptor Family

A fundamental characteristic of the immune system is the ability to distinguish between self and non-self-molecules or antigens. Immune cells are particularly adept at detecting microbial antigens, and the subsequent immune response can clear an infection and provide protection against a future infection. Innate immunity represents the first line of defense against infectious diseases, and cells, such as neutrophils and macrophages, are the first responders. Inflammation is the initial immune response against infectious agents, and the inflammatory response promotes initiation of an adaptive immune response by antigen-specific T and B cells. However, cells of innate immunity do not express antigen-specific receptors, unlike T and B cells of adaptive immunity. Decades ago, Janeway proposed a hypothesis that innate immune cells utilize germline-encoded receptors that are antigen-selective [68], and such receptors were eventually identified many years later. Innate immune cells express pattern-recognition receptors that bind conserved molecular patterns, and engagement of these receptors transduces a signal allowing cells to sense danger in the form of a pathogen or host cellular damage [69, 70]. These receptors are present at the cell surface, in endocytic organelles, or in the cytoplasm permitting perception of both extracellular and intracellular dangers. The major receptor gene families based on protein domain homology include TLRs, retinoid acid-inducible gene-1-like receptors, absent in melanoma-2 receptors, C-type lectin receptors, intracellular DNA sensors, and nucleotide-binding domain, leucine-rich repeat-containing receptors (or nucleotide-binding, oligomerization domain-like receptors) that are discussed in several comprehensive reviews [70–76]. This review focuses on the TLR family, which has been extensively investigated and was the first one discovered.

### 3.1. Toll-Like Receptor Family Members

Toll gene was first identified in *Drosophila* as essential in regulating embryonic development of dorsal-ventral polarity [77, 78]. In addition, Toll has a critical role in resistance to fungal infections in adult flies [79]. This latter discovery was key to understanding innate inflammatory triggers and led to finding the mammalian homologues [80, 81]. Although the number of family members varies among mammalian species, TLRs are evolutionarily conserved type I transmembrane proteins [70–76]. TLRs are predominantly

among mammalian species, TLRs are evolutionarily conserved type I transmembrane proteins [70–76]. TLRs are predominantly expressed by innate immune cells, especially dendritic cells and macrophages, while adaptive immune B and T cells, and nonimmune cells, including fibroblasts and epithelial cells, have limited TLR expression [70–76]. Family members have a highly conserved cytoplasmic Toll/Interleukin-1 receptor (TIR) domain that initiates signal transduction via recruitment of adaptor proteins [70–76]. At present, 10 TLR chains have been identified in humans, while TLR10 is a pseudogene in mice, but three additional chains (TLR11 to TLR13) are expressed in mice [70–76]. Each TLR recognizes a distinct set of molecular patterns [70–76]. Promiscuous ligand recognition, which is determined by the leucine-rich repeat extracellular domain, is indispensable for the handful of TLRs to mediate effective immune defenses against an array of diverse pathogens.

### 3.2. Exogenous and Endogenous Ligands

Regarding mammalian host resistance, TLRs bind pathogen-associated molecular patterns (PAMPs) present within microbial molecules, but absent from mammalian molecules [70–75]. The broad gamut of ligand specificity ranges from hydrophobic lipids to hydrophilic nucleic acids. TLRs are divided into two subfamilies based on their cellular location, and the following discussion will focus on the TLR chains expressed in humans. TLR1 and TLR2, TLR4 through TLR6, and TLR10 are plasma membrane proteins, whereas TLR3 and TLR7 through TLR9 reside in membranes of endocytic organelles. Interestingly, ligand recognition correlates with the cellular location of TLRs [70–75]. Cell surface TLRs sense fungal cell wall components (TLR2), bacterial lipopolysaccharides (TLR4), lipoproteins (TLR1, TLR2, and TLR6), flagella (TLR5), or peptidoglycans (TLR2). On the other hand, intracellular TLRs are specific for viral double-stranded RNA (TLR3), single-stranded RNA (TLR7 and TLR8), DNA (TLR9), or unmethylated CpG DNA (TLR9). In contrast, human TLR10 is an orphan receptor without a known ligand. Receptor compartmentalization influences the types of ligands accessible for cell activation. For example, endosomal TLRs engage when virulent intracellular pathogens infect cells, but do not signal when the pathogen remains outside the cell. Although all TLRs possess a similar TIR domain, cell surface and intracellular receptors, in general, utilize different adaptor molecules to transduce a signal [70–75]. Cell surface TLR signaling mainly relies on TIR-containing adaptor protein (TIRAP) and protein myeloid differentiation primary response 88 (MyD88). Furthermore, TIR domain-containing adaptor-inducing interferon- $\beta$  (TRIF) and TRIF-related adaptor molecule (TRAM), also, transmit TLR signals. The different pairs of adaptor molecules activate distinct transcription factors, and, hence, influence the nature and outcome of the inflammatory response.

For many years, one puzzling aspect of innate immunity has been inflammatory responses in the absence of an infection that contribute to tissue damage during autoimmune diseases and chronic inflammatory diseases. Matzinger proposed that the immune system does not distinguish between self and non-self-antigens per se but rather is designed to detect danger [82]. The apparent paradox of sterile inflammation is resolved by realization that pattern-recognition receptors, including TLRs, recognize endogenous ligands. The endogenous molecules called damage-associated molecular patterns (DAMPs) are created or released upon tissue injury or cell death [69, 76]. Heat shock protein 60 was the first candidate DAMP reported to induce TLR4 activation [83]. Within months, necrotic cells were shown to induce proinflammatory gene expression and dendritic cell maturation via TLR2 [84, 85]. Since then, several DAMPs have been identified, and some are intracellular molecules to which innate immune cells are not normally exposed. Analogous to PAMPs, cell surface and intracellular TLRs recognize different types of DAMPs, although endogenous ligands have not been identified for all TLRs [69, 76]. For example, TLR2 and TLR4 ligands include heat shock proteins, serum amyloid A, and oxidized low-density lipoprotein. Intracellular TLR3 recognizes mRNA, and TLR9 binds antibody-chromatin complexes. Recent evidence indicates that danger signals provided by PAMPs and DAMPs synergistically activate inflammatory responses.

### 3.3. MyD88-Dependent Signal Transduction Pathway

Functional TLRs form dimers and particular receptors associate with a coreceptor and/or an accessory molecule [69–76, 86]. Most TLRs form homodimers with TLR2 as the notable exception pairing with TLR1 or TLR6. These TLR2 heterodimers have different ligand specificities. When a ligand binds, the TIR domains oligomerize recruiting adaptor proteins that initiate downstream signaling events.

TLR4, the prototype and best-studied receptor, is unique among TLRs using four adaptor molecules. The classic TLR4 ligand is lipopolysaccharide (LPS) from Gram-negative bacteria, which causes septic shock. The LPS response requires a molecular complex (Figure 2(a)) consisting of TLR4 homodimer, LPS-binding protein, CD14, and myeloid differentiation-2 protein (MD-2) [69–76]. MD-2 is required for TLR4 dimerization. Upon LPS exposure, the TLR4:MD-2 complex concentrates within cholesterol-rich lipid rafts containing CD14, which is anchored to the plasma membrane by glycosylphosphatidylinositol. The LPS-binding protein, a soluble serum protein that binds lipid A moiety, initiates sequential transfer of LPS monomers to coreceptor CD14 and then to MD-2. Giannini and Weiss estimate that LPS monomers extracted from one bacterium are sufficient to activate 1,000 macrophages [87]. Hence, sequential LPS transfer is thought to heighten sensitivity of innate immune cells, in particular macrophages.

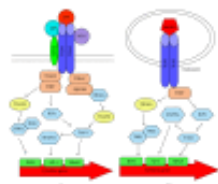


Figure 2

TLR signal transduction pathways. (a) Signaling through TLR4 by bacterial LPS. TLR4 forms a complex with LBP, MD2, and CD14. When LPS binds TLR4, two adaptor complexes are recruited. The MyD88-dependent pathway activates IRAKs eventually leading to activation ...

Adaptor TIRAP binds the TIR domain of TLR4 but lacks a signaling domain [70–75, 86]. TIRAP itself contains a TIR domain that subsequently recruits adaptor MyD88 to the TLR4 complex (Figure 2(a)). The MyD88-dependent signaling pathway triggers IL-1R-associated kinases and MAPKs culminating in activation of transcription factors, nuclear factor- $\kappa$ B, and activator protein-1. These transcription factors induce nitric oxide and proinflammatory cytokine production.

These transcription factors induce nitric oxide and proinflammatory cytokine production.

All TLRs except TLR3 utilize MyD88, and the other cell surface receptors, also, interact with TIRAP similar to TLR4 and lead to NF- $\kappa$ B activation [69–76, 86]. Similar to TLR4, TLR2 heterodimers localize to lipid rafts and require MyD88 via TIRAP for signal transduction. However, TLR2/TLR1 activation involves coreceptor CD14, whereas CD36 serves as the coreceptor for TLR2/6 [70, 88]. CD36 functions as a scavenger receptor in monocytes and macrophages and participates in phagocytosis and endocytosis [89]. CD36 might mediate TLR2/6 internalization to downregulate cell activation.

### 3.4. TRIF-Dependent Signal Transduction Pathway

Unlike other TLRs, TLR4 signals involve a second pair of adaptor proteins resulting in type I interferon production (Figure 2(a)) and a second wave of NF- $\kappa$ B activation [69–76, 86]. In this pathway, adaptor TRAM and TRIF molecules drive cell activation. Analogous to TIRAP, TRAM lacks a signaling domain and recruits a second adaptor molecule, in this case TRIF, to the plasma membrane. TRIF recruits signaling molecules that, in turn, recruit inducible I $\kappa$ B kinase- $\alpha$  and TANK-binding kinase-1 to the complex. Ultimately, transcription factor interferon regulatory factor-3 becomes activated leading to type I interferon synthesis, especially interferon- $\beta$ . Receptor-interacting protein kinase-1 activity eventually leads to TRIF-dependent MAPKs and NF- $\kappa$ B activation.

Both TIRAP and TRAM localize to the plasma membrane; however their binding to TLR4 appears to be mutually exclusive [90]. Colocalization, time kinetics, and endocytosis inhibition studies indicate that TRAM engages after TLR4 internalization [70, 72–75, 86]. A novel model of TLR4 signaling proposes that CD14 mediates trafficking of TLR4 to the endosomes, whereupon the TRIF-dependent pathway is induced [70, 72–75, 86]. Hence, the MyD88-dependent and TRIF-dependent signaling pathways are sequestered from each other, and commence at distinct cellular locations.

### 3.5. Intracellular TLR Signal Transduction Pathways

Intracellular TLRs stimulate cells by divergent pathways compared with TLR4 [70, 72–75, 86]. Intracellular TLR7 to TLR9 do not utilize the TRAM/TRIF pathway. Instead, engagement of these receptors induces type I interferon production via IRF7 and NF- $\kappa$ B activation in a MyD88-dependent manner. The alternative MyD88 pathway triggers IL-1R-associated kinases to activate transcription factors IRF7 and NF- $\kappa$ B. On the other hand, TLR3 employs the adaptor TRIF protein (Figure 2(b)) but does not need either TRAM or MyD88. The high affinity TIR domain of TLR3 directly binds TRIF in the absence of TRAM. Notably, a point mutation within the TIR domain of TLR3 switches its specificity from TRIF to MyD88 [91]. Similar to TLR4, this TRIF-dependent pathway activates transcription factor IRF3 via TANK-binding kinase-1 inducing robust interferon- $\beta$  secretion.

Cell activation by TLR signals is tightly regulated on multiple levels. Critical regulatory mechanisms range from TLR trafficking and cleavage to protein modification of signaling molecules. Furthermore, negative regulators are important in preventing autoimmune and inflammatory diseases. TLR recognition of PAMPs is crucial for host resistance to infectious diseases, and individuals with defective TLR responses are immune compromised. On the flip side, abnormal TLR activation by PAMPs, mutations in TLR signaling molecules, and TLR activation by DAMPs are associated with the development and pathogenesis of numerous diseases, including autoimmune diseases, hypersensitivities, chronic inflammatory diseases, cancer, and cardiovascular diseases. Hence, cannabinoid modulation of TLR signal transduction pathways may have beneficial or detrimental consequences on human health.

[Go to:](#)

## 4. Interaction between Cannabinoid and Toll-Like Receptor Activation

Important innate immune cells expressing TLRs are monocytes, macrophages, microglial cells, and dendritic cells. These myeloid cells are closely related. Monocytes circulate in the blood and mature into macrophages or dendritic cells depending on the stimulus. Microglial cells are resident macrophages in the brain. All these cells express cannabinoid receptors, and cannabinoids influence their immune functions. Of note, alveolar macrophages isolated from chronic marijuana users are compromised in secreting proinflammatory cytokines, such as tumor necrosis factor- $\alpha$  and interleukin-6, in response to LPS [16, 17]. This review discusses cannabinoid modulation of TLR ligand responses by innate immune cells, and vice versa.

### 4.1. Impact of Cannabinoids on Toll-Like Receptor Responses

Cannabinoid studies regarding TLRs have concentrated on bacterial LPS responses via TLR4 as a classic model for inflammation (Table 1). For the most part, exogenous and endogenous cannabinoids interfere with proinflammatory cytokine and nitric oxide production by LPS- or LPS/interferon- $\gamma$ -stimulated monocytes, macrophages, microglia, and macrophage cell lines in culture [10–12, 92, 93]. However, one study reported increased interleukin-1 $\beta$  secretion by LPS-activated resident peritoneal cells caused by  $\Delta^9$ -tetrahydrocannabinol [94] in opposition to other investigations [95, 96]. Cannabinoids display biphasic dose-response curves for cytokine secretion in some culture systems [96, 97], which may account for this apparent discrepancy. Interestingly,  $\Delta^9$ -tetrahydrocannabinol decreases LPS-induced cyclooxygenase-2 expression in mouse macrophage J774 cell line [93], which would diminish endocannabinoid 2-arachidonoyl-glycerol metabolism, thereby augmenting immune suppression. In addition, chronic marijuana use increases CB1 and CB2 receptor expression on peripheral blood monocytes [98], which may enhance cannabinoid sensitivity. Thus, exogenous cannabinoids may alter the endocannabinoid system leading to greater suppression of the LPS response.

Cells	Stimulus	Effect
		$\downarrow$ Inflammation

Cell type	Stimulus	Effect
Alveolar macrophages	LPS	
Monocytes	LPS	↓ inflammation Impairs di
		↓ tumor ne

**Table 1**

Cannabinoid effects on *in vitro* TLR responses.

Cannabinoids directly impair TLR-induced cell activation in culture (Table 1).  $\Delta^9$ -Tetrahydrocannabinol perturbs posttranslational processing of tumor necrosis factor- $\alpha$  protein in LPS-activated mouse macrophages [99, 100]. Furthermore, cannabinoids diminish proinflammatory cytokine production in LPS-stimulated mouse microglial BV-2 cell line that is accompanied by decreased transcription factor NF- $\kappa$ B activity and corresponding cytokine mRNA levels [101]. LPS stimulates nitric oxide production and release through induction of nitric oxide synthase-2 expression under NF- $\kappa$ B regulation. Similar to cytokine suppression, cannabinoids attenuate nitric oxide release, nitric oxide synthase-2 gene expression and enzymatic activity, and transcription factor NF- $\kappa$ B activation in LPS- or LPS/interferon- $\gamma$ -activated myeloid cells [92, 102–104]. Analogously, cannabinoids suppress peptidoglycan-stimulated cell growth of a glioma cell line via TLR2 with concomitant decreased NF- $\kappa$ B activation [105]. These results indicate that cannabinoids directly interfere with TLR signal transduction.

On the other hand, cannabinoids may also indirectly suppress *in vitro* cytokine production (Table 1). For example, a CB2 receptor-selective agonist prevents LPS-upregulated TLR4 expression on mouse bone marrow dendritic cells rendering the cells less LPS responsive [106], although a similar cannabinoid effect upon TLR4 expression has not been reported for other innate immune cells. Moreover, cannabinoids induce apoptosis that has been proposed as an immunosuppressive mechanism [107, 108]. However, the majority of findings regarding cannabinoid inhibition of TLR-mediated responses cannot be attributed to apoptosis or cell toxicity. Lastly, cannabinoids may induce other immune suppressive processes. Anandamide and a CB2 receptor-selective agonist induce production of interleukin-10, an inhibitory cytokine, in LPS/interferon- $\gamma$ -activated myeloid cells [109, 110]. CP55,940 induces interleukin-1 receptor antagonist expression in LPS-stimulated microglial cells [111], which interferes with interleukin-1 signals. Thus, multiple modes of action may mediate cannabinoid suppression of *in vitro* LPS responses.

LPS administration in animals is frequently used as *in vivo* models of inflammation and bacterial sepsis (Table 2). A synthetic cannabinoid diminishes LPS-stimulated proinflammatory cytokine levels in the brain and blood of rats [112]. In the LPS-induced pulmonary inflammation model, exogenous and endogenous cannabinoids dose-dependently decrease tumor necrosis factor- $\alpha$  level in bronchoalveolar fluid and reduce neutrophil infiltration into the lungs in mice [113]. Synthetic cannabinoids rescue *C. parvum*-primed mice from LPS lethality and diminish serum proinflammatory cytokine levels [114]. Likewise, a nonpsychoactive synthetic cannabinoid abolishes LPS-induced hypotensive response in rats and rescues mice from the lethal effects of LPS and D-galactosamine coadministration [115]. A CB2 receptor-selective agonist also protects against mortality and acute liver failure, decreases proinflammatory cytokines levels, and increases inhibitory interleukin-10 level in mice given LPS and D-galactosamine [116]. Upon *in vitro* LPS stimulation, cytokine and nitric oxide production by macrophages from mice previously given  $\Delta^9$ -tetrahydrocannabinol remain suppressed without additional drug in the cultures [102]. Perhaps, cannabinoid immune suppression induced *in vivo* may persist after drug removal. Therefore, the effects of cannabinoids on LPS activation in several animal models, in general, parallel the *in vitro* findings.

Animal model	Cell or tissue	Effect
LPS	Blood & brain	↓ inflammatory cytokines CB1R & CB2R-mediated
	Cardiovascular system	↓ hypotensive response
	Blood	↓ tumor necrosis factor- $\alpha$ ↑ survival

**Table 2**

Cannabinoid effects on *in vivo* TLR responses.

Involvement of cannabinoid receptors in suppressing TLR responses has been established by multiple approaches. One set of criteria is cannabinoid receptor-selective agonists causing inhibition and cannabinoid receptor-selective antagonists reversing inhibition. Cannabinoid suppression of proinflammatory cytokine and nitric oxide production is CB2 receptor-mediated in LPS-stimulated cultured cells, LPS-induced pulmonary inflammation, and LPS/galactosamine-induced acute liver failure [113, 116] (Table 2). On the other hand, protection of *C. parvum*-primed mice from LPS lethality and diminished NF- $\kappa$ B activity in TLR2 ligand-stimulated glioma cells are mediated through the CB1 receptor [105, 114], whereas both cannabinoid receptors participate in decreasing cytokine levels after *in vivo* LPS administration [112]. Mice genetically deficient in cannabinoid receptor expression are the best evidence for receptor participation. CB2 receptor-deficient mice are highly susceptible to induced inflammatory diseases, including contact dermatitis, experimental autoimmune encephalomyelitis, atherosclerosis, and carbon tetrachloride-induced liver damage [15, 117]. Incidence and severity of the diseases are exacerbated in the CB2 receptor-deficient mice compared to wild-type mice [15, 117]. Importantly, the CB2 receptor-deficient mice have lower survival, more pronounced tissue damage, and increased serum interleukin-6 levels in a sepsis model [118]. Mice lacking both cannabinoid receptors have markedly heightened allergic inflammation leading to exacerbated contact dermatitis, delayed-type hypersensitivity, and inflammatory responses to *Influenza* virus [119–121]. Alveolar macrophages and bone marrow dendritic cells from mice deficient in both cannabinoid receptors have a more mature phenotype, have increased expression of major histocompatibility complex class I and class II molecules, and are more efficient in activating T cells [120, 121],

suggesting that the absence of endocannabinoid signals may alter differentiation and maturation of innate immune cells towards hyperresponsiveness. Perhaps, the role of the CB1 receptor is more readily detected in *in vivo* models due to interactions among various cell types. The absence of both cannabinoid receptors has a more dramatic impact on the immune system, indicating the possible interplay of cannabinoid receptors during disease processes, which has important implications in developing cannabinoids as therapeutic agents for inflammatory diseases.

Microglial cells play an important role in neuroinflammation and appear to be a special case in terms of cannabinoid receptor-mediated immune suppression. General consensus is that resting microglial cells express a low level of the CB1 receptor and lack CB2 receptor expression [12, 56, 57]. However, microglial cells from diseased tissues or microglial cells activated in culture gain CB2 receptor expression [12, 56, 57]. Criteria used for cannabinoid receptor involvement in diminished proinflammatory cytokine secretion and nitric oxide release from LPS-activated microglial cells in culture reveal all possible outcomes encompassing both cannabinoid receptors, or the CB1, CB2, or no cannabinoid receptor [103, 109, 111, 123–125]. A receptor-independent mechanism despite cannabinoid receptor expression on the cells implies that cannabinoid receptor expression is too low to exert a biological effect, or the receptors are inactive. A receptor-independent mechanism may involve disruption of lipid rafts due to the hydrophobicity of cannabinoids [141]. As discussed above, lipid rafts are critical for proper assembly of the TLR4 and TLR2 complexes, and their disruption would contribute to a decreased TLR response. Differences in agonist or antagonist concentrations, and cell activation state among the studies, may contribute to disparate findings concerning cannabinoid receptor participation. Additional investigation is needed to resolve this issue.

Cannabinoids exert immune suppression when innate immune cells are activated, but not when the cells are resting or quiescent. When direct suppression is cannabinoid receptor-mediated, the two signal transduction pathways (Figures (Figures 11 and 2(a))) would cross-talk. Transcription factor NF- $\kappa$ B is activated through the MyD88-dependent signal transduction pathway via both TLR4 and TLR2. Hence, cannabinoids must interfere with the MyD88-dependent signal transduction pathway to decrease NF- $\kappa$ B activity along with diminishing cytokine production and cell growth through TLR4 and TLR2. In some cases, cell permeable cAMP to counteract the active G<sub>i/o</sub> subunit reverses cannabinoid inhibition of cytokine secretion and nitric oxide release [10–12, 102, 124] suggesting the involvement of decreased protein kinase A activity in mediating suppression. However, protein kinase A activity is not necessary for cytokine gene expression in TLR-activated cells (Figure 2). Other studies suggest cannabinoid regulation of p42/p44 MAPK activation participates in immune suppression [41, 52]. Activation of the MAPK pathways is required for cytokine gene transcription. In this scenario, too much of a positive signal becomes negative. Excessive MAPK activation may generate a negative feedback loop. Although a remaining question is what is the link between the cannabinoid and TLRs signaling pathways, MAPKs are attractive candidates.

Cannabinoids augment interferon- $\beta$  production during the TLR3 ligand response (Table 1). Very few studies have examined the impact of cannabinoids on TLR3 signal transduction and interferon- $\beta$  production (Figure 2(b)), and, thus, studies with nonimmune cells are discussed below. Interferon- $\beta$  is a type I interferon with antiviral and anti-inflammatory activities and is a treatment for multiple sclerosis patients [142]. WIN 55,212-2 does not suppress but rather enhances interferon- $\beta$  mRNA expression in polyinosinic:polycytidylic acid-activated HEK293 cell line transfected with TLR3 cDNA [127]. Interferon- $\beta$  transcript upregulation is accompanied by increased MAPK and transcription factor IRF3 activities; however tumor necrosis factor- $\alpha$  secretion and transcription factor NF- $\kappa$ B activity decrease in the TLR3-transfected cells [127]. Analogously, WIN 55,212-2 augments interferon- $\beta$  mRNA expression but decreases tumor necrosis factor- $\alpha$  secretion in polyinosinic:polycytidylic acid-activated primary astrocytes and peripheral blood mononuclear cells from multiple sclerosis patients [126, 127]. Perhaps, excessive MAPK activation leads to decreased NF- $\kappa$ B activity as discussed for the LPS response. The opposing effects on IRF3 and NF- $\kappa$ B activities indicate that the cannabinoid alters a signaling step downstream of TRIF binding TLR3.

In striking contrast, WIN 55,212-2 has the opposite effect on interferon- $\beta$  mRNA and transcription factor IRF3 in TLR4-transfected HEK293 cells stimulated with LPS [126] (Table 1). Likewise,  $\Delta^9$ -tetrahydrocannabinol and nonpsychoactive cannabidiol inhibits interferon- $\beta$  mRNA expression and protein secretion in LPS-activated mouse microglial BV-2 cell line [125]. An antagonist of peroxisome proliferator-activated receptor- $\alpha$  blocks the enhanced interferon- $\beta$  level without affecting tumor necrosis factor- $\alpha$  level in TLR3-transfected HEK293 cells [127], indicating sensitivity of transcription factor IRF3, but not NF- $\kappa$ B, activity to peroxisome proliferator-activated receptor- $\alpha$ . However, sensitivity of interferon- $\beta$  inhibition to the peroxisome proliferator-activated receptor- $\alpha$  antagonist was not examined in TLR4-transfected HEK293 cells. The opposing cannabinoid effects on interferon- $\beta$  induced via TLR3 versus TLR4 signaling pathways (Figure 2) raise the question of why peroxisome proliferator-activated receptor- $\alpha$  does not enhance interferon- $\beta$  production in LPS-stimulated cells exposed to cannabinoids, unless the receptor is not activated during TLR4 signaling. The disparate cannabinoid effect on interferon- $\beta$  production implies two different molecular targets in the TLR3 and TLR4 pathways. Perhaps, the TRAM:TRIF and TRIF adaptors, or TRAF3 and TRAF6 used by TLR4 and TLR3, respectively, have differential sensitivity to cannabinoid immune modulation.

#### 4.2. Impact of Toll-Like Receptor Activation on Endocannabinoid System

Cannabinoid receptor expression by immune cells varies depending on the cell type, maturational stage, and activation state. Innate immune cells have a high degree of plasticity, and their cannabinoid receptor expression can be manipulated intentionally (Table 3). Human peripheral blood monocytes, human dendritic cells, and some monocyte/macrophage cell lines constitutively express both CB1 and CB2 receptors [129, 138, 143]. Maturation of human peripheral blood monocytes and monocytic THP-1 cells and differentiation of human promyelocytic HL60 cell line into macrophages by phorbol esters upregulate cannabinoid receptor expression [143–145]. Notably,  $\Delta^9$ -tetrahydrocannabinol impairs LPS-mediated differentiation of human monocytes into dendritic cells [122]. On the other hand, resident mouse macrophages lack detectable CB1 and CB2 receptor mRNA, whereas inflammatory thioglycollate-elicited macrophages express a high level of the CB2 receptor, and interferon- $\gamma$  stimulation may further increase CB2 receptor expression [128]. Microglial cells express no/low level of CB1 receptor mRNA, and CB2 receptor mRNA is undetectable [128, 129, 146]. Stimulation of rodent microglial cells with interferon- $\gamma$  induces CB2 receptor mRNA expression [129, 130]. The level of cannabinoid receptor expression on immune cells affects cannabinoid immune modulation. For example, a nonpsychoactive cannabinoid inhibits LPS-induced interleukin-6 expression only after human monocytes mature into macrophages [147]. Hence,



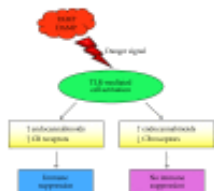
particular stimuli induce or upregulate cannabinoid receptor expression during myeloid cell differentiation, maturation, and activation affecting their sensitivity to cannabinoids.

Cell or tissue	Stimulus <i>in vitro</i> or animal model	Effect
Macrophages	Thioglycollate <i>in vivo</i>	↑ CB2 rec
Microglial cells	Interferon- $\gamma$	Induces CE
Thioglycollate-elicited	LPS	↓ CB2 rec

[Table 3](#)

Inflammatory effects on endocannabinoid system.

The influence of only TLR4 signal transduction has been investigated on the endocannabinoid system in myeloid cells ([Table 3](#)). LPS modulation of cannabinoid receptor expression in myeloid cells depends on the experimental system ([Figure 3](#)). For example, CB2 receptor mRNA level drops in thioglycollate-elicited macrophages in response to LPS [[128](#), [131](#)]. In contrast, LPS activation of mouse macrophage RAW 264.7 cell line induces CB1 receptor mRNA and upregulates CB2 receptor mRNA expression [[129](#), [132](#), [139](#)]. Protein kinases A and C inhibitors partially block the LPS effect on CB1 and CB2 receptor expression [[132](#)], although involvement of the cAMP-protein kinase A pathway in LPS signaling is controversial [[148](#)]. Likewise, *in vivo* LPS administration to rodents upregulates CB2 receptor expression in microglial cells [[132](#), [133](#)]. Importantly, various pathological conditions are associated with altered cannabinoid receptor expression, usually increased CB2 receptor expression [[10](#), [57](#)]. Hence, the differential LPS impact on cannabinoid receptor expression may reflect plasticity of innate immune cells to cues from their microenvironment.



[Figure 3](#)

Interaction between TLR-mediated activation and endocannabinoid system. PAMPs and DAMPs provide dangers signals that activate innate immune cells via TLRs. Activated cells increase endocannabinoid levels that may suppress the inflammatory response. Cell ...

Evidence is growing that endocannabinoid levels change during various disease processes due to altered catalytic activities of the biosynthetic or metabolizing enzymes. In several animal disease models, modified endocannabinoid levels exert pro- or anti-inflammatory effects on innate immune cells based on enzyme inhibitors, transporter inhibitors, and mice genetically deficient in the enzymes. This research area is discussed in detail elsewhere [[56](#), [57](#), [92](#), [133](#), [149](#)].

Danger signals provided to innate immune cells increase endocannabinoid production ([Figure 3](#)). LPS administration *in vivo* decreases metabolizing fatty acid amide hydrolase activity in mouse peripheral blood mononuclear cells [[134](#)], which would increase anandamide levels ([Table 3](#)). Similarly, LPS administration also diminishes 2-arachidonyl glycerol hydrolytic activity within the spleen and liver [[135](#)]. Anandamide is barely detected in rat monocytes and macrophage J774 cell line, whereas the cells contain substantial anandamide levels upon LPS stimulation [[136](#), [140](#)]. In addition, LPS activation of rat macrophages and J774 cells also increases 2-arachidonyl glycerol levels due to decreased 2-arachidonyl glycerol hydrolytic activity in the cells [[137](#)]. Human immature dendritic cells contain enhanced 2-arachidonyl glycerol, but not anandamide, levels upon LPS activation [[138](#)]. Conversely, low dose-LPS activation of macrophage RAW 264.7 cell line increases anandamide, but not 2-arachidonyl glycerol, levels along with enhanced biosynthetic N-acyltransferase and phospholipase D activities [[23](#), [137](#)]. The rapid time kinetics of augmented anandamide level [[23](#)] indicates a direct effect of the TLR4 signal transduction pathway as opposed to autocrine stimulation by secreted cytokines. In support of this possibility, increased anandamide level in RAW 264.7 cells is prevented by MAPK and NF- $\kappa$ B inhibitors [[23](#)], indicating involvement of the MyD88-dependent signal transduction pathway ([Figure 2\(a\)](#)). Although what endocannabinoids increase during LPS stimulation appears to depend on the cell type and experimental conditions, higher endocannabinoid levels are accompanied by increased biosynthetic enzyme activity and/or decreased metabolizing enzyme activity.

[Go to:](#)

## 5. Conclusions

When the immune system encounters a pathogen, innate immune cells recognize the pathogen via TLRs and other pattern-recognition receptors to trigger an inflammatory response. Innate immune cells are an important source of endocannabinoids, and these cells synthesize and metabolize endocannabinoids. TLR-mediated activation of the innate immune cells enhances their endocannabinoid levels ([Figure 3](#)). In the absence of an infection, tissue damage produces DAMPs perceived as danger signals via TLRs to activate innate immune cells. Indeed, local endocannabinoid production increases in response to tissue damage during disease progression and infections [[150](#)]. Abundant evidence demonstrates that cannabinoids have anti-inflammatory activity, which is the desired consequence during sterile inflammation. Considering that 2-arachidonyl glycerol behaves as a chemoattractant [[129](#), [145](#)], locally enhanced endocannabinoid levels may recruit immune cells to the site and mitigate further tissue damage. Thus, innate immune cells may play a role in regulating endocannabinoid homeostasis, and, in turn, the endocannabinoid system modulates local

inflammation. TLR signals also alter cannabinoid receptor expression by innate immune cells, which affects their sensitivity to cannabinoids. During progression of an inflammatory disease, cells may become refractory to cannabinoid immune suppression despite elevated endocannabinoid levels, and the inflammatory response continues and may intensify. Therefore, the final outcome may be enhanced clearance of an infection, facilitation of tissue healing, or exacerbation of tissue damage. Although definition of the link between cannabinoid and TLR signaling pathways awaits further studies, identification of promising molecular targets may provide insights into therapeutic modalities to control injurious inflammation.

[Go to:](#)

## Acknowledgments

The author thanks Dr. Blaine Creasy for assistance with the figures. This work was supported in part by a grant from the VCU Department of Microbiology and Immunology.

[Go to:](#)

## Competing Interests

The author declares that there are no competing interests regarding the publication of this paper.

[Go to:](#)

## References

1. Ben Amar M. Cannabinoids in medicine: a review of their therapeutic potential. *Journal of Ethnopharmacology*. 2006;105(1-2):1–25. doi: 10.1016/j.jep.2006.02.001. [[PubMed](#)] [[Cross Ref](#)]
2. Mackie K. Cannabinoid receptors as therapeutic targets. *Annual Review of Pharmacology and Toxicology*. 2006;46:101–122. doi: 10.1146/annurev.pharmtox.46.120604.141254. [[PubMed](#)] [[Cross Ref](#)]
3. Di Marzo V., De Petrocellis L. Plant, synthetic, and endogenous cannabinoids in medicine. *Annual Review of Medicine*. 2006;57:553–574. doi: 10.1146/annurev.med.57.011205.135648. [[PubMed](#)] [[Cross Ref](#)]
4. Croxford J. L., Yamamura T. Cannabinoids and the immune system: potential for the treatment of inflammatory diseases? *Journal of Neuroimmunology*. 2005;166(1-2):3–18. doi: 10.1016/j.jneuroim.2005.04.023. [[PubMed](#)] [[Cross Ref](#)]
5. Marijuana abuse. *NIDA Research Report Series*. 2005;(NIH Publication No. 05-3859)
6. Zhang M. W., Ho R. C. The cannabis dilemma: a review of its associated risks and clinical efficacy. *Journal of Addiction*. 2015;2015:6. doi: 10.1155/2015/707596.707596 [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
7. Rahn E. J., Hohmann A. G. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. *Neurotherapeutics*. 2009;6(4):713–737. doi: 10.1016/j.nurt.2009.08.002. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
8. Pertwee R. G. Emerging strategies for exploiting cannabinoid receptor agonists as medicines. *British Journal of Pharmacology*. 2009;156(3):397–411. doi: 10.1111/j.1476-5381.2008.00048.x. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
9. Syed Y. Y., McKeage K., Scott L. J. Delta-9-Tetrahydrocannabinol/cannabidiol (Sativex®): A review of its Use in patients with moderate to severe spasticity due to multiple sclerosis. *Drugs*. 2014;74(5):563–578. doi: 10.1007/s40265-014-0197-5. [[PubMed](#)] [[Cross Ref](#)]
10. Klein T. W. Cannabinoid-based drugs as anti-inflammatory therapeutics. *Nature Reviews Immunology*. 2005;5(5):400–411. doi: 10.1038/nri1602. [[PubMed](#)] [[Cross Ref](#)]
11. Klein T. W., Newton C., Larsen K., et al. The cannabinoid system and immune modulation. *Journal of Leukocyte Biology*. 2003;74(4):486–496. doi: 10.1189/jlb.0303101. [[PubMed](#)] [[Cross Ref](#)]
12. Cabral G. A., Marciano-Cabral F. Cannabinoid receptors in microglia of the central nervous system: immune functional relevance. *Journal of Leukocyte Biology*. 2005;78(6):1192–1197. doi: 10.1189/jlb.0405216. [[PubMed](#)] [[Cross Ref](#)]
13. Tashkin D. P., Baldwin G. C., Sarafian T., Dubinett S., Roth M. D. Respiratory and immunologic consequences of marijuana smoking. *Journal of Clinical Pharmacology*. 2002;42(supplement 11):71S–81S. [[PubMed](#)]
14. Roth M. D., Baldwin G. C., Tashkin D. P. Effects of delta-9-tetrahydrocannabinol on human immune function and host defense. *Chemistry and Physics of Lipids*. 2002;121(1-2):229–239. doi: 10.1016/S0009-3084(02)00159-7. [[PubMed](#)] [[Cross Ref](#)]
15. Buckley N. E. The peripheral cannabinoid receptor knockout mice: an update. *British Journal of Pharmacology*. 2008;153(2):309–318. doi: 10.1038/sj.bjp.0707527. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
16. Baldwin G. C., Tashkin D. P., Buckley D. M., Park A. N., Dubinett S. M., Roth M. D. Marijuana and cocaine impair alveolar macrophage function and cytokine production. *American Journal of Respiratory and Critical Care Medicine*. 1997;156(5):1606–1613. doi: 10.1164/ajrccm.156.5.9704146. [[PubMed](#)] [[Cross Ref](#)]
17. Pacifici R., Zuccaro P., Pichini S., et al. Modulation of the immune system in cannabis users. *The Journal of the American Medical Association*. 2003;289(15):1929–1931. doi: 10.1001/jama.289.15.1929-a. [[PubMed](#)] [[Cross Ref](#)]
18. McCoy K. L., Gainey D., Cabral G. A. Δ9-Tetrahydrocannabinol modulates antigen processing by macrophages. *Journal of Pharmacology and Experimental Therapeutics*. 1995;273(3):1216–1223. [[PubMed](#)]
19. Clements D. J., Cabral G. A., McCoy K. L. Δ9-Tetrahydrocannabinol selectively inhibits macrophage costimulatory activity and down-regulates heat-stable antigen expression. *Journal of Pharmacology and Experimental Therapeutics*. 1996;277(3):1315–1321. [[PubMed](#)]
20. McCoy K. L., Matveyeva M., Carlisle S. J., Cabral G. A. Cannabinoid inhibition of the processing of intact lysozyme by macrophages: evidence for CB2 receptor participation. *Journal of Pharmacology and Experimental Therapeutics*. 1999;289(3):1620–1625. [[PubMed](#)]
21. Buckley N. E., McCoy K. L., Mezey É., et al. Immunomodulation by cannabinoids is absent in mice deficient for the cannabinoid CB2 receptor. *European Journal of Pharmacology*. 2000;396(2-3):141–149. doi: 10.1016/S0014-2999(00)00211-9. [[PubMed](#)] [[Cross Ref](#)]
22. Chuchawankul S., Shima M., Buckley N. E., Hartmann C. B., McCoy K. L. Role of cannabinoid receptors in inhibiting macrophage

- costimulatory activity. *International Immunopharmacology*. 2004;4(2):265–278. doi: 10.1016/j.intimp.2003.12.011. [[PubMed](#)] [[Cross Ref](#)]
23. Liu J., Bátkai S., Pacher P., et al. Lipopolysaccharide induces anandamide synthesis in macrophages via CD14/MAPK/phosphoinositide 3-kinase/NF- $\kappa$ B independently of platelet-activating factor. *The Journal of Biological Chemistry*. 2003;278(45):45034–45039. doi: 10.1074/jbc.m306062200. [[PubMed](#)] [[Cross Ref](#)]
24. Pertwee R. G., Howlett A. C., Abood M. E., et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: Beyond CB1 and CB2. *Pharmacological Reviews*. 2010;62(4):588–631. doi: 10.1124/pr.110.003004. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
25. Pertwee R. G. Endocannabinoids and their pharmacological actions. *Handbook of Experimental Pharmacology*. 2015;231:1–37. doi: 10.1007/978-3-319-20825-1\_1. [[PubMed](#)] [[Cross Ref](#)]
26. Hill A. J., Williams C. M., Whalley B. J., Stephens G. J. Phytocannabinoids as novel therapeutic agents in CNS disorders. *Pharmacology & Therapeutics*. 2012;133(1):79–97. doi: 10.1016/j.pharmthera.2011.09.002. [[PubMed](#)] [[Cross Ref](#)]
27. Matsuda L. A., Lolait S. J., Brownstein M. J., Young A. C., Bonner T. I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*. 1990;346(6284):561–564. doi: 10.1038/346561a0. [[PubMed](#)] [[Cross Ref](#)]
28. Thomas B. F., Wei X., Martin B. R. Characterization and autoradiographic localization of the cannabinoid binding site in rat brain using [ $^3$ H]11-OH- $\Delta^9$ -THC-DMH. *Journal of Pharmacology and Experimental Therapeutics*. 1992;263(3):1383–1390. [[PubMed](#)]
29. Munro S., Thomas K. L., Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature*. 1993;365(6441):61–65. doi: 10.1038/365061a0. [[PubMed](#)] [[Cross Ref](#)]
30. Bouaboula M., Rinaldi M., Carayon P., et al. Cannabinoid-receptor expression in human leukocytes. *European Journal of Biochemistry*. 1993;214(1):173–180. doi: 10.1111/j.1432-1033.1993.tb17910.x. [[PubMed](#)] [[Cross Ref](#)]
31. Galiègue S., Mary S., Marchand J., et al. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *European Journal of Biochemistry*. 1995;232(1):54–61. doi: 10.1111/j.1432-1033.1995.tb20780.x. [[PubMed](#)] [[Cross Ref](#)]
32. Van Sickle M. D., Duncan M., Kingsley P. J., et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science*. 2005;310(5746):329–332. doi: 10.1126/science.1115740. [[PubMed](#)] [[Cross Ref](#)]
33. Yiangou Y., Facer P., Durrenberger P., et al. COX-2, CB2 and P2X7-immunoreactivities are increased in activated microglial cells/macrophages of multiple sclerosis and amyotrophic lateral sclerosis spinal cord. *BMC Neurology*. 2006;6, article 12 doi: 10.1186/1471-2377-6-12. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
34. Benito C., Núñez E., Tolón R. M., et al. Cannabinoid CB2 receptors and fatty acid amide hydrolase are selectively overexpressed in neuritic plaque-associated glia in Alzheimer's disease brains. *The Journal of Neuroscience*. 2003;23(35):11136–11141. [[PubMed](#)]
35. Valk P., Verbakel S., Vankan Y., et al. Anandamide, a natural ligand for the peripheral cannabinoid receptor is a novel synergistic growth factor for hematopoietic cells. *Blood*. 1997;90(4):1448–1457. [[PubMed](#)]
36. Noe S. N., Newton C., Widen R., Friedman H., Klein T. W. Anti-CD40, anti-CD3, and IL-2 stimulation induce contrasting changes in CB1 mRNA expression in mouse splenocytes. *Journal of Neuroimmunology*. 2000;110(1-2):161–167. doi: 10.1016/s0165-5728(00)00349-0. [[PubMed](#)] [[Cross Ref](#)]
37. Svensson M., Chen P., Hammarfjord O. Dendritic cell regulation by cannabinoid-based drugs. *Pharmaceuticals*. 2010;3(8):2733–2750. doi: 10.3390/ph3082733. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
38. Malan T. P., Jr., Ibrahim M. M., Lai J., Vanderah T. W., Makriyannis A., Porreca F. CB2 cannabinoid receptor agonists: pain relief without psychoactive effects? *Current Opinion in Pharmacology*. 2003;3(1):62–67. doi: 10.1016/s1471-4892(02)00004-8. [[PubMed](#)] [[Cross Ref](#)]
39. Kinsey S. G., Mahadevan A., Zhao B., et al. The CB<sub>2</sub> cannabinoid receptor-selective agonist O-3223 reduces pain and inflammation without apparent cannabinoid behavioral effects. *Neuropharmacology*. 2011;60(2-3):244–251. doi: 10.1016/j.neuropharm.2010.09.004. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
40. Howlett A. C. Cannabinoid receptor signaling. *Handbook of Experimental Pharmacology*. 2005;168:53–79. doi: 10.1007/3-540-26573-2-2. [[PubMed](#)] [[Cross Ref](#)]
41. Demuth D. G., Molleman A. Cannabinoid signalling. *Life Sciences*. 2006;78(6):549–563. doi: 10.1016/j.lfs.2005.05.055. [[PubMed](#)] [[Cross Ref](#)]
42. Bell M. R., D'Ambra T. E., Kumar V., et al. Antinociceptive (aminoalkyl)indoles. *Journal of Medicinal Chemistry*. 1991;34(3):1099–1110. [[PubMed](#)]
43. Devane W. A., Hanus L., Breuer A., et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*. 1992;258(5090):1946–1949. doi: 10.1126/science.1470919. [[PubMed](#)] [[Cross Ref](#)]
44. Mechoulam R., Ben-Shabat S., Hanus L., et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochemical Pharmacology*. 1995;50(1):83–90. doi: 10.1016/0006-2952(95)00109-d. [[PubMed](#)] [[Cross Ref](#)]
45. Sugiura T., Kondo S., Sukagawa A., et al. 2-arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochemical and Biophysical Research Communications*. 1995;215(1):89–97. doi: 10.1006/bbrc.1995.2437. [[PubMed](#)] [[Cross Ref](#)]
46. Di Marzo V. 2-Arachidonoyl-glycerol as an 'endocannabinoid': limelight for a formerly neglected metabolite. *Biochemistry*. 1998;63(1):13–21. [[PubMed](#)]
47. Howlett A. C., Fleming R. M. Cannabinoid inhibition of adenylate cyclase. Pharmacology of the response in neuroblastoma cell membrane. *Molecular Pharmacology*. 1984;26(3):532–538. [[PubMed](#)]
48. Howlett A. C., Qualy J. M., Khachatrian L. L. Involvement of G(i) in the inhibition of adenylate cyclase by cannabimimetic drugs. *Molecular Pharmacology*. 1986;29(3):307–313. [[PubMed](#)]
49. Rubovitch V., Gafni M., Sarne Y. The involvement of VEGF receptors and MAPK in the cannabinoid potentiation of Ca<sup>2+</sup> flux into N18TG2 neuroblastoma cells. *Molecular Brain Research*. 2004;120(2):138–144. doi: 10.1016/j.molbrainres.2003.10.012. [[PubMed](#)] [[Cross Ref](#)]
50. Bouaboula M., Poinot-Chazel C., Bourrie B., et al. Activation of mitogen-activated protein kinases by stimulation of the central cannabinoid receptor CB1. *Biochemical Journal*. 1995;312(2):637–641. doi: 10.1042/bj3120637. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
51. Carrier E. J., Kearn C. S., Barkmeier A. J., et al. Cultured rat microglial cells synthesize the endocannabinoid 2-arachidonoylglycerol, which increases proliferation via a CB2 receptor-dependent mechanism. *Molecular Pharmacology*. 2004;65(4):999–1007. doi: 10.1124/mol.65.4.999. [[PubMed](#)] [[Cross Ref](#)]

52. Faubert Kaplan B. L., Kaminski N. E. Cannabinoids inhibit the activation of ERK MAPK in PMA/Io-stimulated mouse splenocytes. *International Immunopharmacology*. 2003;3(10-11):1503–1510. doi: 10.1016/s1567-5769(03)00163-2. [[PubMed](#)] [[Cross Ref](#)]
53. Gomez O., Sanchez-Rodriguez M. A., Ortega-Gutierrez S., et al. A basal tone of 2-arachidonoylglycerol contributes to early oligodendrocyte progenitor proliferation by activating phosphatidylinositol 3-kinase (PI3K)/AKT and the Mammalian Target of Rapamycin (mTOR) pathways. *Journal of Neuroimmune Pharmacology*. 2015;10(2):309–317. doi: 10.1007/s11481-015-9609-x. [[PubMed](#)] [[Cross Ref](#)]
54. Palazuelos J., Ortega Z., Díaz-Alonso J., Guzmán M., Galve-Roperh I. CB2 cannabinoid receptors promote neural progenitor cell proliferation via mTORC1 signaling. *The Journal of Biological Chemistry*. 2012;287(2):1198–1209. doi: 10.1074/jbc.m111.291294. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
55. Morell C., Bort A., Vara D., Ramos-Torres A., Rodríguez-Henche N., Díaz-Laviada I. The cannabinoid WIN 55,212-2 prevents neuroendocrine differentiation of LNCaP prostate cancer cells. *Prostate Cancer and Prostatic Diseases*. 2016 doi: 10.1038/pcan.2016.19. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
56. Stella N. Endocannabinoid signaling in microglial cells. *Neuropharmacology*. 2009;56(1):244–253. doi: 10.1016/j.neuropharm.2008.07.037. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
57. Pacher P., Kunos G. Modulating the endocannabinoid system in human health and disease: successes and failures. *FEBS Journal*. 2013;280(9):1918–1943. doi: 10.1111/febs.12260. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
58. Di Marzo V., Fontana A., Cadas H., et al. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. *Nature*. 1994;372(6507):686–691. doi: 10.1038/372686a0. [[PubMed](#)] [[Cross Ref](#)]
59. Walker J. M., Huang S. M., Strangman N. M., Tsou K., Sañudo-Peña M. C. Pain modulation by release of the endogenous cannabinoid anandamide. *Proceedings of the National Academy of Sciences of the United States of America*. 1999;96(21):12198–12203. doi: 10.1073/pnas.96.21.12198. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
60. Stella N., Piomelli D. Receptor-dependent formation of endogenous cannabinoids in cortical neurons. *European Journal of Pharmacology*. 2001;425(3):189–196. doi: 10.1016/S0014-2999(01)01182-7. [[PubMed](#)] [[Cross Ref](#)]
61. Béquet F., Uzabiaga F., Desbazeille M., et al. CB1 receptor-mediated control of the release of endocannabinoids (as assessed by microdialysis coupled with LC/MS) in the rat hypothalamus. *European Journal of Neuroscience*. 2007;26(12):3458–3464. doi: 10.1111/j.1460-9568.2007.05900.x. [[PubMed](#)] [[Cross Ref](#)]
62. Di Marzo V. Targeting the endocannabinoid system: to enhance or reduce? *Nature Reviews Drug Discovery*. 2008;7(5):438–455. doi: 10.1038/nrd2553. [[PubMed](#)] [[Cross Ref](#)]
63. Di Marzo V., De Petrocellis L., Bisogno T. *Cannabinoids*. Vol. 168. Berlin, Germany: Springer; 2005. The biosynthesis, fate and pharmacological properties of endocannabinoids; pp. 147–185. (Handbook in Experimental Pharmacology). [[PubMed](#)] [[Cross Ref](#)]
64. Pandey R., Mousawy K., Nagarkatti M., Nagarkatti P. Endocannabinoids and immune regulation. *Pharmacological Research*. 2009;60(2):85–92. doi: 10.1016/j.phrs.2009.03.019. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
65. Cascio M. G., Marini P. Biosynthesis and fate of endocannabinoids. *Handbook of Experimental Pharmacology*. 2015;231:39–58. doi: 10.1007/978-3-319-20825-1\_2. [[PubMed](#)] [[Cross Ref](#)]
66. Cravatt B. F., Demarest K., Patricelli M. P., et al. Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. *Proceedings of the National Academy of Sciences of the United States of America*. 2001;98(16):9371–9376. doi: 10.1073/pnas.161191698. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
67. Beltramo M., Piomelli D. Carrier-mediated transport and enzymatic hydrolysis of the endogenous cannabinoid 2-arachidonoylglycerol. *NeuroReport*. 2000;11(6):1231–1235. doi: 10.1097/00001756-200004270-00018. [[PubMed](#)] [[Cross Ref](#)]
68. Janeway C. A., Jr. Approaching the asymptote? Evolution and revolution in immunology. *Cold Spring Harbor Symposia on Quantitative Biology*. 1989;54(1):1–13. doi: 10.1101/SQB.1989.054.01.003. [[PubMed](#)] [[Cross Ref](#)]
69. Santoni G., Cardinali C., Morelli B., Santoni M., Nabissi M., Amantini C. Danger- and pathogen-associated molecular patterns recognition by pattern-recognition receptors and ion channels of the transient receptor potential family triggers the inflammasome activation in immune cells and sensory neurons. *Journal of Neuroinflammation*. 2015;12(1, article 21):10. doi: 10.1186/s12974-015-0239-2. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
70. Brubaker S. W., Bonham K. S., Zannoni I., Kagan J. C. Innate immune pattern recognition: a cell biological perspective. *Annual Review of Immunology*. 2015;33:257–290. doi: 10.1146/annurev-immunol-032414-112240. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
71. O'Neill L. A. J. When signaling pathways collide: positive and negative regulation of Toll-like receptor signal transduction. *Immunity*. 2008;29(1):12–20. doi: 10.1016/j.immuni.2008.06.004. [[PubMed](#)] [[Cross Ref](#)]
72. Lee B. L., Barton G. M. Trafficking of endosomal Toll-like receptors. *Trends in Cell Biology*. 2014;24(6):360–369. doi: 10.1016/j.tcb.2013.12.002. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
73. Kawasaki T., Kawai T. Toll-like receptor signaling pathways. *Frontiers in Immunology*. 2014;5, article 461:8. doi: 10.3389/fimmu.2014.00461. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
74. Kagan J. C., Su T., Horng T., Chow A., Akira S., Medzhitov R. TRAM couples endocytosis of Toll-like receptor 4 to the induction of interferon- $\beta$ . *Nature Immunology*. 2008;9(4):361–368. doi: 10.1038/ni1569. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
75. Tanimura N., Saitoh S., Matsumoto F., Akashi-Takamura S., Miyake K. Roles for LPS-dependent interaction and relocation of TLR4 and TRAM in TRIF-signaling. *Biochemical and Biophysical Research Communications*. 2008;368(1):94–99. doi: 10.1016/j.bbrc.2008.01.061. [[PubMed](#)] [[Cross Ref](#)]
76. Piccinini A. M., Midwood K. S. DAMPening inflammation by modulating TLR signalling. *Mediators of Inflammation*. 2010;2010:21. doi: 10.1155/2010/672395.672395 [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
77. Stein D., Roth S., Vogelsang E., Nüsslein-Volhard C. The polarity of the dorsoventral axis in the *Drosophila* embryo is defined by an extracellular signal. *Cell*. 1991;65(5):725–735. doi: 10.1016/0092-8674(91)90381-8. [[PubMed](#)] [[Cross Ref](#)]
78. Hashimoto C., Hudson K. L., Anderson K. V. The *Toll* gene of *Drosophila*, required for dorsal-ventral embryonic polarity, appears to encode a transmembrane protein. *Cell*. 1988;52(2):269–279. doi: 10.1016/0092-8674(88)90516-8. [[PubMed](#)] [[Cross Ref](#)]
79. Lemaitre B., Nicolas E., Michaut L., Reichhart J.-M., Hoffmann J. A. The dorsoventral regulatory gene cassette spatzle/Toll/Cactus controls the potent antifungal response in *Drosophila* adults. *Cell*. 1996;86(6):973–983. doi: 10.1016/S0092-8674(00)80172-5. [[PubMed](#)] [[Cross Ref](#)]
80. Nomura N., Miyajima N., Sazuka T., et al. Prediction of the coding sequences of unidentified human genes. I. The coding sequences of 40 new genes (KIAA0001-KIAA0040) deduced by analysis of randomly sampled cDNA clones from human immature myeloid cell line KG-1. *DNA Research*. 1994;1(1):27–35. doi: 10.1093/dnares/1.1.27. [[PubMed](#)] [[Cross Ref](#)]
81. Medzhitov R., Preston-Hurlburt P., Janeway C. A., Jr. A human homologue of the *Drosophila* Toll protein signals activation of

- adaptive immunity. *Nature*. 1997;388(6640):394–397. doi: 10.1038/41131. [[PubMed](#)] [[Cross Ref](#)]
82. Matzinger P. Essay 1: the danger model in its historical context. *Scandinavian Journal of Immunology*. 2001;54(1-2):4–9. doi: 10.1046/j.1365-3083.2001.00974.x. [[PubMed](#)] [[Cross Ref](#)]
83. Ohashi K., Burkart V., Flohé S., Kolb H. Cutting edge: heat shock protein 60 is a putative endogenous ligand of the toll-like receptor-4 complex. *The Journal of Immunology*. 2000;164(2):558–561. doi: 10.4049/jimmunol.164.2.558. [[PubMed](#)] [[Cross Ref](#)]
84. Basu S., Binder R. J., Suto R., Anderson K. M., Srivastava P. K. Necrotic but not apoptotic cell death releases heat shock proteins, which deliver a partial maturation signal to dendritic cells and activate the NF- $\kappa$ B pathway. *International Immunology*. 2000;12(11):1539–1546. doi: 10.1093/intimm/12.11.1539. [[PubMed](#)] [[Cross Ref](#)]
85. Li M., Carpio D. F., Zheng Y., et al. An essential role of the NF- $\kappa$ B/toll-like receptor pathway in induction of inflammatory and tissue-repair gene expression by necrotic cells. *The Journal of Immunology*. 2001;166(12):7128–7135. doi: 10.4049/jimmunol.166.12.7128. [[PubMed](#)] [[Cross Ref](#)]
86. Qian C., Cao X. Regulation of Toll-like receptor signaling pathways in innate immune responses. *Annals of the New York Academy of Sciences*. 2013;1283(1):67–74. doi: 10.1111/j.1749-6632.2012.06786.x. [[PubMed](#)] [[Cross Ref](#)]
87. Gioannini T. L., Weiss J. P. Regulation of interactions of Gram-negative bacterial endotoxins with mammalian cells. *Immunologic Research*. 2007;39(1–3):249–260. doi: 10.1007/s12026-007-0069-0. [[PubMed](#)] [[Cross Ref](#)]
88. Hoebe K., Georgel P., Rutschmann S., et al. CD36 is a sensor of diacylglycerides. *Nature*. 2005;433(7025):523–527. doi: 10.1038/nature03253. [[PubMed](#)] [[Cross Ref](#)]
89. Silverstein R. L., Febbraio M. CD36, a scavenger receptor involved in immunity, metabolism, angiogenesis, and behavior. *Science Signaling*. 2009;2(72, article re3):16. doi: 10.1126/scisignal.272re3. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
90. Miguel R. N., Wong J., Westoll J. F., et al. A dimer of the toll-like receptor 4 cytoplasmic domain provides a specific scaffold for the recruitment of signalling adaptor proteins. *PLoS ONE*. 2007;2(8, article e788) doi: 10.1371/journal.pone.0000788. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
91. Verstak B., Arnot C. J., Gay N. J. An alanine-to-proline mutation in the BB-loop of TLR3 Toll/IL-1R domain switches signalling adaptor specificity from TRIF to MyD88. *The Journal of Immunology*. 2013;191(12):6101–6109. doi: 10.4049/jimmunol.1300849. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
92. Mestre L., Correa F., Arévalo-Martín A., et al. Pharmacological modulation of the endocannabinoid system in a viral model of multiple sclerosis. *Journal of Neurochemistry*. 2005;92(6):1327–1339. doi: 10.1111/j.1471-4159.2004.02979.x. [[PubMed](#)] [[Cross Ref](#)]
93. Chang Y.-H., Lee S. T., Lin W.-W. Effects of cannabinoids on LPS-stimulated inflammatory mediator release from macrophages: involvement of eicosanoids. *Journal of Cellular Biochemistry*. 2001;81(4):715–723. doi: 10.1002/jcb.1103. [[PubMed](#)] [[Cross Ref](#)]
94. Zhu W., Newton C., Daaka Y., Friedman H., Klein T. W.  $\Delta^9$ -tetrahydrocannabinol enhances the secretion of interleukin 1 from endotoxin-stimulated macrophages. *Journal of Pharmacology and Experimental Therapeutics*. 1994;270(3):1334–1339. [[PubMed](#)]
95. Zurier R. B., Rossetti R. G., Burstein S. H., Bidinger B. Suppression of human monocyte interleukin-1 $\beta$  production by ajulemic acid, a nonpsychoactive cannabinoid. *Biochemical Pharmacology*. 2003;65(4):649–655. doi: 10.1016/S0006-2952(02)01604-0. [[PubMed](#)] [[Cross Ref](#)]
96. Watzl B., Scuderi P., Watson R. R. Marijuana components stimulate human peripheral blood mononuclear cell secretion of interferon- $\gamma$  and suppress interleukin-1  $\alpha$  in vitro. *International Journal of Immunopharmacology*. 1991;13(8):1091–1097. doi: 10.1016/0192-0561(91)90160-9. [[PubMed](#)] [[Cross Ref](#)]
97. Berdyshev E. V., Boichot E., Germain N., Allain N., Anger J.-P., Lagente V. Influence of fatty acid ethanolamides and  $\Delta^9$ -tetrahydrocannabinol on cytokine and arachidonate release by mononuclear cells. *European Journal of Pharmacology*. 1997;330(2-3):231–240. doi: 10.1016/s0014-2999(97)01007-8. [[PubMed](#)] [[Cross Ref](#)]
98. Nong L., Newton C., Cheng Q., Friedman H., Roth M. D., Klein T. W. Altered cannabinoid receptor mRNA expression in peripheral blood mononuclear cells from marijuana smokers. *Journal of Neuroimmunology*. 2002;127(1-2):169–176. doi: 10.1016/S0165-5728(02)00113-3. [[PubMed](#)] [[Cross Ref](#)]
99. Zheng Z.-M., Specter S. C. Delta-9-tetrahydrocannabinol suppresses tumor necrosis factor  $\alpha$  maturation and secretion but not its transcription in mouse macrophages. *International Journal of Immunopharmacology*. 1996;18(1):53–68. doi: 10.1016/0192-0561(95)00107-7. [[PubMed](#)] [[Cross Ref](#)]
100. Fischer-Stenger K., Pettit D. A. D., Cabral G. A.  $\Delta^9$ -tetrahydrocannabinol inhibition of tumor necrosis factor- $\alpha$ : suppression of post-translational events. *Journal of Pharmacology and Experimental Therapeutics*. 1993;267(3):1558–1565. [[PubMed](#)]
101. More S. V., Park J.-Y., Kim B.-W., et al. Anti-neuroinflammatory activity of a novel cannabinoid derivative by inhibiting the NF- $\kappa$ B signaling pathway in lipopolysaccharide-induced BV-2 microglial cells. *Journal of Pharmacological Sciences*. 2013;121(2):119–130. doi: 10.1254/jphs.12170fp. [[PubMed](#)] [[Cross Ref](#)]
102. Coffey R. G., Yamamoto Y., Snella E., Pross S. Tetrahydrocannabinol inhibition of macrophage nitric oxide production. *Biochemical Pharmacology*. 1996;52(5):743–751. doi: 10.1016/0006-2952(96)00356-5. [[PubMed](#)] [[Cross Ref](#)]
103. Puffenbarger R. A., Boothe A. C., Cabral G. A. Cannabinoids inhibit LPS-inducible cytokine mRNA expression in rat microglial cells. *Glia*. 2000;29(1):58–69. doi: 10.1002/(sici)1098-1136(2000101)29:138::aid-glia63.0.co;2-w. [[PubMed](#)] [[Cross Ref](#)]
104. Jeon Y. L., Yang K. H., Pulaski J. T., Kaminski N. E. Attenuation of inducible nitric oxide synthase gene expression by delta 9-tetrahydrocannabinol is mediated through the inhibition of nuclear factor- $\kappa$ B/Rel activation. *Molecular Pharmacology*. 1996;50(2):334–341. [[PubMed](#)]
105. Echigo R., Sugimoto N., Yachie A., Ohno-Shosaku T. Cannabinoids inhibit peptidoglycan-induced phosphorylation of NF- $\kappa$ B and cell growth in U87MG human malignant glioma cells. *Oncology Reports*. 2012;28(4):1176–1180. doi: 10.3892/or.2012.1937. [[PubMed](#)] [[Cross Ref](#)]
106. Xu H., Cheng C. L., Chen M., et al. Anti-inflammatory property of the cannabinoid receptor-2-selective agonist JWH-133 in a rodent model of autoimmune uveoretinitis. *Journal of Leukocyte Biology*. 2007;82(3):532–541. doi: 10.1189/jlb.0307159. [[PubMed](#)] [[Cross Ref](#)]
107. Guzmán M. Effects on cell viability. *Handbook of Experimental Pharmacology*. 2005;168:627–642. [[PubMed](#)]
108. Rieder S. A., Chauhan A., Singh U., Nagarkatti M., Nagarkatti P. Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression. *Immunobiology*. 2010;215(8):598–605. doi: 10.1016/j.imbio.2009.04.001. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
109. Correa F., Mestre L., Docagne F., Guaza C. Activation of cannabinoid CB<sub>2</sub> receptor negatively regulates IL-12p40 production in murine macrophages: role of IL-10 and ERK1/2 kinase signaling. *British Journal of Pharmacology*. 2005;145(4):441–448. doi: 10.1038/sj.bjp.0706215. [[PMC free article](#)] [[PubMed](#)] [[Cross Ref](#)]
110. Correa F., Hernandez M., Mestre L., et al. Anandamide enhances IL-10 production in activated macrophages by targeting CB<sub>2</sub>

110. Correa F., Hernandez-Gomez M., Mestre L., et al. Anandamide enhances IL-10 production in activated microglia by targeting CB<sub>2</sub> receptors: roles of ERK1/2, JNK, and NF- $\kappa$ B. *Glia*. 2010;58(2):135–147. doi: 10.1002/glia.20907. [PubMed] [Cross Ref]
111. Molina-Holgado F., Pinteaux E., Moore J. D., et al. Endogenous interleukin-1 receptor antagonist mediates anti-inflammatory and neuroprotective actions of cannabinoids in neurons and glia. *Journal of Neuroscience*. 2003;23(16):6470–6474. [PubMed]
112. Roche M., Diamond M., Kelly J. P., Finn D. P. In vivo modulation of LPS-induced alterations in brain and peripheral cytokines and HPA axis activity by cannabinoids. *Journal of Neuroimmunology*. 2006;181(1-2):57–67. doi: 10.1016/j.jneuroim.2006.08.001. [PubMed] [Cross Ref]
113. Berdyshev E., Boichot E., Corbel M., Germain N., Lagente V. Effects of cannabinoid receptor ligands on LPS-induced pulmonary inflammation in mice. *Life Sciences*. 1998;63(8):125–129. [PubMed]
114. Smith S. R., Terminelli C., Denhardt G. Effects of cannabinoid receptor agonist and antagonist ligands on production of inflammatory cytokines and anti-inflammatory interleukin-10 in endotoxemic mice. *Journal of Pharmacology and Experimental Therapeutics*. 2000;293(1):136–150. [PubMed]
115. Gallily R., Yamin A., Waksman Y., et al. Protection against septic shock and suppression of tumor necrosis factor  $\alpha$  and nitric oxide production by dexanabinol (HU-211), a nonpsychotropic cannabinoid. *Journal of Pharmacology and Experimental Therapeutics*. 1997;283(2):918–924. [PubMed]
116. Tomar S., Zumbun E. E., Nagarkatti M., Nagarkatti P. S. Protective role of cannabinoid receptor 2 activation in galactosamine/lipopolysaccharide-induced acute liver failure through regulation of macrophage polarization and MicroRNAs. *Journal of Pharmacology and Experimental Therapeutics*. 2015;353(2):369–379. doi: 10.1124/jpet.114.220368. [PMC free article] [PubMed] [Cross Ref]
117. Malfitano A. M., Basu S., Maresz K., Bifulco M., Dittel B. N. What we know and do not know about the cannabinoid receptor 2 (CB<sub>2</sub>) *Seminars in Immunology*. 2014;26(5):369–379. doi: 10.1016/j.smim.2014.04.002. [PMC free article] [PubMed] [Cross Ref]
118. Tschöp J., Kasten K. R., Nogueiras R., et al. The cannabinoid receptor 2 is critical for the host response to sepsis. *The Journal of Immunology*. 2009;183(1):499–505. doi: 10.4049/jimmunol.0900203. [PMC free article] [PubMed] [Cross Ref]
119. Karsak M., Gaffal E., Date R., et al. Attenuation of allergic contact dermatitis through the endocannabinoid system. *Science*. 2007;316(5830):1494–1497. doi: 10.1126/science.1142265. [PubMed] [Cross Ref]
120. Buchweitz J. P., Karmaus P. W. F., Williams K. J., Harkema J. R., Kaminski N. E. Targeted deletion of cannabinoid receptors CB<sub>1</sub> and CB<sub>2</sub> produced enhanced inflammatory responses to influenza A/PR/8/34 in the absence and presence of  $\Delta^9$ -tetrahydrocannabinol. *Journal of Leukocyte Biology*. 2008;83(3):785–796. doi: 10.1189/jlb.0907618. [PubMed] [Cross Ref]
121. Karmaus P. W. F., Chen W., Crawford R., Kaplan B. L. F., Kaminski N. E.  $\Delta^9$ -Tetrahydrocannabinol impairs the inflammatory response to influenza infection: role of antigen-presenting cells and the cannabinoid receptors 1 and 2. *Toxicological Sciences*. 2013;131(2):419–433. doi: 10.1093/toxsci/kfs315. [PMC free article] [PubMed] [Cross Ref]
122. Roth M. D., Castaneda J. T., Kiertscher S. M. Exposure to  $\Delta^9$ -tetrahydrocannabinol impairs the differentiation of human monocyte-derived dendritic cells and their capacity for T cell activation. *Journal of Neuroimmune Pharmacology*. 2015;10(2):333–343. doi: 10.1007/s11481-015-9587-z. [PMC free article] [PubMed] [Cross Ref]
123. Merighi S., Gessi S., Varani K., et al. Cannabinoid CB<sub>2</sub> receptors modulate ERK-1/2 kinase signalling and NO release in microglial cells stimulated with bacterial lipopolysaccharide. *British Journal of Pharmacology*. 2012;165(6):1773–1788. doi: 10.1111/j.1476-5381.2011.01673.x. [PMC free article] [PubMed] [Cross Ref]
124. Waksman Y., Olson J. M., Carlisle S. J., Cabral G. A. The central cannabinoid receptor CB<sub>1</sub> mediates inhibition of nitric oxide production by rat microglial cells. *Journal of Pharmacology and Experimental Therapeutics*. 1999;288(3):1357–1366. [PubMed]
125. Kozela E., Pietr M., Juknat A., Rimmerman N., Levy R., Vogel Z. Cannabinoids  $\Delta^9$ -tetrahydrocannabinol and cannabidiol differentially inhibit the lipopolysaccharide-activated NF- $\kappa$ B and interferon- $\beta$ /STAT proinflammatory pathways in BV-2 microglial cells. *The Journal of Biological Chemistry*. 2010;285(3):1616–1626. doi: 10.1074/jbc.m109.069294. [PMC free article] [PubMed] [Cross Ref]
126. Downer E. J., Clifford E., Gran B., Nel H. J., Fallon P. G., Moynagh P. N. Identification of the synthetic cannabinoid R(+)-WIN55,212-2 as a novel regulator of IFN regulatory factor 3 activation and IFN- $\beta$  expression: relevance to therapeutic effects in models of multiple sclerosis. *Journal of Biological Chemistry*. 2011;286(12):10316–10328. doi: 10.1074/jbc.m110.188599. [PMC free article] [PubMed] [Cross Ref]
127. Downer E. J., Clifford E., Amu S., Fallon P. G., Moynagh P. N. The synthetic cannabinoid R(+)-WIN55,212-2 augments interferon- $\beta$  expression via peroxisome proliferator-activated receptor- $\alpha$ . *Journal of Biological Chemistry*. 2012;287(30):25440–25453. doi: 10.1074/jbc.m112.371757. [PMC free article] [PubMed] [Cross Ref]
128. Carlisle S. J., Marciano-Cabral F., Staab A., Ludwick C., Cabral G. A. Differential expression of the CB<sub>2</sub> cannabinoid receptor by rodent macrophages and macrophage-like cells in relation to cell activation. *International Immunopharmacology*. 2002;2(1):69–82. doi: 10.1016/s1567-5769(01)00147-3. [PubMed] [Cross Ref]
129. Walter L., Franklin A., Witting A., et al. Nonpsychotropic cannabinoid receptors regulate microglial cell migration. *The Journal of Neuroscience*. 2003;23(4):1398–1405. [PubMed]
130. Maresz K., Carrier E. J., Ponomarev E. D., Hillard C. J., Dittel B. N. Modulation of the cannabinoid CB<sub>2</sub> receptor in microglial cells in response to inflammatory stimuli. *Journal of Neurochemistry*. 2005;95(2):437–445. doi: 10.1111/j.1471-4159.2005.03380.x. [PubMed] [Cross Ref]
131. Cabral G. A., Raborn E. S., Griffin L., Dennis J., Marciano-Cabral F. CB<sub>2</sub> receptors in the brain: role in central immune function. *British Journal of Pharmacology*. 2008;153(2):240–251. doi: 10.1038/sj.bjp.0707584. [PMC free article] [PubMed] [Cross Ref]
132. Mukhopadhyay S., Das S., Williams E. A., et al. Lipopolysaccharide and cyclic AMP regulation of CB<sub>2</sub> cannabinoid receptor levels in rat brain and mouse RAW 264.7 macrophages. *Journal of Neuroimmunology*. 2006;181(1-2):82–92. doi: 10.1016/j.jneuroim.2006.08.002. [PubMed] [Cross Ref]
133. Concannon R. M., Okine B. N., Finn D. P., Dowd E. Differential upregulation of the cannabinoid CB<sub>2</sub> receptor in neurotoxic and inflammation-driven rat models of Parkinson's disease. *Experimental Neurology*. 2015;269:133–141. doi: 10.1016/j.expneurol.2015.04.007. [PubMed] [Cross Ref]
134. Wolfson M. L., Aisemberg J., Salazar A. I., Domínguez Rubio A. P., Vercelli C. A., Franchi A. M. Progesterone reverts LPS-reduced FAAH activity in murine peripheral blood mononuclear cells by a receptor-mediated fashion. *Molecular and Cellular Endocrinology*. 2013;381(1-2):97–105. doi: 10.1016/j.mce.2013.07.020. [PubMed] [Cross Ref]
135. Saefan B., Barozzi A., Lee J. H., Ross M. K., Kaplan B. L. F. Lipopolysaccharide suppresses cannabinoid CB<sub>2</sub> activity and




135. Szallasi Z., Borazjani A., Lee J. H., Ross M. K., Kapari B. L. F. Lipopolysaccharide suppresses carboxylesterase 2G activity and 2-arachidonoylglycerol hydrolysis: a possible mechanism to regulate inflammation. *Prostaglandins and Other Lipid Mediators*. 2015;121:199–206. doi: 10.1016/j.prostaglandins.2015.09.005. [PMC free article] [PubMed] [Cross Ref]
136. Varga K., Wagner J. A., Bridgen D. T., Kunos G. Platelet- and macrophage-derived endogenous cannabinoids are involved in endotoxin-induced hypotension. *FASEB Journal*. 1998;12(11):1035–1044. [PubMed]
137. Pestonjamas V. K., Burstein S. H. Anandamide synthesis is induced by arachidonate mobilizing agonists in cells of the immune system. *Biochimica et Biophysica Acta (BBA)—Lipids and Lipid Metabolism*. 1998;1394(2-3):249–260. doi: 10.1016/s0005-2760(98)00110-6. [PubMed] [Cross Ref]
138. Matias I., Pochard P., Orlando P., Salzet M., Pestel J., Di Marzo V. Presence and regulation of the endocannabinoid system in human dendritic cells. *European Journal of Biochemistry*. 2002;269(15):3771–3778. doi: 10.1046/j.1432-1033.2002.03078.x. [PubMed] [Cross Ref]
139. Friedman H., Klein T. W., Newton C., Daaka Y. Marijuana, receptors and immunomodulation. *Advances in Experimental Medicine and Biology*. 1995;373:103–113. doi: 10.1007/978-1-4615-1951-5\_15. [PubMed] [Cross Ref]
140. Di Marzo V., Bisogno T., De Petrocellis L., et al. Biosynthesis and inactivation of the endocannabinoid 2-arachidonoylglycerol in circulating and tumoral macrophages. *European Journal of Biochemistry*. 1999;264(1):258–267. doi: 10.1046/j.1432-1327.1999.00631.x. [PubMed] [Cross Ref]
141. Hillard C. J., Harris R. A., Bloom A. S. Effects of the cannabinoids on physical properties of brain membranes and phospholipid vesicles: fluorescence studies. *Journal of Pharmacology and Experimental Therapeutics*. 1985;232(3):579–588. [PubMed]
142. <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicalapplications/ucm080402.htm>.
143. Han K. H., Lim S., Ryu J., et al. CB1 and CB2 cannabinoid receptors differentially regulate the production of reactive oxygen species by macrophages. *Cardiovascular Research*. 2009;84(3):378–386. doi: 10.1093/cvr/cvp240. [PubMed] [Cross Ref]
144. Daaka Y., Klein T. W., Friedman H. Expression of cannabinoid receptor mRNA in murine and human leukocytes. *Advances in Experimental Medicine and Biology*. 1995;373:91–96. doi: 10.1007/978-1-4615-1951-5\_13. [PubMed] [Cross Ref]
145. Kishimoto S., Gokoh M., Oka S., et al. 2-arachidonoylglycerol induces the migration of HL-60 cells differentiated into macrophage-like cells and human peripheral blood monocytes through the cannabinoid CB2 receptor-dependent mechanism. *Journal of Biological Chemistry*. 2003;278(27):24469–24475. doi: 10.1074/jbc.m301359200. [PubMed] [Cross Ref]
146. Klegeris A., Bissonnette C. J., McGeer P. L. Reduction of human monocytic cell neurotoxicity and cytokine secretion by ligands of the cannabinoid-type CB2 receptor. *British Journal of Pharmacology*. 2003;139(4):775–786. doi: 10.1038/sj.bjp.0705304. [PMC free article] [PubMed] [Cross Ref]
147. Parker J., Atez F., Rossetti R. G., Skulas A., Patel R., Zurier R. B. Suppression of human macrophage interleukin-6 by a nonpsychoactive cannabinoid acid. *Rheumatology International*. 2008;28(7):631–635. doi: 10.1007/s00296-007-0489-0. [PubMed] [Cross Ref]
148. Avni D., Ernst O., Philosoph A., Zor T. Role of CREB in modulation of TNF $\alpha$  and IL-10 expression in LPS-stimulated RAW264.7 macrophages. *Molecular Immunology*. 2010;47(7-8):1396–1403. doi: 10.1016/j.molimm.2010.02.015. [PubMed] [Cross Ref]
149. Maccarrone M., Bari M., Battista N., Finazzi-Agrò A. Endocannabinoid degradation, endotoxic shock and inflammation. *Current Drug Targets—Inflammation and Allergy*. 2002;1(1):53–63. doi: 10.2174/1568010023344878. [PubMed] [Cross Ref]
150. Stella N. Cannabinoid signaling in glial cells. *Glia*. 2004;48(4):267–277. doi: 10.1002/glia.20084. [PubMed] [Cross Ref]

Articles from *Mediators of Inflammation* are provided here courtesy of **Hindawi**

## Formats:

- Article
- |
- [PubReader](#)
- |
- [ePub \(beta\)](#)
- |
- [PDF \(917K\)](#)
- |
- [Citation](#)

## Share

-  [Facebook](#)
-  [Twitter](#)
-  [Google+](#)

## Save items

[Add to Favorites](#) [View more options](#)

loading

## Similar articles in PubMed

- [Cannabinoids and innate immunity: taking a toll on neuroinflammation.](#)[ScientificWorldJournal. 2011]
- [Cannabinoids and the immune system: an overview.](#)[Immunobiology. 2010]
- [RAGE and TLRs: relatives, friends or neighbours?](#)[Mol Immunol. 2013]
- [Toll-like receptors in central nervous system glial inflammation and homeostasis.](#)[J Neurosci Res. 2006]
- [The innate immune system, toll-like receptors and dermal wound healing: A review.](#)[Vascul Pharmacol. 2015]

[See reviews...See all...](#)

## Cited by other articles in PMC

- [Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment—a Systematic Review](#)[Journal of Medical Toxicology...]
- [Modulation of Human Peripheral Blood Mononuclear Cell Signaling by Medicinal Cannabinoids](#)[Frontiers in Molecular Neurosc...]

[See all...](#)

## Links

- [PubMed](#)
- [Taxonomy](#)

## Recent Activity

ClearTurn OffTurn On

- [Interaction between Cannabinoid System and Toll-Like Receptors Controls Inflammation](#)  
Interaction between Cannabinoid System and Toll-Like Receptors Controls Inflammation Mediators of Inflammation. 2016; 2016()
- [Stimulation of the midkine/ALK axis renders glioma cells resistant to cannabinoid antitumoral action](#)  
Stimulation of the midkine/ALK axis renders glioma cells resistant to cannabinoid antitumoral action Cell Death and Differentiation. 2011 Jun; 18(6):959
- [Cannabidiol enhances the inhibitory effects of Δ9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival](#)  
Cannabidiol enhances the inhibitory effects of Δ9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival NIHPA Author Manuscripts. 2010 Jan; 9(1):180
- [Molecular Targets of Cannabidiol in Neurological Disorders](#)  
Molecular Targets of Cannabidiol in Neurological Disorders Neurotherapeutics. 2015 Oct; 12(4):699
- [The craniospinal venous system.](#)  
The craniospinal venous system. Eur Neurol. 2006;56(2):136-8. Epub 2006 Sep 8. PubMed

Your browsing activity is empty.

Activity recording is turned off.

[Turn recording back on](#)

[See more...](#)

- [Review Cannabinoid-based drugs as anti-inflammatory therapeutics.](#)[Nat Rev Immunol. 2005]  
Klein TW  
Nat Rev Immunol. 2005 May; 5(5):400-11.
- [Review Cannabinoid receptors in microglia of the central nervous system: immune functional relevance.](#)[J Leukoc Biol. 2005]  
Cabral GA, Marciano-Cabral F  
J Leukoc Biol. 2005 Dec; 78(6):1192-7.
- [Review The peripheral cannabinoid receptor knockout mice: an update.](#)[Br J Pharmacol. 2008]  
Buckley NE  
Br J Pharmacol. 2008 Jan; 153(2):309-18.
- [Marijuana and cocaine impair alveolar macrophage function and cytokine production.](#)[Am J Respir Crit Care Med. 1997]  
Baldwin GC, Tashkin DP, Buckley DM, Park AN, Dubinett SM, Roth MD  
Am J Respir Crit Care Med. 1997 Nov; 156(5):1606-13.
- [Modulation of the immune system in cannabis users.](#)[JAMA. 2003]  
Pacifci R, Zuccaro P, Pichini S, Roset PN, Poudevida S, Farré M, Segura J, De la Torre R



- JAMA. 2003 Apr 16; 289(15):1929-31.
- [delta 9-Tetrahydrocannabinol modulates antigen processing by macrophages.](#)[J Pharmacol Exp Ther. 1995] McCoy KL, Gainey D, Cabral GA J Pharmacol Exp Ther. 1995 Jun; 273(3):1216-23.
  - [Cannabinoid inhibition of the processing of intact lysozyme by macrophages: evidence for CB2 receptor participation.](#)[J Pharmacol Exp Ther. 1999] McCoy KL, Matveyeva M, Carlisle SJ, Cabral GA J Pharmacol Exp Ther. 1999 Jun; 289(3):1620-5.
  - [Immunomodulation by cannabinoids is absent in mice deficient for the cannabinoid CB\(2\) receptor.](#)[Eur J Pharmacol. 2000] Buckley NE, McCoy KL, Mezey E, Bonner T, Zimmer A, Felder CC, Glass M, Zimmer A Eur J Pharmacol. 2000 May 19; 396(2-3):141-9.
  - [Role of cannabinoid receptors in inhibiting macrophage costimulatory activity.](#)[Int Immunopharmacol. 2004] Chuchawankul S, Shima M, Buckley NE, Hartmann CB, McCoy KL Int Immunopharmacol. 2004 Feb; 4(2):265-78.
  - [Lipopolysaccharide induces anandamide synthesis in macrophages via CD14/MAPK/phosphoinositide 3-kinase/NF-kappaB independently of platelet-activating factor.](#)[J Biol Chem. 2003] Liu J, Batkai S, Pacher P, Harvey-White J, Wagner JA, Cravatt BF, Gao B, Kunos G J Biol Chem. 2003 Nov 7; 278(45):45034-9.
  - [Review International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB<sub>1</sub> and CB<sub>2</sub>.](#)[Pharmacol Rev. 2010] Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA Pharmacol Rev. 2010 Dec; 62(4):588-631.
  - [Review Phytocannabinoids as novel therapeutic agents in CNS disorders.](#)[Pharmacol Ther. 2012] Hill AJ, Williams CM, Whalley BJ, Stephens GJ Pharmacol Ther. 2012 Jan; 133(1):79-97.
  - [Structure of a cannabinoid receptor and functional expression of the cloned cDNA.](#)[Nature. 1990] Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI Nature. 1990 Aug 9; 346(6284):561-4.
  - [Cannabinoid-receptor expression in human leukocytes.](#)[Eur J Biochem. 1993] Bouaboula M, Rinaldi M, Carayon P, Carillon C, Delpech B, Shire D, Le Fur G, Casellas P Eur J Biochem. 1993 May 15; 214(1):173-80.
  - [Characterization and autoradiographic localization of the cannabinoid binding site in rat brain using \[3H\]11-OH-delta 9-THC-DMH.](#)[J Pharmacol Exp Ther. 1992] Thomas BF, Wei X, Martin BR J Pharmacol Exp Ther. 1992 Dec; 263(3):1383-90.
  - [Molecular characterization of a peripheral receptor for cannabinoids.](#)[Nature. 1993] Munro S, Thomas KL, Abu-Shaar M Nature. 1993 Sep 2; 365(6441):61-5.
  - [Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations.](#)[Eur J Biochem. 1995] Gallègue S, Mary S, Marchand J, Dussossoy D, Carrière D, Carayon P, Bouaboula M, Shire D, Le Fur G, Casellas P Eur J Biochem. 1995 Aug 15; 232(1):54-61.
  - [Identification and functional characterization of brainstem cannabinoid CB2 receptors.](#)[Science. 2005] Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, Stella N, Makriyannis A, Piomelli D, Davison JS, Marnett LJ, Di Marzo V, Pittman QJ, Patel KD, Sharkey KA Science. 2005 Oct 14; 310(5746):329-32.
  - [COX-2, CB2 and P2X7-immunoreactivities are increased in activated microglial cells/macrophages of multiple sclerosis and amyotrophic lateral sclerosis spinal cord.](#)[BMC Neurol. 2006] Yiangou Y, Facer P, Durrenberger P, Chessell IP, Naylor A, Bountra C,

Banati RR, Anand P

BMC Neurol. 2006 Mar 2; 6():12.

- [Cannabinoid CB2 receptors and fatty acid amide hydrolase are selectively overexpressed in neuritic plaque-associated glia in Alzheimer's disease brains.](#)[J Neurosci. 2003]  
Benito C, Núñez E, Tolón RM, Carrier EJ, Rábano A, Hillard CJ, Romero J  
J Neurosci. 2003 Dec 3; 23(35):11136-41.
- [Anandamide, a natural ligand for the peripheral cannabinoid receptor is a novel synergistic growth factor for hematopoietic cells.](#)[Blood. 1997]  
Valk P, Verbakel S, Vankan Y, Hol S, Mancham S, Ploemacher R, Mayen A, Löwenberg B, Delwel R  
Blood. 1997 Aug 15; 90(4):1448-57.

[See more ...](#)

- [Review International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB<sub>1</sub> and CB<sub>2</sub>.](#)[Pharmacol Rev. 2010]  
Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA  
Pharmacol Rev. 2010 Dec; 62(4):588-631.
- [Review Endocannabinoids and Their Pharmacological Actions.](#)[Handb Exp Pharmacol. 2015]  
Pertwee RG  
Handb Exp Pharmacol. 2015; 231():1-37.

[See more ...](#)

- [Review International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB<sub>1</sub> and CB<sub>2</sub>.](#)[Pharmacol Rev. 2010]  
Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA  
Pharmacol Rev. 2010 Dec; 62(4):588-631.
- [Review Endocannabinoids and Their Pharmacological Actions.](#)[Handb Exp Pharmacol. 2015]  
Pertwee RG  
Handb Exp Pharmacol. 2015; 231():1-37.
- [Review Phytocannabinoids as novel therapeutic agents in CNS disorders.](#)[Pharmacol Ther. 2012]  
Hill AJ, Williams CM, Whalley BJ, Stephens GJ  
Pharmacol Ther. 2012 Jan; 133(1):79-97.
- [Review International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB<sub>1</sub> and CB<sub>2</sub>.](#)[Pharmacol Rev. 2010]  
Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA  
Pharmacol Rev. 2010 Dec; 62(4):588-631.
- [Review Endocannabinoids and Their Pharmacological Actions.](#)[Handb Exp Pharmacol. 2015]  
Pertwee RG  
Handb Exp Pharmacol. 2015; 231():1-37.
- [Review International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB<sub>1</sub> and CB<sub>2</sub>.](#)[Pharmacol Rev. 2010]  
Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA  
Pharmacol Rev. 2010 Dec; 62(4):588-631.
- [Review Endocannabinoids and Their Pharmacological Actions.](#)[Handb Exp Pharmacol. 2015]  
Pertwee RG  
Handb Exp Pharmacol. 2015; 231():1-37.

[See more ...](#)

- [Review International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB<sub>1</sub> and CB<sub>2</sub>.](#)[Pharmacol

Rev. 2010]

Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA

Pharmacol Rev. 2010 Dec; 62(4):588-631.

- [Review Endocannabinoids and Their Pharmacological Actions.](#)[Handb Exp Pharmacol. 2015]  
Pertwee RG  
Handb Exp Pharmacol. 2015; 231():1-37.
- [Isolation and structure of a brain constituent that binds to the cannabinoid receptor.](#)[Science. 1992]  
Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R  
Science. 1992 Dec 18; 258(5090):1946-9.
- [Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors.](#)[Biochem Pharmacol. 1995]  
Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, Gopher A, Almog S, Martin BR, Compton DR  
Biochem Pharmacol. 1995 Jun 29; 50(1):83-90.
- [2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain.](#)[Biochem Biophys Res Commun. 1995]  
Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, Yamashita A, Waku K  
Biochem Biophys Res Commun. 1995 Oct 4; 215(1):89-97.

[See more ...](#)

- [Review International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB<sub>1</sub> and CB<sub>2</sub>.](#)[Pharmacol Rev. 2010]  
Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA  
Pharmacol Rev. 2010 Dec; 62(4):588-631.
- [Review Endocannabinoids and Their Pharmacological Actions.](#)[Handb Exp Pharmacol. 2015]  
Pertwee RG  
Handb Exp Pharmacol. 2015; 231():1-37.
- [Structure of a cannabinoid receptor and functional expression of the cloned cDNA.](#)[Nature. 1990]  
Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI  
Nature. 1990 Aug 9; 346(6284):561-4.
- [Cannabinoid-receptor expression in human leukocytes.](#)[Eur J Biochem. 1993]  
Bouaboula M, Rinaldi M, Carayon P, Carillon C, Delpuch B, Shire D, Le Fur G, Casellas P  
Eur J Biochem. 1993 May 15; 214(1):173-80.
- [Cannabinoid inhibition of adenylate cyclase. Pharmacology of the response in neuroblastoma cell membranes.](#)[Mol Pharmacol. 1984]  
Howlett AC, Fleming RM  
Mol Pharmacol. 1984 Nov; 26(3):532-8.
- [Involvement of Gi in the inhibition of adenylate cyclase by cannabimimetic drugs.](#)[Mol Pharmacol. 1986]  
Howlett AC, Qualy JM, Khachatrian LL  
Mol Pharmacol. 1986 Mar; 29(3):307-13.

[See more ...](#)

- [Activation of mitogen-activated protein kinases by stimulation of the central cannabinoid receptor CB<sub>1</sub>.](#)[Biochem J. 1995]  
Bouaboula M, Poinot-Chazel C, Bourrié B, Canat X, Calandra B, Rinaldi-Carmona M, Le Fur G, Casellas P  
Biochem J. 1995 Dec 1; 312 ( Pt 2):637-41.
- [Review Cannabinoid signalling.](#)[Life Sci. 2006]  
Demuth DG, Molleman A  
Life Sci. 2006 Jan 2; 78(6):549-63.
- [Cultured rat microglial cells synthesize the endocannabinoid 2-arachidonoylglycerol, which increases proliferation via a CB<sub>2</sub> receptor-dependent mechanism.](#)[Mol Pharmacol. 2004]  
Carrier EJ, Kearn CS, Barkmeier AJ, Breese NM, Yang W, Nithipatikom K, Pfister SL, Campbell WB, Hillard CJ

- Mol Pharmacol. 2004 Apr; 65(4):999-1007.
- [Cannabinoids inhibit the activation of ERK MAPK in PMA/Io-stimulated mouse splenocytes.](#)[Int Immunopharmacol. 2003]  
Faubert Kaplan BL, Kaminski NE  
Int Immunopharmacol. 2003 Oct; 3(10-11):1503-10.
  - [A Basal Tone of 2-Arachidonoylglycerol Contributes to Early Oligodendrocyte Progenitor Proliferation by Activating Phosphatidylinositol 3-Kinase \(PI3K\)/AKT and the Mammalian Target of Rapamycin \(mTOR\) Pathways.](#)[J Neuroimmune Pharmacol. 2015]  
Gomez O, Sanchez-Rodriguez MA, Ortega-Gutierrez S, Vazquez-Villa H, Guaza C, Molina-Holgado F, Molina-Holgado E  
J Neuroimmune Pharmacol. 2015 Jun; 10(2):309-17.
  - [CB2 cannabinoid receptors promote neural progenitor cell proliferation via mTORC1 signaling.](#)[J Biol Chem. 2012]  
Palazuelos J, Ortega Z, Díaz-Alonso J, Guzmán M, Galve-Roperh I  
J Biol Chem. 2012 Jan 6; 287(2):1198-209.
  - [The cannabinoid WIN 55,212-2 prevents neuroendocrine differentiation of LNCaP prostate cancer cells.](#)[Prostate Cancer Prostatic Dis. 2016]  
Morell C, Bort A, Vara D, Ramos-Torres A, Rodríguez-Henche N, Díaz-Laviada I  
Prostate Cancer Prostatic Dis. 2016 Sep; 19(3):248-57.
  - [Review Cannabinoid receptor signaling.](#)[Handb Exp Pharmacol. 2005]  
Howlett AC  
Handb Exp Pharmacol. 2005; (168):53-79.
  - [Review Cannabinoid receptor signaling.](#)[Handb Exp Pharmacol. 2005]  
Howlett AC  
Handb Exp Pharmacol. 2005; (168):53-79.
  - [Review Cannabinoid signalling.](#)[Life Sci. 2006]  
Demuth DG, Molleman A  
Life Sci. 2006 Jan 2; 78(6):549-63.
  - [The involvement of VEGF receptors and MAPK in the cannabinoid potentiation of Ca<sup>2+</sup> flux into N18TG2 neuroblastoma cells.](#)[Brain Res Mol Brain Res. 2004]  
Rubovitch V, Gafni M, Sarne Y  
Brain Res Mol Brain Res. 2004 Jan 5; 120(2):138-44.
  - [Review Endocannabinoid signaling in microglial cells.](#)[Neuropharmacology. 2009]  
Stella N  
Neuropharmacology. 2009; 56 Suppl 1():244-53.
  - [Review Modulating the endocannabinoid system in human health and disease--successes and failures.](#)[FEBS J. 2013]  
Pacher P, Kunos G  
FEBS J. 2013 May; 280(9):1918-43.
  - [Formation and inactivation of endogenous cannabinoid anandamide in central neurons.](#)[Nature. 1994]  
Di Marzo V, Fontana A, Cadas H, Schinelli S, Cimino G, Schwartz JC, Piomelli D  
Nature. 1994 Dec 15; 372(6507):686-91.
  - [CB1 receptor-mediated control of the release of endocannabinoids \(as assessed by microdialysis coupled with LC/MS\) in the rat hypothalamus.](#)[Eur J Neurosci. 2007]  
Béquet F, Uzabiaga F, Desbazeille M, Ludwiczak P, Maftouh M, Picard C, Scatton B, Le Fur G  
Eur J Neurosci. 2007 Dec; 26(12):3458-64.
  - [Review Targeting the endocannabinoid system: to enhance or reduce?](#)[Nat Rev Drug Discov. 2008]  
Di Marzo V  
Nat Rev Drug Discov. 2008 May; 7(5):438-55.
  - [Review Biosynthesis and Fate of Endocannabinoids.](#)[Handb Exp Pharmacol. 2015]  
Cascio MG, Marini P  
Handb Exp Pharmacol. 2015; 231():39-58.
  - [Review The biosynthesis, fate and pharmacological properties of endocannabinoids.](#)[Handb Exp Pharmacol. 2005]  
Di Marzo V, De Petrocellis L, Bisogno T  
Handb Exp Pharmacol. 2005; (168):147-85.
  - [Review Endocannabinoids and immune regulation.](#)[Pharmacol Res. 2009]  
Pandey R, Mousawy K, Nagarkatti M, Nagarkatti P  
Pharmacol Res. 2009 Aug; 60(2):85-92.

- [Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase.](#)[Proc Natl Acad Sci U S A. 2001]  
Cravatt BF, Demarest K, Patricelli MP, Bracey MH, Giang DK, Martin BR, Lichtman AH  
Proc Natl Acad Sci U S A. 2001 Jul 31; 98(16):9371-6.
- [Carrier-mediated transport and enzymatic hydrolysis of the endogenous cannabinoid 2-arachidonylethanolamide.](#)[Neuroreport. 2000]  
Beltramo M, Piomelli D  
Neuroreport. 2000 Apr 27; 11(6):1231-5.
- [Review The biosynthesis, fate and pharmacological properties of endocannabinoids.](#)[Handb Exp Pharmacol. 2005]  
Di Marzo V, De Petrocellis L, Bisogno T  
Handb Exp Pharmacol. 2005; (168):147-85.
- [Review Biosynthesis and Fate of Endocannabinoids.](#)[Handb Exp Pharmacol. 2015]  
Cascio MG, Marini P  
Handb Exp Pharmacol. 2015; 231():39-58.
- [Review Endocannabinoids and Their Pharmacological Actions.](#)[Handb Exp Pharmacol. 2015]  
Pertwee RG  
Handb Exp Pharmacol. 2015; 231():1-37.
- [Review Endocannabinoid signaling in microglial cells.](#)[Neuropharmacology. 2009]  
Stella N  
Neuropharmacology. 2009; 56 Suppl 1():244-53.

[See more ...](#)

- [Review Approaching the asymptote? Evolution and revolution in immunology.](#)[Cold Spring Harb Symp Quant Biol. 1989]  
Janeway CA Jr  
Cold Spring Harb Symp Quant Biol. 1989; 54 Pt 1():1-13.
- [Review Danger- and pathogen-associated molecular patterns recognition by pattern-recognition receptors and ion channels of the transient receptor potential family triggers the inflammasome activation in immune cells and sensory neurons.](#)[J Neuroinflammation. 2015]  
Santoni G, Cardinali C, Morelli MB, Santoni M, Nabissi M, Amantini C  
J Neuroinflammation. 2015 Feb 3; 12():21.
- [Review Innate immune pattern recognition: a cell biological perspective.](#)[Annu Rev Immunol. 2015]  
Brubaker SW, Bonham KS, Zanoni I, Kagan JC  
Annu Rev Immunol. 2015; 33():257-90.
- [Review DAMPening inflammation by modulating TLR signalling.](#)[Mediators Inflamm. 2010]  
Piccinini AM, Midwood KS  
Mediators Inflamm. 2010; 2010():.
- [The polarity of the dorsoventral axis in the Drosophila embryo is defined by an extracellular signal.](#)[Cell. 1991]  
Stein D, Roth S, Vogelsang E, Nüsslein-Volhard C  
Cell. 1991 May 31; 65(5):725-35.
- [The Toll gene of Drosophila, required for dorsal-ventral embryonic polarity, appears to encode a transmembrane protein.](#)[Cell. 1988]  
Hashimoto C, Hudson KL, Anderson KV  
Cell. 1988 Jan 29; 52(2):269-79.
- [The dorsoventral regulatory gene cassette spätzle/Toll/cactus controls the potent antifungal response in Drosophila adults.](#)[Cell. 1996]  
Lemaître B, Nicolas E, Michaut L, Reichhart JM, Hoffmann JA  
Cell. 1996 Sep 20; 86(6):973-83.
- [Prediction of the coding sequences of unidentified human genes. I. The coding sequences of 40 new genes \(K1A0001-K1A0040\) deduced by analysis of randomly sampled cDNA clones from human immature myeloid cell line KG-1.](#)[DNA Res. 1994]  
Nomura N, Miyajima N, Sazuka T, Tanaka A, Kawarabayashi Y, Sato S, Nagase T, Seki N, Ishikawa K, Tabata S  
DNA Res. 1994; 1(1):27-35.
- [A human homologue of the Drosophila Toll protein signals activation of adaptive immunity.](#)[Nature. 1997]  
Medzhitov R, Preston-Hurlburt P, Janeway CA Jr  
Nature. 1997 Jul 24; 388(6640):394-7.
- [Review Innate immune pattern recognition: a cell biological perspective](#)

- [Review Innate immune pattern recognition: a cell biological perspective.](#)  
[Annu Rev Immunol. 2015]  
Brubaker SW, Bonham KS, Zanoni I, Kagan JC  
Annu Rev Immunol. 2015; 33():257-90.
- [Review DAMPening inflammation by modulating TLR signalling.](#)[Mediators Inflamm. 2010]  
Piccinini AM, Midwood KS  
Mediators Inflamm. 2010; 2010():.
- [Review Innate immune pattern recognition: a cell biological perspective.](#)  
[Annu Rev Immunol. 2015]  
Brubaker SW, Bonham KS, Zanoni I, Kagan JC  
Annu Rev Immunol. 2015; 33():257-90.
- [Roles for LPS-dependent interaction and relocation of TLR4 and TRAM in TRIF-signaling.](#)[Biochem Biophys Res Commun. 2008]  
Tanimura N, Saitoh S, Matsumoto F, Akashi-Takamura S, Miyake K  
Biochem Biophys Res Commun. 2008 Mar 28; 368(1):94-9.
- [Review Essay 1: the Danger model in its historical context.](#)[Scand J Immunol. 2001]  
Matzinger P  
Scand J Immunol. 2001 Jul-Aug; 54(1-2):4-9.
- [Review Danger- and pathogen-associated molecular patterns recognition by pattern-recognition receptors and ion channels of the transient receptor potential family triggers the inflammasome activation in immune cells and sensory neurons.](#)[J Neuroinflammation. 2015]  
Santoni G, Cardinali C, Morelli MB, Santoni M, Nabissi M, Amantini C  
J Neuroinflammation. 2015 Feb 3; 12():21.
- [Review DAMPening inflammation by modulating TLR signalling.](#)[Mediators Inflamm. 2010]  
Piccinini AM, Midwood KS  
Mediators Inflamm. 2010; 2010():.
- [Cutting edge: heat shock protein 60 is a putative endogenous ligand of the toll-like receptor-4 complex.](#)[J Immunol. 2000]  
Ohashi K, Burkart V, Flohé S, Kolb H  
J Immunol. 2000 Jan 15; 164(2):558-61.
- [Necrotic but not apoptotic cell death releases heat shock proteins, which deliver a partial maturation signal to dendritic cells and activate the NF-kappa B pathway.](#)[Int Immunol. 2000]  
Basu S, Binder RJ, Suto R, Anderson KM, Srivastava PK  
Int Immunol. 2000 Nov; 12(11):1539-46.
- [An essential role of the NF-kappa B/Toll-like receptor pathway in induction of inflammatory and tissue-repair gene expression by necrotic cells.](#)[J Immunol. 2001]  
Li M, Carpio DF, Zheng Y, Bruzzo P, Singh V, Ouaz F, Medzhitov RM, Beg AA  
J Immunol. 2001 Jun 15; 166(12):7128-35.
- [Review Danger- and pathogen-associated molecular patterns recognition by pattern-recognition receptors and ion channels of the transient receptor potential family triggers the inflammasome activation in immune cells and sensory neurons.](#)[J Neuroinflammation. 2015]  
Santoni G, Cardinali C, Morelli MB, Santoni M, Nabissi M, Amantini C  
J Neuroinflammation. 2015 Feb 3; 12():21.

[See more ...](#)

- [Review Danger- and pathogen-associated molecular patterns recognition by pattern-recognition receptors and ion channels of the transient receptor potential family triggers the inflammasome activation in immune cells and sensory neurons.](#)[J Neuroinflammation. 2015]  
Santoni G, Cardinali C, Morelli MB, Santoni M, Nabissi M, Amantini C  
J Neuroinflammation. 2015 Feb 3; 12():21.
- [Review DAMPening inflammation by modulating TLR signalling.](#)[Mediators Inflamm. 2010]  
Piccinini AM, Midwood KS  
Mediators Inflamm. 2010; 2010():.
- [Review Regulation of interactions of Gram-negative bacterial endotoxins with mammalian cells.](#)[Immunol Res. 2007]  
Gioannini TL, Weiss JP  
Immunol Res. 2007; 39(1-3):249-60.
- [Review Innate immune pattern recognition: a cell biological perspective.](#)

- [Annu Rev Immunol. 2015]  
Brubaker SW, Bonham KS, Zanoni I, Kagan JC  
Annu Rev Immunol. 2015; 33():257-90.
- [Roles for LPS-dependent interaction and relocation of TLR4 and TRAM in TRIF-signaling.](#)[Biochem Biophys Res Commun. 2008]  
Tanimura N, Saitoh S, Matsumoto F, Akashi-Takamura S, Miyake K  
Biochem Biophys Res Commun. 2008 Mar 28; 368(1):94-9.

[See more ...](#)

- [Review Danger- and pathogen-associated molecular patterns recognition by pattern-recognition receptors and ion channels of the transient receptor potential family triggers the inflammasome activation in immune cells and sensory neurons.](#)[J Neuroinflammation. 2015]  
Santoni G, Cardinali C, Morelli MB, Santoni M, Nabissi M, Amantini C  
J Neuroinflammation. 2015 Feb 3; 12():21.
- [Review DAMPening inflammation by modulating TLR signalling.](#)[Mediators Inflamm. 2010]  
Piccinini AM, Midwood KS  
Mediators Inflamm. 2010; 2010():.

[See more ...](#)

- [Review Danger- and pathogen-associated molecular patterns recognition by pattern-recognition receptors and ion channels of the transient receptor potential family triggers the inflammasome activation in immune cells and sensory neurons.](#)[J Neuroinflammation. 2015]  
Santoni G, Cardinali C, Morelli MB, Santoni M, Nabissi M, Amantini C  
J Neuroinflammation. 2015 Feb 3; 12():21.
- [Review DAMPening inflammation by modulating TLR signalling.](#)[Mediators Inflamm. 2010]  
Piccinini AM, Midwood KS  
Mediators Inflamm. 2010; 2010():.
- [Review Regulation of Toll-like receptor signaling pathways in innate immune responses.](#)[Ann N Y Acad Sci. 2013]  
Qian C, Cao X  
Ann N Y Acad Sci. 2013 Apr; 1283():67-74.
- [A dimer of the Toll-like receptor 4 cytoplasmic domain provides a specific scaffold for the recruitment of signalling adaptor proteins.](#)[PLoS One. 2007]  
Núñez Miguel R, Wong J, Westoll JF, Brooks HJ, O'Neill LA, Gay NJ, Bryant CE, Monie TP  
PLoS One. 2007 Aug 29; 2(8):e788.
- [Review Innate immune pattern recognition: a cell biological perspective.](#)  
[Annu Rev Immunol. 2015]  
Brubaker SW, Bonham KS, Zanoni I, Kagan JC  
Annu Rev Immunol. 2015; 33():257-90.

[See more ...](#)

- [Review Innate immune pattern recognition: a cell biological perspective.](#)  
[Annu Rev Immunol. 2015]  
Brubaker SW, Bonham KS, Zanoni I, Kagan JC  
Annu Rev Immunol. 2015; 33():257-90.
- [Review Trafficking of endosomal Toll-like receptors.](#)[Trends Cell Biol. 2014]  
Lee BL, Barton GM  
Trends Cell Biol. 2014 Jun; 24(6):360-9.
- [Roles for LPS-dependent interaction and relocation of TLR4 and TRAM in TRIF-signaling.](#)[Biochem Biophys Res Commun. 2008]  
Tanimura N, Saitoh S, Matsumoto F, Akashi-Takamura S, Miyake K  
Biochem Biophys Res Commun. 2008 Mar 28; 368(1):94-9.
- [Review Regulation of Toll-like receptor signaling pathways in innate immune responses.](#)[Ann N Y Acad Sci. 2013]  
Qian C, Cao X  
Ann N Y Acad Sci. 2013 Apr; 1283():67-74.
- [An alanine-to-proline mutation in the BB-loop of TLR3 Toll/IL-1R domain switches signalling adaptor specificity from TRIF to MyD88.](#)[J Immunol. 2013]  
Verstak B, Arnot CJ, Gay NJ  
J Immunol. 2013 Dec 15; 191(12):6101-9.

- [Marijuana and cocaine impair alveolar macrophage function and cytokine production.](#)[Am J Respir Crit Care Med. 1997]  
Baldwin GC, Tashkin DP, Buckley DM, Park AN, Dubinett SM, Roth MD  
Am J Respir Crit Care Med. 1997 Nov; 156(5):1606-13.
- [Modulation of the immune system in cannabis users.](#)[JAMA. 2003]  
Pacifci R, Zuccaro P, Pichini S, Roset PN, Poudevida S, Farré M, Segura J, De la Torre R  
JAMA. 2003 Apr 16; 289(15):1929-31.
- [Review Cannabinoid-based drugs as anti-inflammatory therapeutics.](#)[Nat Rev Immunol. 2005]  
Klein TW  
Nat Rev Immunol. 2005 May; 5(5):400-11.
- [Review Cannabinoid receptors in microglia of the central nervous system: immune functional relevance.](#)[J Leukoc Biol. 2005]  
Cabral GA, Marciano-Cabral F  
J Leukoc Biol. 2005 Dec; 78(6):1192-7.
- [Pharmacological modulation of the endocannabinoid system in a viral model of multiple sclerosis.](#)[J Neurochem. 2005]  
Mestre L, Correa F, Arévalo-Martín A, Molina-Holgado E, Valenti M, Ortar G, Di Marzo V, Guaza C  
J Neurochem. 2005 Mar; 92(6):1327-39.
- [Effects of cannabinoids on LPS-stimulated inflammatory mediator release from macrophages: involvement of eicosanoids.](#)[J Cell Biochem. 2001]  
Chang YH, Lee ST, Lin WW  
J Cell Biochem. 2001; 81(4):715-23.
- [delta 9-Tetrahydrocannabinol enhances the secretion of interleukin 1 from endotoxin-stimulated macrophages.](#)[J Pharmacol Exp Ther. 1994]  
Zhu W, Newton C, Daaka Y, Friedman H, Klein TW  
J Pharmacol Exp Ther. 1994 Sep; 270(3):1334-9.
- [Suppression of human monocyte interleukin-1beta production by ajulemic acid, a nonpsychoactive cannabinoid.](#)[Biochem Pharmacol. 2003]  
Zurier RB, Rossetti RG, Burstein SH, Bidinger B  
Biochem Pharmacol. 2003 Feb 15; 65(4):649-55.

[See more ...](#)

- [Delta-9-tetrahydrocannabinol suppresses tumor necrosis factor alpha maturation and secretion but not its transcription in mouse macrophages.](#)[Int J Immunopharmacol. 1996]  
Zheng ZM, Specter SC  
Int J Immunopharmacol. 1996 Jan; 18(1):53-68.
- [Delta 9-tetrahydrocannabinol inhibition of tumor necrosis factor-alpha: suppression of post-translational events.](#)[J Pharmacol Exp Ther. 1993]  
Fischer-Stenger K, Dove Pettit DA, Cabral GA  
J Pharmacol Exp Ther. 1993 Dec; 267(3):1558-65.
- [Anti-neuroinflammatory activity of a novel cannabinoid derivative by inhibiting the NF-κB signaling pathway in lipopolysaccharide-induced BV-2 microglial cells.](#)[J Pharmacol Sci. 2013]  
More SV, Park JY, Kim BW, Kumar H, Lim HW, Kang SM, Koppula S, Yoon SH, Choi DK  
J Pharmacol Sci. 2013; 121(2):119-30.
- [Pharmacological modulation of the endocannabinoid system in a viral model of multiple sclerosis.](#)[J Neurochem. 2005]  
Mestre L, Correa F, Arévalo-Martín A, Molina-Holgado E, Valenti M, Ortar G, Di Marzo V, Guaza C  
J Neurochem. 2005 Mar; 92(6):1327-39.
- [Tetrahydrocannabinol inhibition of macrophage nitric oxide production.](#)[Biochem Pharmacol. 1996]  
Coffey RG, Yamamoto Y, Snella E, Pross S  
Biochem Pharmacol. 1996 Sep 13; 52(5):743-51.

[See more ...](#)

- [Anti-inflammatory property of the cannabinoid receptor-2-selective agonist JWH-133 in a rodent model of autoimmune uveoretinitis.](#)[J Leukoc Biol. 2007]  
Xu H, Cheng CL, Chen M, Manivannan A, Cabay L, Pertwee RG, Coutts A, Forrester JV  
J Leukoc Biol. 2007 Sep; 82(3):532-41.
- [Review Effects on cell viability.](#)[Handb Exp Pharmacol. 2005]  
Guzmán M



- Handb Exp Pharmacol. 2005; (168):627-42.
- [Review Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression.](#)[Immunobiology. 2010]  
Rieder SA, Chauhan A, Singh U, Nagarkatti M, Nagarkatti P  
Immunobiology. 2010 Aug; 215(8):598-605.
  - [Activation of cannabinoid CB2 receptor negatively regulates IL-12p40 production in murine macrophages: role of IL-10 and ERK1/2 kinase signaling.](#)[Br J Pharmacol. 2005]  
Correa F, Mestre L, Docagne F, Guaza C  
Br J Pharmacol. 2005 Jun; 145(4):441-8.
  - [Anandamide enhances IL-10 production in activated microglia by targeting CB\(2\) receptors: roles of ERK1/2, JNK, and NF-kappaB.](#)[Glia. 2010]  
Correa F, Hernangómez M, Mestre L, Loria F, Spagnolo A, Docagne F, Di Marzo V, Guaza C  
Glia. 2010 Jan 15; 58(2):135-47.
  - [Endogenous interleukin-1 receptor antagonist mediates anti-inflammatory and neuroprotective actions of cannabinoids in neurons and glia.](#)[J Neurosci. 2003]  
Molina-Holgado F, Pinteaux E, Moore JD, Molina-Holgado E, Guaza C, Gibson RM, Rothwell NJ  
J Neurosci. 2003 Jul 23; 23(16):6470-4.
  - [In vivo modulation of LPS-induced alterations in brain and peripheral cytokines and HPA axis activity by cannabinoids.](#)[J Neuroimmunol. 2006]  
Roche M, Diamond M, Kelly JP, Finn DP  
J Neuroimmunol. 2006 Dec; 181(1-2):57-67.
  - [Effects of cannabinoid receptor ligands on LPS-induced pulmonary inflammation in mice.](#)[Life Sci. 1998]  
Berdyshev E, Boichot E, Corbel M, Germain N, Lagente V  
Life Sci. 1998; 63(8):PL125-9.
  - [Effects of cannabinoid receptor agonist and antagonist ligands on production of inflammatory cytokines and anti-inflammatory interleukin-10 in endotoxemic mice.](#)[J Pharmacol Exp Ther. 2000]  
Smith SR, Terminelli C, Denhardt G  
J Pharmacol Exp Ther. 2000 Apr; 293(1):136-50.
  - [Protection against septic shock and suppression of tumor necrosis factor alpha and nitric oxide production by dexanabinol \(HU-211\), a nonpsychotropic cannabinoid.](#)[J Pharmacol Exp Ther. 1997]  
Gallily R, Yamin A, Waksman Y, Ovadia H, Weidenfeld J, Bar-Joseph A, Biegon A, Mechoulam R, Shohami E  
J Pharmacol Exp Ther. 1997 Nov; 283(2):918-24.
  - [Protective role of cannabinoid receptor 2 activation in galactosamine/lipopolysaccharide-induced acute liver failure through regulation of macrophage polarization and microRNAs.](#)[J Pharmacol Exp Ther. 2015]  
Tomar S, Zumbun EE, Nagarkatti M, Nagarkatti PS  
J Pharmacol Exp Ther. 2015 May; 353(2):369-79.
  - [Tetrahydrocannabinol inhibition of macrophage nitric oxide production.](#)[Biochem Pharmacol. 1996]  
Coffey RG, Yamamoto Y, Snella E, Pross S  
Biochem Pharmacol. 1996 Sep 13; 52(5):743-51.
  - [Effects of cannabinoid receptor ligands on LPS-induced pulmonary inflammation in mice.](#)[Life Sci. 1998]  
Berdyshev E, Boichot E, Corbel M, Germain N, Lagente V  
Life Sci. 1998; 63(8):PL125-9.
  - [Protective role of cannabinoid receptor 2 activation in galactosamine/lipopolysaccharide-induced acute liver failure through regulation of macrophage polarization and microRNAs.](#)[J Pharmacol Exp Ther. 2015]  
Tomar S, Zumbun EE, Nagarkatti M, Nagarkatti PS  
J Pharmacol Exp Ther. 2015 May; 353(2):369-79.
  - [Cannabinoids inhibit peptidoglycan-induced phosphorylation of NF-kB and cell growth in U87MG human malignant glioma cells.](#)[Oncol Rep. 2012]  
Echigo R, Sugimoto N, Yachie A, Ohno-Shosaku T  
Oncol Rep. 2012 Oct; 28(4):1176-80.
  - [Effects of cannabinoid receptor agonist and antagonist ligands on production of inflammatory cytokines and anti-inflammatory interleukin-10 in endotoxemic mice.](#)[J Pharmacol Exp Ther. 2000]  
Smith SR, Terminelli C, Denhardt G  
J Pharmacol Exp Ther. 2000 Apr; 293(1):136-50.
  - [In vivo modulation of LPS-induced alterations in brain and peripheral](#)

- [in vivo modulation of LPS-induced alterations in brain and peripheral cytokines and HPA axis activity by cannabinoids.](#)[J Neuroimmunol. 2006] Roche M, Diamond M, Kelly JP, Finn DP  
J Neuroimmunol. 2006 Dec; 181(1-2):57-67.
- [Review The peripheral cannabinoid receptor knockout mice: an update.](#)[Br J Pharmacol. 2008] Buckley NE  
Br J Pharmacol. 2008 Jan; 153(2):309-18.
- [Review What we know and do not know about the cannabinoid receptor 2 \(CB2\).](#)[Semin Immunol. 2014] Malfitano AM, Basu S, Maresz K, Bifulco M, Dittel BN  
Semin Immunol. 2014 Oct; 26(5):369-79.
- [The cannabinoid receptor 2 is critical for the host response to sepsis.](#)[J Immunol. 2009] Tschöp J, Kasten KR, Nogueiras R, Goetzman HS, Cave CM, England LG, Dattilo J, Lentsch AB, Tschöp MH, Caldwell CC  
J Immunol. 2009 Jul 1; 183(1):499-505.
- [Attenuation of allergic contact dermatitis through the endocannabinoid system.](#)[Science. 2007] Karsak M, Gaffal E, Date R, Wang-Eckhardt L, Rehnelt J, Petrosino S, Starowicz K, Steuder R, Schlicker E, Cravatt B, Mechoulam R, Buettner R, Werner S, Di Marzo V, Tüting T, Zimmer A  
Science. 2007 Jun 8; 316(5830):1494-7.
- [Delta9-tetrahydrocannabinol impairs the inflammatory response to influenza infection: role of antigen-presenting cells and the cannabinoid receptors 1 and 2.](#)[Toxicol Sci. 2013] Karmaus PW, Chen W, Crawford R, Kaplan BL, Kaminski NE  
Toxicol Sci. 2013 Feb; 131(2):419-33.
- [Targeted deletion of cannabinoid receptors CB1 and CB2 produced enhanced inflammatory responses to influenza A/PR/8/34 in the absence and presence of Delta9-tetrahydrocannabinol.](#)[J Leukoc Biol. 2008] Buchweitz JP, Karmaus PW, Williams KJ, Harkema JR, Kaminski NE  
J Leukoc Biol. 2008 Mar; 83(3):785-96.
- [Review Cannabinoid receptors in microglia of the central nervous system: immune functional relevance.](#)[J Leukoc Biol. 2005] Cabral GA, Marciano-Cabral F  
J Leukoc Biol. 2005 Dec; 78(6):1192-7.
- [Review Endocannabinoid signaling in microglial cells.](#)[Neuropharmacology. 2009] Stella N  
Neuropharmacology. 2009; 56 Suppl 1():244-53.
- [Review Modulating the endocannabinoid system in human health and disease--successes and failures.](#)[FEBS J. 2013] Pacher P, Kunos G  
FEBS J. 2013 May; 280(9):1918-43.
- [Cannabinoids inhibit LPS-inducible cytokine mRNA expression in rat microglial cells.](#)[Glia. 2000] Puffenbarger RA, Boothe AC, Cabral GA  
Glia. 2000 Jan 1; 29(1):58-69.
- [Activation of cannabinoid CB2 receptor negatively regulates IL-12p40 production in murine macrophages: role of IL-10 and ERK1/2 kinase signaling.](#)[Br J Pharmacol. 2005] Correa F, Mestre L, Docagne F, Guaza C  
Br J Pharmacol. 2005 Jun; 145(4):441-8.
- [Endogenous interleukin-1 receptor antagonist mediates anti-inflammatory and neuroprotective actions of cannabinoids in neurons and glia.](#)[J Neurosci. 2003] Molina-Holgado F, Pinteaux E, Moore JD, Molina-Holgado E, Guaza C, Gibson RM, Rothwell NJ  
J Neurosci. 2003 Jul 23; 23(16):6470-4.
- [Cannabinoid CB\(2\) receptors modulate ERK-1/2 kinase signalling and NO release in microglial cells stimulated with bacterial lipopolysaccharide.](#)[Br J Pharmacol. 2012] Merighi S, Gessi S, Varani K, Simioni C, Fazzi D, Mirandola P, Borea PA  
Br J Pharmacol. 2012 Mar; 165(6):1773-1788.

[See more ...](#)

- [Review Cannabinoid-based drugs as anti-inflammatory therapeutics.](#)[Nat Rev Immunol. 2005] Klein TW  
Nat Rev Immunol. 2005 May; 5(5):469-81

Nat Rev Immunol. 2005 May; 5(5):400-11.

- [Review Cannabinoid receptors in microglia of the central nervous system: immune functional relevance.](#) [J Leukoc Biol. 2005]  
Cabral GA, Marciano-Cabral F  
J Leukoc Biol. 2005 Dec; 78(6):1192-7.
- [Tetrahydrocannabinol inhibition of macrophage nitric oxide production.](#) [Biochem Pharmacol. 1996]  
Coffey RG, Yamamoto Y, Snella E, Pross S  
Biochem Pharmacol. 1996 Sep 13; 52(5):743-51.
- [The central cannabinoid receptor \(CB1\) mediates inhibition of nitric oxide production by rat microglial cells.](#) [J Pharmacol Exp Ther. 1999]  
Waksman Y, Olson JM, Carlisle SJ, Cabral GA  
J Pharmacol Exp Ther. 1999 Mar; 288(3):1357-66.
- [Review Cannabinoid signalling.](#) [Life Sci. 2006]  
Demuth DG, Molleman A  
Life Sci. 2006 Jan 2; 78(6):549-63.
- [Cannabinoids inhibit the activation of ERK MAPK in PMA/Io-stimulated mouse splenocytes.](#) [Int Immunopharmacol. 2003]  
Faubert Kaplan BL, Kaminski NE  
Int Immunopharmacol. 2003 Oct; 3(10-11):1503-10.
- [The synthetic cannabinoid R\(+\)-WIN55,212-2 augments interferon- \$\beta\$  expression via peroxisome proliferator-activated receptor- \$\alpha\$ .](#) [J Biol Chem. 2012]  
Downer EJ, Clifford E, Amu S, Fallon PG, Moynagh PN  
J Biol Chem. 2012 Jul 20; 287(30):25440-53.
- [Identification of the synthetic cannabinoid R\(+\)-WIN55,212-2 as a novel regulator of IFN regulatory factor 3 activation and IFN-beta expression: relevance to therapeutic effects in models of multiple sclerosis.](#) [J Biol Chem. 2011]  
Downer EJ, Clifford E, Gran B, Nel HJ, Fallon PG, Moynagh PN  
J Biol Chem. 2011 Mar 25; 286(12):10316-28.
- [Identification of the synthetic cannabinoid R\(+\)-WIN55,212-2 as a novel regulator of IFN regulatory factor 3 activation and IFN-beta expression: relevance to therapeutic effects in models of multiple sclerosis.](#) [J Biol Chem. 2011]  
Downer EJ, Clifford E, Gran B, Nel HJ, Fallon PG, Moynagh PN  
J Biol Chem. 2011 Mar 25; 286(12):10316-28.
- [Cannabinoids Delta\(9\)-tetrahydrocannabinol and cannabidiol differentially inhibit the lipopolysaccharide-activated NF-kappaB and interferon-beta/STAT proinflammatory pathways in BV-2 microglial cells.](#) [J Biol Chem. 2010]  
Kozela E, Pietr M, Juknat A, Rimmerman N, Levy R, Vogel Z  
J Biol Chem. 2010 Jan 15; 285(3):1616-26.
- [The synthetic cannabinoid R\(+\)-WIN55,212-2 augments interferon- \$\beta\$  expression via peroxisome proliferator-activated receptor- \$\alpha\$ .](#) [J Biol Chem. 2012]  
Downer EJ, Clifford E, Amu S, Fallon PG, Moynagh PN  
J Biol Chem. 2012 Jul 20; 287(30):25440-53.
- [Nonpsychotropic cannabinoid receptors regulate microglial cell migration.](#) [J Neurosci. 2003]  
Walter L, Franklin A, Witting A, Wade C, Xie Y, Kunos G, Mackie K, Stella N  
J Neurosci. 2003 Feb 15; 23(4):1398-405.
- [Presence and regulation of the endocannabinoid system in human dendritic cells.](#) [Eur J Biochem. 2002]  
Matias I, Pochard P, Orlando P, Salzet M, Pestel J, Di Marzo V  
Eur J Biochem. 2002 Aug; 269(15):3771-8.
- [CB1 and CB2 cannabinoid receptors differentially regulate the production of reactive oxygen species by macrophages.](#) [Cardiovasc Res. 2009]  
Han KH, Lim S, Ryu J, Lee CW, Kim Y, Kang JH, Kang SS, Ahn YK, Park CS, Kim JJ  
Cardiovasc Res. 2009 Dec 1; 84(3):378-86.
- [2-arachidonoylglycerol induces the migration of HL-60 cells differentiated into macrophage-like cells and human peripheral blood monocytes through the cannabinoid CB2 receptor-dependent mechanism.](#) [J Biol Chem. 2003]  
Kishimoto S, Gokoh M, Oka S, Muramatsu M, Kajiwara T, Waku K, Sugiura T  
J Biol Chem. 2003 Jul 4; 278(27):24469-75.
- [Exposure to  \$\Delta\$ 9-Tetrahydrocannabinol Impairs the Differentiation of Human](#)

[Monocyte-derived Dendritic Cells and their Capacity for T cell Activation.](#)[J Neuroimmune Pharmacol. 2015]

Roth MD, Castaneda JT, Kiertscher SM

J Neuroimmune Pharmacol. 2015 Jun; 10(2):333-43.

- [Differential expression of the CB2 cannabinoid receptor by rodent macrophages and macrophage-like cells in relation to cell activation.](#)[Int Immunopharmacol. 2002]  
Carlisle SJ, Marciano-Cabral F, Staab A, Ludwick C, Cabral GA  
Int Immunopharmacol. 2002 Jan; 2(1):69-82.
- [Reduction of human monocytic cell neurotoxicity and cytokine secretion by ligands of the cannabinoid-type CB2 receptor.](#)[Br J Pharmacol. 2003]  
Klegeris A, Bissonnette CJ, McGeer PL  
Br J Pharmacol. 2003 Jun; 139(4):775-86.
- [Modulation of the cannabinoid CB2 receptor in microglial cells in response to inflammatory stimuli.](#)[J Neurochem. 2005]  
Maresz K, Carrier EJ, Ponomarev ED, Hillard CJ, Dittel BN  
J Neurochem. 2005 Oct; 95(2):437-45.
- [Suppression of human macrophage interleukin-6 by a nonpsychoactive cannabinoid acid.](#)[Rheumatol Int. 2008]  
Parker J, Atez F, Rossetti RG, Skulas A, Patel R, Zurier RB  
Rheumatol Int. 2008 May; 28(7):631-5.
- [Differential expression of the CB2 cannabinoid receptor by rodent macrophages and macrophage-like cells in relation to cell activation.](#)[Int Immunopharmacol. 2002]  
Carlisle SJ, Marciano-Cabral F, Staab A, Ludwick C, Cabral GA  
Int Immunopharmacol. 2002 Jan; 2(1):69-82.
- [Review CB2 receptors in the brain: role in central immune function.](#)[Br J Pharmacol. 2008]  
Cabral GA, Raborn ES, Griffin L, Dennis J, Marciano-Cabral F  
Br J Pharmacol. 2008 Jan; 153(2):240-51.
- [Nonpsychotropic cannabinoid receptors regulate microglial cell migration.](#)[J Neurosci. 2003]  
Walter L, Franklin A, Witting A, Wade C, Xie Y, Kunos G, Mackie K, Stella N  
J Neurosci. 2003 Feb 15; 23(4):1398-405.
- [Lipopolysaccharide and cyclic AMP regulation of CB\(2\) cannabinoid receptor levels in rat brain and mouse RAW 264.7 macrophages.](#)[J Neuroimmunol. 2006]  
Mukhopadhyay S, Das S, Williams EA, Moore D, Jones JD, Zahm DS, Ndengele MM, Lechner AJ, Howlett AC  
J Neuroimmunol. 2006 Dec; 181(1-2):82-92.
- [Review Marijuana, receptors and immunomodulation.](#)[Adv Exp Med Biol. 1995]  
Friedman H, Klein TW, Newton C, Daaka Y  
Adv Exp Med Biol. 1995; 373():103-13.
- [Role of CREB in modulation of TNFalpha and IL-10 expression in LPS-stimulated RAW264.7 macrophages.](#)[Mol Immunol. 2010]  
Avni D, Ernst O, Philosoph A, Zor T  
Mol Immunol. 2010 Apr; 47(7-8):1396-403.

[See more ...](#)

- [Review Endocannabinoid signaling in microglial cells.](#)[Neuropharmacology. 2009]  
Stella N  
Neuropharmacology. 2009; 56 Suppl 1():244-53.
- [Review Modulating the endocannabinoid system in human health and disease--successes and failures.](#)[FEBS J. 2013]  
Pacher P, Kunos G  
FEBS J. 2013 May; 280(9):1918-43.

[See more ...](#)

- [Progesterone reverts LPS-reduced FAAH activity in murine peripheral blood mononuclear cells by a receptor-mediated fashion.](#)[Mol Cell Endocrinol. 2013]  
Wolfson ML, Aisemberg J, Salazar AI, Domínguez Rubio AP, Vercelli CA, Franchi AM  
Mol Cell Endocrinol. 2013 Dec 5; 381(1-2):97-105.
- [Lipopolysaccharide suppresses carboxylesterase 2g activity and 2-arachidonoylglycerol hydrolysis: A possible mechanism to regulate](#)

- [inflammation](#). [Prostaglandins Other Lipid Mediat. 2015]
- Szafran B, Borazjani A, Lee JH, Ross MK, Kaplan BL  
Prostaglandins Other Lipid Mediat. 2015 Sep; 121(Pt B):199-206.
- [Platelet- and macrophage-derived endogenous cannabinoids are involved in endotoxin-induced hypotension](#). [FASEB J. 1998]  
Varga K, Wagner JA, Bridgen DT, Kunos G  
FASEB J. 1998 Aug; 12(11):1035-44.
  - [Biosynthesis and inactivation of the endocannabinoid 2-arachidonoylglycerol in circulating and tumoral macrophages](#). [Eur J Biochem. 1999]  
Di Marzo V, Bisogno T, De Petrocellis L, Melck D, Orlando P, Wagner JA, Kunos G  
Eur J Biochem. 1999 Aug; 264(1):258-67.
  - [Anandamide synthesis is induced by arachidonate mobilizing agonists in cells of the immune system](#). [Biochim Biophys Acta. 1998]  
Pestonjamas V, Burstein SH  
Biochim Biophys Acta. 1998 Nov 2; 1394(2-3):249-60.
  - [Presence and regulation of the endocannabinoid system in human dendritic cells](#). [Eur J Biochem. 2002]  
Matias I, Pochard P, Orlando P, Salzet M, Pestel J, Di Marzo V  
Eur J Biochem. 2002 Aug; 269(15):3771-8.
  - [Lipopolysaccharide induces anandamide synthesis in macrophages via CD14/MAPK/phosphoinositide 3-kinase/NF-kappaB independently of platelet-activating factor](#). [J Biol Chem. 2003]  
Liu J, Batkai S, Pacher P, Harvey-White J, Wagner JA, Cravatt BF, Gao B, Kunos G  
J Biol Chem. 2003 Nov 7; 278(45):45034-9.
  - [Review Cannabinoid signaling in glial cells](#). [Glia. 2004]  
Stella N  
Glia. 2004 Dec; 48(4):267-77.
  - [Nonpsychotropic cannabinoid receptors regulate microglial cell migration](#). [J Neurosci. 2003]  
Walter L, Franklin A, Witting A, Wade C, Xie Y, Kunos G, Mackie K, Stella N  
J Neurosci. 2003 Feb 15; 23(4):1398-405.
  - [2-arachidonoylglycerol induces the migration of HL-60 cells differentiated into macrophage-like cells and human peripheral blood monocytes through the cannabinoid CB2 receptor-dependent mechanism](#). [J Biol Chem. 2003]  
Kishimoto S, Gokoh M, Oka S, Muramatsu M, Kajiwara T, Waku K, Sugiura T  
J Biol Chem. 2003 Jul 4; 278(27):24469-75.

[Support Center](#) [Support Center](#)

External link. Please review our [privacy policy](#).

[NLM](#)

[NIH](#)

[DHHS](#)

[USA.gov](#)

[National Center for Biotechnology Information, U.S. National Library of Medicine](#) 8600 Rockville Pike, Bethesda MD, 20894 USA

[Policies and Guidelines](#) | [Contact](#)

•

On 8 September 2017 at 15:40, Angela Hoare <[durgape@gmail.com](mailto:durgape@gmail.com)> wrote:

Rider,

Another possible lead is the combination of an igf1 inhibitor and docosahexaenoic acid. The igf1 inhibitors have not been very effective but the combination with fenofibrate was promising. Of course, fenofibrate does not cross the blood brain barrier but docosahexaenoic acid is actively transported and this work was done with D384 cells which have some characteristics of group 4 medulloblastomas. It bears repeating the studies with docosahexaenoic acid in various concentration and the same and different medulloblastoma cell lines.

We attempted next to sensitize human medulloblastoma cell lines to fenofibrate by utilizing low concentrations of a specific IGF-IR inhibitor, NVP-AEW541 (Novartis). We have previously shown that medulloblastomas are sensitive to 1  $\mu$ M NVP-AEW541 treatment when kept in suspension cultures, and were much more resistant to the same treatment when cultured in monolayer.<sup>11</sup> The results depicted in [Fig. 6](#) indicate that simultaneous treatment of Daoy and D384 cells with fenofibrate (25  $\mu$ M) and NVP-AEW541 (0.5  $\mu$ M) caused almost complete inhibition of the clonogenic growth of Daoy cells ([Fig. 6a](#)), and inhibited colony formation of D384 cells in soft agar ([Fig. 6b](#)). We have obtained 97.3% inhibition of the colony formation in soft agar in the presence of 0.5  $\mu$ M NVP AEW541 (ref.) and 25  $\mu$ M fenofibrate ([Fig. 6b](#)). Note also that D384 cells were partially resistant to 1  $\mu$ M NVP AEW541 in soft agar assay.<sup>11</sup>

Results in [Figure 6C](#) revealed that cell cycle distribution of D384 cell growing in suspension was quite different from the cell cycle obtained from BsB8 and Daoy cells, which grew as monolayer cultures (compare [Figs. 4b](#),





















