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Role of Endocannabinoid Activation of Peripheral CB1 Receptors in the Regulation of Autoimmune Disease

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Abstract

The impact of the endogenous cannabinoids (AEA, 2-AG, PEA, and virodamine) on the immune cell expressed cannabinoid receptors (CB1, CB2, TRPV-1, and GPR55) and consequent regulation of immune function is an exciting area of research with potential implications in the prevention and treatment of inflammatory and autoimmune diseases. Despite significant advances in understanding the mechanisms through which cannabinoids regulate immune functions, not much is known about the role of endocannabinoids in the pathogenesis or prevention of autoimmune diseases. Inasmuch as CB2 expression on immune cells and its role has been widely reported, the importance of CB1 in immunological disorders has often been overlooked especially because it is not highly expressed on naive immune cells. Therefore, the current review aims at delineating the effect of endocannabinoids on CB1 receptors in T cell driven autoimmune diseases. This review will also highlight some autoimmune diseases in which there is evidence indicating a role for endocannabinoids in the regulation of autoimmune pathogenesis. Overall, based on the evidence presented using the endocannabinoids, specifically AEA, we propose that the peripheral CB1 receptor is involved in the regulation and amelioration of inflammation associated with autoimmune diseases.

Keywords

2-AG; anandamide; cannabinoid receptors; cannabinoids; endocannabinoid system; T cell-mediated disease

INTRODUCTION

Human immunity has been tested time and time again against pathogens and microbes. The ability of the immune system to recognize foreign antigens and thereby protect against infections helps in the survival of the species. It is however, when the body reacts to itself that immunity can become problematic. As a form of protection, the immune system is built upon safe guards which serve to ensure that self-tolerance is maintained. It is a loss of this ability to distinguish self from nonself which underlies autoimmune diseases, ranging from

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

mild irritations to severe life threatening symptoms [1]. Autoimmune diseases are complex immunological disorders in which it now appears that the endocannabinoid (EC) system plays an integral role [2].

The EC system was discovered while attempting to gain a more complete understanding of the mechanisms through which exogenous cannabinoids acted on the immune system [2]. Perhaps the most notable exogenous cannabinoid is Δ-9-tetrahydrocannabinol (THC), a psychoactive component of the *Cannabis sativa* plant, which was first described in a 1964 paper by Gaoni and Mechoulam [3]. After THC was isolated and synthesized, it was found that this cannabinoid was a ligand for two receptors termed cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2), discovered in 1990 and 1992 respectively [4, 5]. Not long after the discovery of the cannabinoid receptors, endogenous ligands, which act as lipid messengers derived from cellular membranes, were found [6]. The first EC discovered, N-arachidonyl ethanolamide (AEA), was named anandamide from Sanskrit for “internal bliss” [7]. Anandamide was first found in the porcine brain in 1992 [2]. In 1995, another endogenous cannabinoid, 2-arachidonoyl glycerol (2-AG), was isolated by two independent groups [8, 9].

ECs are synthesized locally as needed rather than being stored within vesicles [10]. The synthesis of AEA can occur in two main ways: one is through N-arachidonoyl phosphatidylethanolaminephospholipase, which converts phosphatidylcholine and phosphatidylethanolamine to N-arachidonoyl phosphatidylethanolamine (NAPE), the anandamide precursor [11]. The other accepted pathway is through phospholipase C hydrolysis of NAPE and phosphoanandamide, which is then dephosphorylated [12]. However, 2-AG follows a different pathway where 2-arachidonate-containing phosphoinositols, converted to diacylglycerols (DAGs), are finally hydrolyzed by DAG lipase [13]. Upon synthesis these lipid messengers, due to the hydrophobic nature of the molecules, remain membrane bound till a high-affinity mechanism allows for cellular uptake to occur [14]. Maintenance of EC levels occurs through intercellular metabolism via the catabolic enzyme, fatty acid amide hydrolysis (FAAH), and monoacylglyceride lipase for AEA and 2-AG respectively [15–17].

While AEA and 2-AG may be the most widely studied ECs, they were only the first to be discovered. Since then, interest in palmitoylethanolamide (PEA) and O-arachidonyl ethanolamide (virodamine) has also been increasing [18, 19]. AEA has been found to be produced by neurons as well as immune cells and shows more selectivity for CB1 than CB2 [2]. AEA has also been shown to be an agonist at noncannabinoid receptors including vanilloid receptor-type 1 (TRPV-1) and GPR55 [20, 21]. 2-AG, which can stimulate through both CB1 and CB2 receptors equally, is found in higher concentrations in the immune system, plasma, and brain than AEA [22]. PEA has been found in the immune system and has been shown to interact with mast cells through the CB2 receptor [23]. PEA is also considered to have “entourage effect” where it is able to enhance the effectiveness of AEA and 2-AG [24]. Virodamine has been found to act as a partial antagonist at the CB1 receptor and as an agonist on CB2 [19].

All receptors associated with the EC system are G-protein coupled receptors (GPR) consisting of seven transmembrane helices, an extracellular N-terminus, and an intracellular C-terminus [2]. Somewhat controversial is the inclusion of the vanilloid and orphan GPR55 receptors to the EC system. The vanilloid receptor, which can be activated by voltage, protons, vanilloid compounds (such as capsaicin), as well as AEA, is found in the CNS and on immune cells [25–27]. However, as many non-cannabinoid molecules can act as activators for this receptor, it cannot be considered exclusively part of the EC system. GPR55 is present in tissues, including the adrenals, gastrointestinal tract, and central nervous system, and also affects the G_{13} peptide [21, 28]. The issue with including this receptor in the EC system is that while AEA, 2-AG, PEA, and virodamine have been found to activate the GPR55 in transformed human embryonic kidney cells (HEK293), these results are not always reproducible [21, 29]. The main cannabinoid receptors, CB1 and CB2, have been found to reside in numerous organ systems with CB1 having the highest rate of expression in the central nervous system and CB2, in the immune system [30, 31]. However, CB1 receptors have also been found in the immune system, in particular on activated T cells, and CB2 receptors have been found in the CNS as well as other periphery tissues [31, 32]. While CB receptors interact with multiple ligands, specificity is maintained through structural and conformation requirements. CB1 receptor binding requires 20–22 carbon fatty acid chains, no less than three homoallylic double bonds, and at least five saturated carbons at the end of the acyl chain [33]. Additionally, amino acid disparity in binding sites, due to single nucleotide polymorphisms, affects CB receptor affinity for individual ligands including the selectivity of AEA for the CB1 receptor [34–38].

There is little doubt that ECs affect the immune system. However, the discussion seems to be whether the endogenous cannabinoids are immunosuppressive or stimulatory. This is due to the differences observed in the use of *invitro* versus *invivo* models and in the concentration of ECs used. *In vitro* studies with exogenous cannabinoids found that a micromolar concentration elicits inhibitory effects while a nanomolar concentration causes stimulation of the immune system [39]. The conflicting nature of these results may be, in part, due to a biphasic response related to the concentration of CB receptors and affinity of the CB ligands [40, 41]. With this in mind, it appears that the role of the EC system in immune response is more complex than originally expected [41]. To better understand the conflicting nature of ECs, this review will focus on the role of the CB1 receptor in amelioration of T cell driven autoimmune diseases.

Role of CB1 in Systemic Immune Response

At first glance, the link between the EC system and autoimmune disease may appear tenuous or limited to neuroimmune disorders inasmuch as the CB1 receptor was initially understood to be CNS specific. However, in depth studies of the Jurkat T cell line has shown that CB1 transcript expression is significantly increased, 29-fold, upon CD3/CD28 activation compared to non-stimulated cells [42]. Even nonimmortalized primary human T cells, isolated form peripheral blood, exhibit an eightfold increase in CB1 transcript when activated [42]. This is of great importance in the understanding of autoimmune diseases as T cells are a major component of the adaptive immune system and are direct mediators of a number of autoimmune diseases including multiple sclerosis (MS) and autoimmune hepatitis

or provide help to B cells to produce autoantibodies. Focusing first on 2-AG, it was found that its addition to anti-CD3 mAb-induced T cells inhibited proliferation, but only at low cell density [43]. Additionally, *in vitro* incubation with 2-AG was found to suppress IL-2 in activated Jurkat T cells at micromolar concentrations as well as in primary splenocytes [44, 45]. Looking at the mitogen-induced proliferation of T cells, a dose-dependent inhibition was observed when AEA was administered *in vitro* [46]. In an *in vivo* experiment, it was found that when AEA was added at micromolar concentrations, prior to OVA stimulation, it caused decrease in IFN-γ production in ConA-stimulated splenocytes [41].

As mentioned earlier, both AEA and 2-AG have been shown to act through the CB1 receptor. The G-proteins that CB1 receptors activate include G_i, inhibitory proteins, which are known to modulate adenylate cyclase [47]. Furthermore, the CB1 receptor upon activation has been found to increase ceramide, a bioactive lipid implicated in cellular differentiation, proliferation, and apoptosis [48]. Additionally, recent findings show that AEA (micromolar) works in a CB1 dependent manner to induce myeloid-derived suppressor cells, a regulatory cell type which has been shown to inhibit inflammatory responses to T cell activation [49]. These data support the EC system working through the CB1 receptor to elicit an anti-inflammatory response, upon activation of immune cells. Based on the fact that every autoimmune disorder represents a unique and complex pathological event, it is hard to make an overarching statement on how ECs will impact autoimmunity [2]. Nonetheless, in some autoimmune disorders it has been shown that increases in cannabinoid receptor density and EC concentration cause a reduction in clinical symptoms [50]. Below, we have highlighted the regulatory impact of ECs on certain autoimmune diseases.

Role of Endocannabinoids on the Regulation of Autoimmune Disease

Multiple sclerosis—MS is an autoimmune disease which causes chronic inflammation in the central nervous system, due to infiltration of Th17 and Th1 cells as well as macrophage activation [51]. Together, the T cell infiltration and macrophage activation can cause oligodendrocyte death, demyelination, and damage to axons [52]. The autoimmune responses to oligodendrocytes and myelin sheaths are considered to be hallmarks of MS; however, neurodegeneration, including loss of motor coordination as well as sensory deficits, occurs constituently along with neuroinflammation [6, 53]. MS can be divided into the more neuroinflammatory, relapsing-remitting (RRMS) disease which is more common in early adulthood, or the more neurodegenerative, secondary-progressive (SPMS) disease which often occurs later in life [54]. RRMS is characterized by acute relapses in disease followed by periods of recovery, however, in SPMS the disease continues to worsen without relapses [55]. Looking at both sides of MS, the EC system seems to have a good fit with cannabinoid receptors playing a part in the physiological function of both the central nervous system and the immune system [56].

The EC system has been examined to a great extent in both neuroinflammatory and neurodegenerative disease as the central nervous system is known to express both CB1 and CB2 receptors as well as the endogenous cannabinoids [4, 9]. In the beginning stages of neuroinflammation, microglia become activated and release proinflammatory cytokines including TNF-α and IL-6 which are cytotoxic and increase blood brain barrier breakdown

by causing astrocyte activation [56]. As a source of suppression, it has been found that activated CB2 receptors can alter the proinflammatory tone to that of a Th2 anti-inflammatory tone, and that proinflammatory cytokines and reactive oxygen species produced by microglia or astrocytes can be modulated by AEA [57, 58]. Specifically, it has been shown that upon CB2 receptor activation the Th2 cytokine IL-4 is increased causing an induction of CB1 receptor transcripts [59]. Furthermore, neuronal degeneration often includes over activation of glutamate, which leads to generation of free radicals and secondary excitotoxicity among other pathologies [56]. However, AEA activation of CB1 receptors induces protection against excitotoxicity in murine brain [60]. As the CB1 receptor is associated with calcium channel inhibition, EC activation of this receptor helps in the restoration of calcium homeostasis [61, 62]. It has also been found that AEA signaling is involved in maintaining a healthy central nervous system as it suppresses microglial attacks on undamaged neurons [63].

Experimental autoimmune encephalomyelitis (EAE) is a murine model of MS. It is commonly induced by injection of myelin oligodendrocyte glycoprotein (MOG) peptide mixed with an adjuvant, into C57BL/6 mice, to mimic RRMS [64]. In a study by Witting et al., it was found that during EAE the levels of AEA and 2-AG did not significantly increase when compared to normal brain, most likely due to the elevated levels of IFN-γ [65]. IFN--γ is believed to be able to affect 2-AG production via its effect on monoacyglycerol lipase or phospholipase C both of which are necessary enzymatic steps in this ECs production [66]. However, a recent study found that exogenously administered 2-AG was able to ameliorate MOG-induced EAE as well as increase CB1 receptor expression in neuronal and inflammatory cells [67]. Focusing on AEA, a study by Centonze et al. observed that the endogenous level as well as the level of NAPE-PLD activity, an enzyme in AEA production, was increased in the striatum of the EAE murine brain, but not in the cortex [64]. Centonze et al. also showed that the level of FAAH activity was decreased in the striatum significantly, compared to normal controls [64].

Another murine model of MS is induced by a virus, Theiler's murine encephalomyelitis virus, which causes demyelinating disease (TMEV-IDD) in SJL/J mice. This strain is highly susceptible to this form of encephalomyelitis and this model of murine MS mimics the progressive MS models [53]. A study that used UCM707, an EC uptake inhibitor, found that the levels of TNF-α and IL-1β were decreased in the TMEV-IDD MS model [53]. Similar results were reported by Ortega-Gutierrez et al. who administered methanandamide (Met-AEA), a known stable AEA analog, as well as used UCM707, with a suboptimal dose of AEA, in the loss of motor function seen in TMEV-IDD MS [53]. In a TMEV-IDD study, where EC levels were analyzed in spinal cord, 2-AG and PEA were found to be significantly increased [52]. Upon PEA treatment, Loria et al. found that TNF-α and IL-1β were both decreased compared to TMEV-IDD controls, and that microglia cell activation was decreased compared to the control mice [52]. While the effects of PEA treatment were anti-inflammatory, Loria et al. were unable to deduce if PEA itself was ameliorating the disease or if it was acting through possible "entourage" effect with AEA [52]. Looking at the levels of IL-12p70 and IL-23, which are involved in production of IFN-γ, a significant increase is seen in TMEV-infected spinal cords, and with AEA treatment, the levels of both IL-12p70

and IL-23 were decreased while IL-10 was increased in peripheral blood when compared to the levels in MS control [68]. Correa et al. also observed a reduction in the loss of motor function in both AEA and FAAH inhibitor treated mice [68]. An *in vitro* study using a mixed culture of cortical neurons and astrocytes, AEA at micromolar concentrations was able to exhibit neuroprotective effects in both NMDA and AMPA induced excitotoxicity, and that 2-AG and UCM707 were able to mimic these results in AMPA induced excitotoxicity [69]. Recent evidence was able to link not just ECs to the modulation of virus induced EAE disease symptoms, but also the importance of the CB1 receptor [70]. Rossi et al. found that loss of function at the CB1 receptor resulted in an increase of disease severity [70]. Additionally, they showed that FAAH knockout mice, with functional CB1 receptors, have decreased disease symptomology providing a possible link for AEA working through CB1 [70].

In a study of both RRMS and SPMS patients, EC levels were analyzed in plasma (nanomolar) during a time when no immunomodulatory drugs were given and the RRMS patients were in clinical remission [51]. Jean-Gilles et al. found that AEA and PEA levels were significantly increased in both RRMS and SPMS patients compared to healthy controls, and neither RRMS or SPMS patients exhibited increased levels of 2-AG in blood plasma [51]. It was also found that SPMS patients had significantly increased levels of AEA and PEA compared to RRMS patients, and also had significantly less FAAH present in whole blood samples possibly due to pro-inflammatory cytokines such as IFN-γ and IL-12 [51]. A cytokine-mediated reduction in FAAH could be affecting the EC levels seen in MS patients [71]. In a study of RRMS patients by Centonze et al. cerebrospinal fluid (CSF) showed a 6-fold increase for AEA in MS patients compared to normal controls [64]. Significantly higher levels of AEA and NAPE-PLD was found in the peripheral lymphocytes of RRMS patients when compared to healthy controls, while both FAAH activity and protein levels were decreased significantly [64]. RRMS patients with MRI gadolinium enhancing lesions were found to have higher levels of AEA, 2-AG, and virodamine in CSF than RRMS or SPMS patients without the lesions [72]. Taken together this suggests that ECs could be acting as a protective mechanism against neurological degradation and inflammation [64].

Autoimmune hepatitis—Autoimmune hepatitis (AIH) is one of many autoimmune liver diseases and can occur either in acute or chronic form [10]. One of the distinguishing hallmarks of AIH is autoantibodies against either smooth muscle actin, cytochrome P450, or soluble liver antigen [73,74]. While this immune response involves many inflammatory cytokines and cell types, it is believed to be T-cell mediated [75]. It was found that immunosuppressive treatment could greatly improve 10-year survival and the percentage of treatment failure in AIH patients with and without cirrhosis [76]. Standard treatment for this disease is based on research from nearly 30 years ago and includes prednisone alone or in combination with azathioprine, which must be reduced before 24 months to avoid severe side effects [77].

CB1 and CB2 receptors are expressed in the liver at low levels with an increase found during disease conditions, such as hepatocellular carcinoma [78]. Additionally, serum samples from cirrhotic rats as well as humans showed that AEA levels increase up to

threefold when compared to normal controls [79]. Elevated AEA levels have been associated with reduced hypertension [80]. Also, in hepatic encephalopathy, believed to be partly derived from a systematic inflammatory response, a positive modulation of the disease was observed with exogenous 2-AG treatment [81]. Furthermore, AEA and 2-AG were increased in a murine model of hepatic ischemia [82]. These findings suggest an important role for ECs in various liver diseases.

In a study from Hegde et al., the effects of AEA were investigated in a concanavalin A (ConA)-induced hepatitis model in C57BL/6 mice [83]. It was found that when the mice were treated with CB1/CB2 mixed agonists such as CP55.939 and WIN55212, ConA-induced hepatitis could be suppressed, and that this suppression was lost upon the blocking of either cannabinoid receptor [83]. Treatment with AEA, which has a stronger binding affinity at CB1 receptors than CB2, was able to cause a dose dependent reduction in ConA-induced hepatitis as well as a decrease in TNF-α levels [83]. To further show that AEA could affect the severity of T-cell mediated hepatitis, ConA-induced hepatitis was studied in FAAH knockout mice. It was found that FAAH knockout mice showed resistance to the development of hepatitis [83]. AEA was also shown to cause hepatic stellate cell apoptosis which was found to be associated with a resolution of liver fibrosis [84,85]. Siegmund et al. also found 2-AG to cause apoptosis in the same hepatic stellate cells a year later [86]. However, when the CB2 receptor was preferentially activated and CB1 was blocked pharmacologically with SR141716A, liver fibrosis was reduced [87]. This suggests that activation of the CB1 receptor is beneficial in the modulation of acute rather than chronic liver disease as it has not yet been found to help directly in fibrotic conditions.

Rheumatoid arthritis—Rheumatoid arthritis (RA) is a common form of systemic inflammatory autoimmune disease [88, 89]. RA presents seemingly benign symptom such as pain, swelling, or stiffness of the joints; however, in a matter of months, the synovium is attacked causing hypertrophy [90]. The pathology of the synovium includes inflammation due to infiltration of T and B cells among other lymphocytes [89]. It is believed that T cells do not directly cause synovial deformation rather they work to initiate the systemic inflammation affecting the cytokine levels in the synovium [91]. TNF-α and IL-1 are the largest contributors to the cytokine profile in RA and have been proven as necessary factors in synovial destruction inasmuch as treatment with antibodies for TNF-α and IL-1 mitigated RA symptoms [92,93]. Classically, RA has been treated with nonsteroidal anti-inflammatory drugs in combination with disease modifying antirheumatic drugs, including methotrexate and cyclosporine [89]. More recently, treatments using biological response modifiers such as anti-TNF agents have been gaining favor, but all current treatments have the potential to cause side effects or toxicity with long-term use [89].

Research showing the impact of endogenous cannabinoids in RA is sparse. Recently, Naidu et al. looked into how FAAH inhibition affected inflammatory pain [94]. It was found that when WIN 55212–2, a CB1/CB2 mixed agonist, was given along with LPS, edema and pain sensitivity were reduced [95]. Along this same line, when FAAH was pharmacologically and irreversibly inhibited, by URB597 in a murine LPS paw edema model, a reduction was found in the TNF-α as well as in paw edema [94]. AEA may be important in the anti-inflammatory response observed upon FAAH inhibition; suggesting that as blockade of

FAAH increased the anti-inflammatory response and analgesic effects, it could be useful in RA treatment [94]. Another study from Eros et al. examined how dietary phosphatidylcholine (PC) can affect a collagen-induced arthritis (CIA) murine model of RA [96]. Eros et al. found that when PC, a precursor of AEA, was given prior to onset of clinical signs of inflammation, CIA-induced pain were abrogated, and that damage to the synovium, cartilage, and bone was decreased when compared to disease control and treatment after the onset of symptoms [96]. Upon further examination, these data suggested that AEA may cause reductions in pain and inflammation in RA models either through exogenous additions or via inhibition of endogenous degradation.

With AEA being known to preferentially work through the CB1 receptor, these data provide indirect evidence of the importance of peripheral CB1. However, a more direct connection for the CB1 receptor in reducing cartilage destruction in RA has recently been found [97]. It was shown that adhesion of synovial fibroblasts was necessary for migration to and invasion of cartilage [97]. Lowin et al. has found that AEA, either through FAAH inhibition or exogenous treatment, causes adhesion of synovial fibroblasts to fibronectin, in a CB1-dependent manner, decreasing the migratory potential of these cells [97]. Together, these data strengthen the claim that the peripheral CB1 receptor is not only involved but important in the immunosuppression of autoimmune disease.

Furthermore, a study was done to directly assess the EC system in the synovial fluid and tissue of RA patients [98]. Richardson et al. found that AEA and 2-AG, while found to be below detectable levels in healthy controls, were both present in RA synovial fluid, and that PEA and virodamine were highly expressed in healthy samples and decreased in RA samples [98]. As no healthy control synovial tissue was collected for comparison, it can only be said that the levels of all four ECs were expressed more in the tissue (pico mole/gram) than in the fluid (pico mole/milliliter), which showed that levels in synovial fluid are not reflective of EC synthesis in the synovium [98]. Taken together, these data suggested that the EC system does play a part in RA with the loss of PEA possibly contributing to disease progression [98].

CONCLUSION

At a cellular level, ECs impact both the innate and adaptive immune systems. The findings that exogenous addition of ECs cause significant decreases in T cell proliferation and pro-inflammatory cytokine levels, suggests that as a whole, ECs, while elevated during autoimmune disease progression, appear to be enacting an anti-inflammatory tone. In particular AEA seems to be protective as inhibition of the degradative enzyme FAAH reduces disease severity in many T cell-mediated autoimmune disorders. The role of AEA in disease modulation is tied to the peripheral expression of the CB1 receptor. Inasmuch as CB2 expression on immune cells and its role has been widely reported, the importance of CB1 in immunological disorders has often been overlooked especially because it is not highly expressed on naive immune cells. However, due to the significant increase in CB1 expression on activated T cells, it should be considered an integral component of the EC system's response to autoimmunity-induced inflammation. T cells play a critical role in the pathogenesis of autoimmune disorders by either directly causing tissue damage through

production of proinflammatory cytokines, or through activation of other cells such as macrophages and B cells thereby driving the progression of the disease. This review looked at the CB1 receptor in various autoimmune diseases, primarily where T cells are considered disease mediators, finding that activation of CB1 correlates with reduced symptomology. This suggests that FAAH inhibitors or AEA could be used as therapeutics in certain autoimmune disease models. While a plethora of research has been conducted to better understand the EC system as a whole, the direct impact of this system in autoimmune disease models is lacking. A continuation of research into varied and diverse disease models will lead to a more thorough understanding of the effects and potential applications of ECs to prevent and treat inflammatory and autoimmune disease. Also, while it is commonly believed that the peripheral immune cells express CB2 receptors, the role of CB1 expression on immune cells is not well understood. Studies on CB1-mediated regulation of the immune response may help to better understand the role of psychotropic drugs, which act through CB1 receptors, on immune regulation.

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Abbreviations

2-AG	2-Arachidonoyl glycerol
AEA	Anandamide
AIH	Autoimmune hepatitis
CB1	Cannabinoid receptor 1
CB2	Cannabinoid receptor 2
CIA	Collagen-induced arthritis
CNS	Central nervous system
ConA	Concanavalin A
CSF	Cerebral spinal fluid
EAE	Experimental autoimmune encephalomyelitis
EC	Endocannabinoid
FAAH	Fatty acid amide hydrolysis
GPR	G-protein coupled receptor
MDSC	Myeloid derived suppressor cells(s)
MOG	Myelin oligodendrocyte glycoprotein
MS	Multiple sclerosis
NAPE	N-arachidonoyl phosphatidylethanolamine

PEA	Palmitoylethanolamide
PC	Phosphatidylcholine
RA	Rheumatoid arthritis
RRMS	Relapse-remitting multiple sclerosis
SPMS	Secondary-progressive multiple sclerosis
THC	Δ9-Tetrahydrocannabinol
TMEV-IDD	Theiler's murine encephalomyelitis virus-induced demyelinating disease

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