Immunobiology 215 (2010) 588–597

Contents lists available at ScienceDirect

Immunobiology

journal homepage: www.elsevier.de/imbio

Cannabinoids and the immune system: An overview

Radu Tanasescu [a], Cris S. Constantinescu [b,*]

[a] Department of Neurology, Colentina Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[b] Division of Clinical Neurology, University of Nottingham, B Floor Medical School, Queen's Medical Centre, Nottingham NG7 2UH, UK

ARTICLE INFO

Article history:
Received 20 February 2009
Received in revised form
15 December 2009
Accepted 17 December 2009

Keywords:
Cannabinoids
Cannabinoid receptors
Endocannabinoids
Immune response
Cytokines

ABSTRACT

Cannabinoids can influence the immune network. Data on the impact of exogenous cannabinoid ligands on immune function serve not only to understand how the endocannabinoid system modulates immune phenomena associated with infection or inflammation, but also to identify therapeutic targets for immune diseases. Cannabinoids can modulate immune reactions in the periphery but also in the brain, influence T cell subset balance and cytokine expression and play a role in the balance between neuroinflammation and neurodegeneration. Immune cells can synthesize endocannabinoids and also be influenced by cannabinoid analogues. Cannabinoid receptors show different expression on immune cells depending on activation status and stimuli. The complexity of relation between cannabinoid ligands of various classes and cannabinoid receptors brought the need to refine the simple conceptual frame of agonist–antagonists and offered potential implications for understanding interactions in pathological conditions. The immune influence of cannabinoid ligands is not fully elucidated. However, aspects of their immunomodulatory effects provide the basis for a context-dependent targeted therapeutic approach, thus leading to the possibility for the use of cannabinoids in the treatment of inflammatory disease.

Introduction

Cannabinoids, the biologically active constituents of marijuana, have been used for thousands of years for their psychoactive properties. The potential for marijuana to be both a therapeutic for a variety of conditions and a drug of abuse generated major efforts in order to clarify the biology and physiological role of cannabinoids in humans.

The marijuana plant contains more than 60 distinct chemical cannabinoids. Among them, D9-tetrahydrocannabinol (D9-THC) is the main psychoactive constituent, first structurally described in 1964 (Gaoni and Mechoulam, 1964) and giving the name for this class of compounds. In 1992, the first endogenous cannabinoid was isolated from porcine brain and identified as arachidonyl ethanolamide (anandamide; from the Sanskrit for "internal bliss") (Devane et al., 1992). A second endocannabinoid was later identified (2-arachidonoyl glycerol) (Howlett et al., 2002). Since then, several synthetic cannabinoid analogues have been proven to induce similar *in vivo* effects such as analgesia and behavioral changes.

The study of the mechanism of action of cannabinoids led to the identification of a novel system of intercellular signaling, the endocannabinoid system. This system consists of endogenous ligands and receptors being subject to modulation by natural and synthetic cannabinoid agonists, and plays important modulatory functions in the brain and also in the periphery (Klein et al., 2003). The endocannabinoid system has been conserved during evolution. Binding sites with stereoselectivity were demonstrated in invertebrate microglia and immune cells (Salzet et al., 2000).

CB1R receptor is the most abundant G-protein-coupled receptor (GPCR) within the adult nervous system (Howlett et al., 2002). CB1R is localized to a number of functional brain structures, regulates synaptic neurotransmission and thus mediates psychoactive effects, and also providing a target for the use of cannabinoids as therapeutic agents for a number of neurological disorders (Croxford, 2003). CB2R receptor was described in 1993. It is not thought to be involved in psychoactive effects of cannabinoids and was initially found in the periphery, particularly in immune cells (mainly B cells and macrophages), but seems also to play a critical immune role in the CNS (Munro et al., 1993; Cabral et al., 2008).

The immunomodulatory and anti-inflammatory effects of cannabinoids are not fully elucidated. These effects have been reviewed over the years (Hollister, 1986; Cabral and Dove Pettit, 1998; Klein et al., 1998; Berdyshev et al., 2001; Roth et al., 2002; Croxford and Yamamura, 2005; Massi et al., 2006). Here, we review some aspects of the immune mechanisms affected by cannabinoids and, in this light, the therapeutic potential of these drugs in the treatment of immune diseases.

* Corresponding author. Tel.: +44 115 8754597; fax: +44 115 9709738
E-mail address: cris.constantinescu@nottingham.ac.uk (C.S. Constantinescu).

0171-2985/$ - see front matter © 2010 Elsevier GmbH. All rights reserved.
doi:10.1016/j.imbio.2009.12.005

Cannabinoid receptors

The two main subtypes of cannabinoid receptors (CBR) classically described (CB1R and CB2R) are single polypeptides with an extracellular N-terminus, an intracellular C-terminus and seven transmembrane helices. Both activate G proteins (Gi proteins) inhibitory to adenylate cyclase (AC) thus inhibiting the conversion of ATP to cyclic AMP (cAMP) (Howlett and Mukhopadhyay, 2000). However, they can also activate AC through stimulating G proteins (Gs proteins) (Glass and Northup, 1999), and both are positively coupled to mitogen-activated protein kinase (MAPK) (Woelkart et al., 2008). CB1R is coupled with ion channels, inhibiting D-type K+, N and P/Q-type Ca2+ currents, and activating inward and A-type rectifying K+ currents (Croxford and Yamamura, 2005). For CB2R, the ion channel modulation is more variable (Mackie, 2008). CB2R signaling mechanisms also involve the activation of the phosphatidylinositol 3-kinase and Akt (PI3K–Akt) pathway and increases the synthesis of the sphingolipid messenger ceramide, thus having a pro-survival and a pro-apoptotic effect, respectively (Molina-Holgado et al., 2002; Carracedo et al., 2006).

Besides the CBR pathway, endocannabinoids also interact with other GPCR (Mackie, 2008) like the vanilloid receptor-type 1 (TRPV-1) activated by anandamide, and also K+ channels, 5-HT3 receptors and alpha7 nicotinic receptors (Szallasi and Di Marzo, 2000; Oz, 2006). It is not clear which of these interactions are relevant for the physiologic effects of cannabinoids or just a consequence of their lipophilic character (Mackie, 2008).

Some effects of the classical cannabinoids such as anti-emesis may not be mediated only by the CB1R–CB2R receptor system (Bueb et al., 2001; Parker et al., 2004). Some evidence suggests the existence of additional cannabinoid receptor subtypes possibly responsible for these alternative mechanisms (Breivogel et al., 2001; Howlett et al., 2002). Recent studies focus on GPR55, suggesting that this receptor can be activated by anandamide and 2-AG (Ryberg et al., 2007).

The localization of CBR is highly relevant for their functions. CB1R, first identified in mouse spleen cells (Kaminski et al., 1992), is located mainly on hippocampus and basal ganglia and highly expressed in the brain regions expected from the psychoactive effects of D9-THC (Mackie, 2005). In the forebrain, immunocytochemistry studies show that CB1R are expressed mainly by axons of GABAergic interneurones containing cholecystokinin basket cells (Bodor et al., 2005; Nyiri et al., 2005). The endocannabinoids can act instantly or their effects may be long-lasting (Bacci et al., 2004). Central CB1R can be implicated in short-term and long-term neuroplasticity (Chevaleyre et al., 2006).

In peripheral tissues, CB1R is found in adipocytes, liver, pancreas, skeletal muscle – possibly implicated in the metabolic cannabinoid effects. Activated somatic CB1R receptors can result in neuronal hyperpolarisation (Bacci et al., 2004; Cavuoto et al., 2007; Cota, 2007).

Recent data show that CB1R, like several GPCR, exist as homo- or heteromultimers (Milligan, 2004), with the possibility that this might be able to enhance the receptor signaling repertoire (Mackie, 2005).

CB1R receptors are expressed in T lymphocytes, and may be involved in cannabinoid-induced T helper cell biasing. Although they are less expressed in the basal state, CB1R receptors are up-regulated in T cells by stimuli such as cannabinoids themselves, and this effect is mediated by IL-4 (Borner et al., 2008).

CB2R are generally expressed at lower levels than CB1R, and highly selective antibodies for CB2R are difficult to be generated (Van Sickle et al., 2005). There is strong evidence that CB2R receptors are expressed on immune cells (especially those macrophage-derived: microglia, osteoclasts) and neurons (Galiegue et al., 1995; Ofek et al., 2006). CB2R was also found in other peripheral structures, such as peripheral nerve terminals in mouse (Griffin et al., 1997; Lu et al., 2000).

Within the immune system, CB2R level is usually higher than that of CB1R (Massi et al., 2006) (Gong et al., 2006). CB2R mRNA is found in decresing amounts in human B cells, NK cells, monocytes, polymorphonuclear neutrophils and T cells (Galiegue et al., 1995). In the immune organs, CB2R expression was demonstrated in thymus and spleen. The presence of CB2R in dendritic cells, potent antigen-presenting cells, suggests a role for cannabinoids in modulating antigen presentation (Matias et al., 2002). The expression of CB2R depends of the cell activation state and can be influenced by immune modulators, as shown by the studies on rodent peritoneal macrophages (Carlisle et al., 2002).

Immune consequences of CB2R activation include changes in cytokine release from immune cells and migration of immune cells inside or outside the central nervous system (CNS) (Cabral and Staab, 2005).

Initially, northern analysis, quantitative RT-PCR analysis and autoradiography could not elicit the CB2R presence in the brain, but Western blot analysis and immunohistochemistry demonstrated its presence in astrocytes and microglia (Croxford and Yamamura, 2005). Because CB2R expression on microglia is related to the cell activation status, it was suggested that it may be induced by local inflammation, infection or stress (Carlisle et al., 2002; Croxford and Yamamura, 2005; Wotherspoon et al., 2005), but further studies demonstrated that CB2R is present in astrocytes, microglia, neural subpopulations and oligodendroglial progenitors in healthy brains (Stella, 2004; Maresz et al., 2005; Van Sickle et al., 2005; Beltramo et al., 2006; Onaivi et al., 2006; Palazuelos et al., 2006).

The presence of CB2R receptors in the brain opens new pathways for studies on endocannabinoid system relation to neuroprotection and neuroinflammation. Microglia is related to macrophages and represent a major cell type responsible for chronic neurodegenerative and neuroinflammatory processes. Microglia also express CB1R and produce endocannabinoids (2-AG and anandamide) (Carrier et al., 2004, 2005). CB2R expression is higher in microglial activation states, like ‘primed’ and ‘responsive’ microglia (Carlisle et al., 2002; Cabral et al., 2008). During these states, cannabinoids exert a stronger influence on activated microglia functions. It is suggested thus that a CB2R-dependent “time-window” for functional modulation of microglial actions exists, and that synthetic and endogenous cannabinoid analogues have different modulator effects at this level (Marciano-Cabral et al., 2001; Walter et al., 2003; Cabral et al., 2008).

Endocannabinoids may play a modulating role between neurogenesis and neurodegeneration, via the immune system or on independent pathways (Fernandez-Ruiz et al., 2007; Wolf and Ullrich, 2008). Therefore, the CB2R receptor in the CNS is an attractive target for drug development targeting neuroinflammation and neurodegeneration.

Finally, it must be said that CBR have particularities of reaction to stimulation that can explain some of the discordant results of experiments using artificial cannabinoid analogues. These particularities include partial agonism, inverse agonism and functional selectivity, and assume the model of receptors existing in equilibrium between active and inactive conformations (Mackie, 2008). Also, for both CB1R and CB2R, different conformations are corresponding to different agonists stimuli, consequently activating different signaling pathways (functional selectivity) (Kenakin, 2001; Mackie, 2008).

Moreover, agonist and antagonist cannabinoid analogues have different consequences on receptor activation that are related to

the basal level of signaling of the system receptor. Effects of CB1R and CB2R modulators are difficult to distinguish *in vivo*, since the difference between effects of inverse agonist and neutral antagonists cannot clearly be separated (Kenakin, 2001; Mackie, 2008; Yao et al., 2006).

The cannabinoid receptor-associated signal transduction and the immune system

CBR stimulation is implicated in the regulation of DNA binding of different nuclear factors in the immune cells (Massi et al., 2006). These effects are mainly achieved via down-regulation of cAMP formation and signal transduction involving AC (Koh et al., 1995). Rapid and transient bursts in AC activity are associated with preceding lymphocyte activation by mitogens, and cytokine transcription in macrophages is regulated via cAMP signaling cascade (Kaminski et al., 1994). cAMP analogues variably inhibit or stimulate immune responses in a concentration-dependent manner, and can antagonize the effect of cannabinoids on T lymphocyte-dependent production of antibodies (Koh et al., 1995).

CBR stimulation seems to antagonize the regulatory role of cAMP pathway in the early events in immune cell activation, but again these effects are probably more complex, since natural cannabinoids, unlike synthetic cannabinoids, act as inverse AC agonists or antagonists in some circumstances (Bayewitch et al., 1996) (Massi et al., 2006). cAMP regulates PKA signaling cascade, which targets multiple intracellular units such as the family of cAMP response element-binding protein/activation transcription factor (CREB/ATF). Stimulation by D9-THC inhibits IL-2 secretion and transcription after the reduction of cAMP formation via CB2R (Condie et al., 1996; Yea et al., 2000). D9-THC also inhibits protein kinase A and cAMP response element (CRE)-specific transcription factor binding and nuclear factor binding to CRE and kB in mouse splenocytes and thymocytes (Koh et al., 1997; Herring et al., 1998; Herring and Kaminski, 1999). A similar mechanism was demonstrated in the macrophage cell line RAW264.7, leading to down-regulation of inducible NO synthase (Jeon et al., 1996)

Besides cAMP-mediated effects, stimulation of cannabinoid receptors can act through Gi proteins and have a dual influence on MAPK activity depending on the ligand and cell type. Cannabinoid agonists can have different modulator inducing effects on MAPK signaling pathway. CB2R is probably involved in MAPK phosphorylation after stimulation with 2-AG (Kobayashi et al., 2001).

Indirect evidence suggests the involvement of Gi–Go proteins, since the response induced by 2-AG is blocked by pertussis (Kaminski et al., 1994). Therefore, CBR stimulation generates complex cellular regulation cascades of DNA binding, mainly but not solely via cAMP pathway, implying also Gi- and Gs-binding proteins and MAPK stimulation.

Cannabinoid-based analogues and ligands

There are two main groups of cannabinoid ligands, with varying affinities for actually described receptors. The first group is based on the structure of marijuana cannabinoids and includes natural compounds [D9-THC, D8-THC, cannabichromen (CBC), cannabigerol (CBG) and tetrahydrocannabivarin (D9-THCV) – all psychoactive, cannabinol and cannabidiol – both without psychoactive proprieties] and synthetic ligands [CP55940, HU-210, HU-211, ab-cannabidiol, ajulemic acid].

The main representative members of the second group are arachidonic acid metabolites N-arachidonyl ethanolamide or anandamide (AEA), 2-arachidonoyl glycerol (2-AG), palmitoylethanolamide (PEA), 2-arachidonylglycerylether (noladin ether) and O-arachidonyl ethanolamine (virodhamine) (Fowler et al., 2005; Porter et al., 2002).

Several CB1R- and CB2R-selective agonists and antagonists have been developed. CB1R-selective antagonists include SR141716A (rimonabant), AM251, AM281 and LY320135; SR144528 and AM630 are CB2R-selective antagonists (Pertwee, 2005). Neutral cannabinoid receptor antagonists apparently lacking inverse agonist activity have also been developed (Pertwee, 2006).

Endocannabinoids: AEA is produced by immune cells and neurons, and is more selective for CB1R than CB2R. It is found in brain, spleen, skin, kidney and uterus (Yang et al., 1999; Croxford and Yamamura, 2005). AEA is highly produced by brain areas where CB1R is highly represented (striatum, hippocampus, cerebellum) and is implicated in cannabis-related effects like nociception and catalepsy. Evidence exists that AEA can activate TRPV-1 receptors as well as acting on CB1R and CB2R (Pertwee, 2005).

2-AG was first isolated from canine gut tissue (Mechoulam et al., 1995). 2-AG is present in higher quantities than AEA in the immune system and has lower affinity for CB1R. 2-AG can stimulate through CB2R the chemotactic response of microglial cells, and these effects are antagonized by exogenous cannabinoids (D9-THC, CP55940) (Cabral et al., 2008)

PEA is generated by neurons and immune cells. It is produced during inflammation and inhibits mast cells via CB2R and downregulates inflammation (Calignano et al., 1998; Facci et al., 1995). However, even though CB2R antagonists can counteract its cannabinoid-like effects, it was suggested that it does not bind either CB1 or CB2 (Facci et al., 1995; Croxford and Yamamura, 2005).

The receptor response to a specific endocannabinoid is influenced by the ligand concentration, the presence of other cannabinoid ligands molecules, the receptor density and state of activation and the quantities of signaling proteins.

The pharmacology of plant-derived ligands was recently reviewed (Pertwee, 2008). Phytocannabinoids can stimulate the cannabinoid system via CB1R or CB2R, like D9-THC, but nonpsychotropic ligands (cannabinol, cannabidiol) can exert anti-inflammatory effects despite a low affinity for CBR (Malfait et al., 2000).

D9-THC is a partial agonist which can block activation by other ligands of both cannabinoid receptors, but can also induce stimulatory effects, depending on the receptor expression level, coupling efficiency and endogenous cannabinoid release (Patel and Hillard, 2006; Straiker and Mackie, 2006; Pertwee, 2008). The influence of the conversion of D9-THC in 11-OH-D9-THC, a stronger agonist, on the balance of agonist/antagonist actions is subject to discussion (Pertwee, 2008). D9-THC can have modulator effects on both cell-mediated and humoral immunity. It may suppress T cell proliferation, by inhibiting IFN-γ production and influencing Th1/Th2 balance via a CB2R-mediated mechanism that could be reversed by SR144528 (Jan et al., 2003; Yuan et al., 2002). It also affects its antioxidant capacity (Arends, 1997; Woelkart et al., 2008).

Cannabidiol, by antagonizing CB1R/CB2R agonists, can inhibit immune cell migration and thus induce anti-inflammatory effects (Walter et al., 2003; Lunn et al., 2006).

D9-THCV is *in vitro* a CB2R partial agonist at concentrations in the low nanomolar range, and a CB1 antagonist with tissue specificity (Pertwee, 2008). *In vivo*, D9-THCV can act as an antagonist or, at higher doses, as an agonist for CB1R. It is not known if D9-THCV has CB2R agonist activity *in vivo* and if it can act on other targets as CB1R or CB2R (Mallat et al., 2007).

Alkamides derived from *Echinacea* sp. have structural similarities with AEA and affinity for CB2R (Raduner et al., 2006). In low nanomolar concentrations, they can exert effects on cytokine and chemokine expression in human blood (Woelkart et al., 2006). It was shown that IL-6 produced by B cells or macrophages can be increased by alkamides and AEA in a CB2R-dependent manner (Jones, 2005; Woelkart et al., 2008). By alternative non-CB2R mechanisms, same compounds can inhibit the LPS-stimulated expression of TNF-α, IL-1β and IL-12p70, but not IL-6 and IL-8 (Raduner et al., 2006). The immune effects (anti- or proinflammatory) of alkamides are concentration-dependent and influenced by the stimulus applied and degree of unsaturation of the lipophilic tail (Raduner et al., 2006). This higher metabolic stability compared with AEA suggests a promising therapeutic potential for alkamides.

Synthetic cannabinoids have different structure from endocannabinoids. CP55,940 and HU-210 are non-CBR selective agonists more potent than D9-THC, and WIN55,212 has agonist affinity for both CB1R and CB2R.

The complexity of endocannabinoid network and the different effects of endocannabinoid ligands, phytocannabinoids and synthetic cannabinoid analogues in modulating signal trasmission via cannabinoid receptors or alternate pathways raise difficulties in studying immune effects of different cannabinoid agonists. The discrepancies between many studies demonstrating inhibitory effects on the immune system and recent studies showing a stimulatory action on immune cells can be explained by the heterogeneity in the types and concentrations of cannabinoid ligands, methods and experimental protocols.

The immune effects modulated by cannabinoids must be considered in regard to a concentration-dependent activity. There is a biphasic response associated to the cannabinoid ligand concentration. Thus, *in vitro*, a molecule can be simulatory in nanomolar concentration, and have inhibitory effects in micromolar concentration range – that means more than ten-fold higher than those observed in cannabis smokers' blood (Croxford and Yamamura, 2005). Moreover, the partial agonist effect of phytocannabinoid D9-THC is antagonistic for the endocannabinoid agonist 2-AG, the difficulty in defining a clear picture of the cannabinoids immune modulation thus rising also from the complexity of interactions.

Cannabinoid receptor expression by immune cells

Expression levels seem to be correlated with the cell activation status and activating stimuli (Croxford and Yamamura, 2005). Mitogen stimulation decreases CB1R expression in T cells but produces the inverse effect in B cells (Noe et al., 2000). The human Jurkat T-cell line and mouse macrophages express more CB1R when they are activated (Daaka et al., 1996; Klein et al., 1998) and splenocyte CB2R mRNA is less abundantly expressed after LPS-stimulation and more expressed after anti-CD40 co-stimulation (Lee et al., 2001).

Marijuana use and anti-CD40 costimulation can increase both CB1R and CB2R expression, LPS and phytohemagglutinin (PHA) can increase only CB1R expression, whereas PMA and IFN-γ may stimulate CB2R expression. Suppressor stimuli of CB1R expression are anti-CD3 antibody, LPS and ionomycin, and inhibitors for CB2R expression are LPS and TGF-β (Klein et al., 2003). Conversely, the influence of cannabinoids on immune function mediated through cannabinoid receptors is supported by their lack of effect in CB2R deficient T helper cells (Buckley et al., 2000). Recently it was shown that CB1R expression can be up-regulated by IL-4 in T lymphocytes, which enables CB1R-mediated communication to neuronal cells (Borner et al., 2008).

Cannabinoid effects on cellular immunity

Since 1970, when the first studies on marijuana smoking effects on immune cells were reported, the effects of cannabinoids on immune function have been extensively studied.

T cells: Cannabinoids can influence T cell immunity in various manners: they can affect T cell number and proliferation, but may also have important effects on T helper 1- and 2-specific cytokines and TGF-β secretion (Croxford and Yamamura, 2005).

Initial studies done on T cells from blood of marijuana smokers showed inhibitory effects such as decreases in number or sensitivity (Nahas et al., 1977; El-Gohary and Eid, 2004), but other studies failed to confirm these findings (White et al., 1975; Lau et al., 1976). This variability of results can be partly explained by the heterogeneity of the studies, with different routes of administration, type and quantity of marijuana used, THC concentration, frequency of smoking and duration of inhalation. Secondly, moderate marijuana smoking has different effects on immune cells exposed directly to smoke than on cells of systemic immunity. Alveolar macrophages in smokers have less cytokine production and responsiveness and lesser antimicrobial activity (Shay et al., 2003; Baldwin et al., 1997; Klein et al., 2003). Lymphocyte recruitment to the pulmonary airways is decreased in D9-THC-treated mice challenged with influenza virus A/PR/8/34 (PR8) when compared with mice challenged with PR8 alone. In the same model, targeted deletion of CB1R and CB2R produced enhanced inflammatory responses to influenza PR84 in the absence and presence of D9-THC, suggesting involvement of CB1R/CB2R-dependent and -independent mechanisms in D9-THC effects (Buchweitz et al., 2008).

Acute exposure-related immune effects have also to be distinguished from those produced by chronic exposure to cannabinoids that may result in modulation of CBR expression, decreasing in T cell number and increased incidence of infection and head and neck squamous carcinoma (Sidney et al., 1997; Zhang et al., 1999; Nong et al., 2002; El-Gohary and Eid, 2004)

Early studies on the D9-THC treatment of mice and rats or in animal and human immune cell cultures had shown a suppressive effect on cellular functions in T and B cells, natural killer cells or macrophages (Nahas et al., 1977). Nevertheless, in some situations a biphasic effect was shown, with low (micromolar) doses of D9-THC being stimulatory and higher concentrations inhibitory (Patrini et al., 1997). Non-psychoactive ligands had slightly stronger effects than D9-THC, and alternative non-CB1R/CB2R mechanisms were suggested for T cell suppression (Tashkin et al., 2002; Croxford and Yamamura, 2005).

In the human Jurkat T cell line, activation can induce upregulation of CB1R transcription. It was suggested that this phenomenon, together with the constitutive expression of CB2R, enables cellular responses to cannabinoids by both receptor-mediated pathways (Borner et al., 2007).

Acute, but not chronic CP55,940 treatment inhibits PHA-induced splenocyte proliferation, possibly by CB2R down-regulation after chronic exposure (Massi et al., 1997). On the other hand, several-days D9-THC treatment inhibited splenocyte proliferation induced by ConA, whereas acute injection had no effect (Massi et al., 1998; Patrini et al., 1997).

CD8 cells seem to be more sensitive to cannabinoid action (Klein et al., 1991)than CD4 cells. Cannabinoids can affect the cytolytic capacity of cytotoxic T lymphocytes, but apparently not inhibit the T cell binding to the target cell (Fischer-Stenger et al., 1992). T cell stimulation is reduced also via cannabinoids effects on dendritic cells (DC), by reducing the DC surface expression of MHC class II molecules in a CB1-dependent manner (Wacnik et al., 2008).

A very important point in analyzing the immune influence of the cannabinoids on T cell function is the modulation of T helper

cell subsets (Th1 and Th2). The effects on the more recently described Th17 subsets have not been extensively studied. Cannabinoids produce a biasing in the balance between the two types of Th cells, suppressing Th1 and enhancing Th2, both CB1R and CB2R being involved in this immune deviation (Yuan et al., 2002). IFN-γ, IL-12, and IL-12 receptors are decreased by D9-THC treatment, whereas the Th2 and Th2-promoting cytokines are increased. This bias has several mechanisms. It was suggested to be partly explained by different expression of cannabinoid receptors on Th subpopulations and on antigen-presenting cells. A part of this effect is due to modulation of cytokines generated by dendritic cells (Lu et al., 2006). Moreover, induction of Th2 associated cytokines can subsequently inhibit Th1 cells (Croxford and Yamamura, 2005). Nevertheless, recent data showed that cannabinoids can directly induce B cell class switching from IgM to IgE, thus biasing toward Th2 type immunity, and this involves CB2R receptors (Agudelo et al., 2008).

Of much interest are the immune effects of endocannabinoids. AEA may produce, in a concentration equivalent to those that regulate neuronal response, a dose-dependent inhibition on mitogen-induced T and B human lymphocyte proliferation (Schwarz et al., 1994). It is suggested that AEA can influence cell growth by cannabinoid receptor-independent mechanisms (Derocq et al., 1998). AEA was also demonstrated to have a pro-proliferative effect on hematopoietic cell lines, acting synergistically with other growth stimuli. These effects were not seen for other natural or synthetic cannabinoid ligands (Valk et al., 1997). 2-AG was shown to have strong immunomodulatory activity on mitogen-induced T cell proliferation in mouse splenocytes, enhancing it at high cell density and producing the inverse effect at low cell density conditions. Its rapid degradation to arachidonic acid may activate other pathways of lymphocyte proliferation (Lee et al., 1995). Recently it was shown that cannabidiol, which suppresses IL-2 production from activated murine splenocytes, can suppress T cell function, and that cannabinoid receptors play a role in modulating the magnitude of these effects (Kaplan et al., 2008).

The cannabinoid effects on cytokine production related to Th cells are of particular importance in regard to the therapeutic potential that these targets can represent. D9-THC can inhibit IFN-γ secretion in a CB2R-dependent way (Yuan et al., 2002) and cannabinoid ligands can suppress the expression of other cytokines that may potentiate inflammation, such as TNF-α, IL-1, IL-2, IL-6, IL-12 (reviewed by Croxford and Yamamura, 2005). Targeting and blocking Th1 associated cytokines and potentiation of Th2 type cytokine pathways have shown promising results in animal models of inflammatory conditions such as experimental autoimmune encephalomyelitis and experimental arthritis (Racke et al., 1991; Mageed et al., 1998; Triantaphyllopoulos et al., 1999; Croxford and Miller, 2003; Massi et al., 2006). Regulatory T cells are involved in the attenuation of experimental autoimmune hepatitis by exogenous and endogenous cannabinoids (Hegde et al., 2008); these data potentially opens the way for cannabinoid-based future therapies of inflammatory disease in humans.

Natural killer cells (NK): NK cell numbers are lowered by ingestion of "bhang", a form of marijuana extracted from cannabis leaves and used as a drink or smoked (El-Gohary and Eid, 2004). Various animal studies showed that both proliferation and cellular cytolytic activity can be influenced by cannabinoid treatment, and that these effects can be mediated by CB1R and CB2R (Massi et al., 2006). However, in humans, NK cell functions do not seem to be significantly affected by cannabinoids.

Macrophages: Macrophages exert important roles in both innate and adaptive immunity and express both cannabinoid receptors, but predominantly CB2R (Sinha et al., 1998). As with other immune cells, the relation between cannabinoids and macrophage functions is bidirectional. Cannabinoid ligands can interfere, predominantly by inhibition, with macrophage migration (CB2R mediated) (Raborn et al., 2008), antigen presentation to T cells and phagocytic capacity (Sacerdote et al., 2005). They can also influence the release of inflammatory mediators such as nitric oxide (CB1R mediated), TNFα, IL-1, IL-6, IL-10 and IL-12, and the production of arachidonic acid metabolites in macrophage cultures via CBR (Berdyshev et al., 2001; Cabral et al., 1995). On the other hand, macrophages can synthesize endocannabinoids such as anandamide and 2-AG, which can modulate immune response and cell differentiation through cannabinoid receptor-dependent and -independent mechanisms (Ross et al., 2000; Massi et al., 2006; Croxford and Yamamura, 2005). The pattern of CB2R expression and thus the cannabinoid effects on macrophages are dependent of their state of activation, being maximal in "primed" and "responsive" states and minimal in "resting" and "fully activated" states. In this "activation window", macrophage properties include antigen processing and presentation, chemotaxis and phagocytosis, and cannabinoids can influence specific proteases, whose function is requisite for processing of specific antigens, thus the nature of antigen being related to a particular ligand effect (Klein and Cabral, 2006).

Neutrophils: Cannabinoid receptors can be expressed by neutrophils(Galiegue et al., 1995). However, endocannabinoids, phytocannabinoids and related ligands are potent inhibitors of human neutrophil migration, possibly by non-CBR-dependent mechanisms, though such effects on healthy human neutrophils were not observed with low doses of THC (Deusch et al., 2003). Cannabinoid ligands such as CP55,940, but not AEA, can inhibit neutrophil lysosomal enzyme release (Kraft et al., 2004).

Mast cells (MC). MC are found in nervous system, mucosal and connective tissue, and are involved in allergic and inflammatory responses. Despite controversy on CBR expression and cannabinoid effects on MC (Croxford and Yamamura, 2005), it is accepted that CB2R can be expressed by MC, although PEA can control MC degranulation via a CB1R/CB2R-independent mechanism (Giudice et al., 2007; De Filippis et al., 2008). Cannabinoid ligands, including PEA and related compounds, may act to control mast cell activation and degranulation early during the inflammatory response (De Filippis et al., 2008).

Cannabinoid effects on B cells and humoral immunity

Cannabinoid compounds may affect B cells number, proliferation, migration, Ig production or isotype switching (Croxford and Yamamura, 2005). In mice, 2-AG preferentially attracts unstimulated naive B cells, thus probably influencing the structure of B cell compartments in secondary lymphoid tissues (Tanikawa et al., 2007). B cells, IgG and IgM, and some complement proteins are decreased in bhang users (El-Gohary and Eid, 2004) and antibody production in smokers' blood is differentially influenced by cannabinoid ingestion (Rachelefsky et al., 1976; Nahas and Osserman, 1991). Also, antibody production is suppressed in splenocyte cultures by either synthetic or plant CBR ligands, possibly by a G-protein-coupled receptor mechanism (Kaminski et al., 1994; Massi et al., 2006). In ovalbumin-sensitized mice, cannabidiol suppression of humoral immunity could be mediated by the impaired functions of splenocytes (Jan et al., 2007). Recently, it was shown that both THC and anandamide can induce dose-related immunosuppression in both the primary and secondary *in vitro* plaque-forming cell assays of antibody formation, via CB2R receptors (Eisenstein et al., 2007). B cell proliferation and migration can be differentially influenced by cannabinoid ligands, in a

concentration-dependent manner – a biphasic effect similar to the one seen in T cell studies, with low doses acting as proliferation inducers, and in a class specific way – synthetic and phytocannabinoids being inhibitory, and endocannabinoids having positive effects (Croxford and Yamamura, 2005). CB2R pathway seems to be involved as well in some of the cannabinoid influence on B cell migration and differentiation (Jorda et al., 2002; Ziring et al., 2006). CB2R receptors can mediate B cell shift from IgM to IgE, thus contributing to Th2 biasing (Agudelo et al., 2008). It is suggested that endocannabinoids play a positive role in mobilizing B cells during immune responses, but cannabinoid effects on B cells are, at least in part, indirectly mediated through macrophages and T cells required for B cell activation (Croxford and Yamamura, 2005). Moreover, the cannabinoid impact on serum Ig titers can be also via the profile of T helper-derived cytokines.

Cytokines: The relation between cannabinoids and cytokines is discussed separately in this special issue. However, some features are noted here. Firstly, there is no doubt that psychoactive and non-psychoactive ligands have demonstrated either *in vivo* or *in vitro* effects on the production and function of a variety of cytokines through both cannabinoid receptor-dependent and -independent mechanisms (Klein et al., 2000). The endocannabinoid system modulates the cytokine network and related immune interactions. Synthetic low affinity ligands and phytocannabinoids have been proven to inhibit TNF-α and other acute phase cytokines, but some of these ligands have also been shown to increase in some conditions TNF-α and other inflammatory cytokine or chemokine expression (Klein et al., 2000). Moreover, depending upon the model system, the cannabinoid effects on cytokines are often conflicting. Although the current compounds offer considerable information regarding the physiological roles of the endocannabinoid system, the lack of compounds selectively interfering with the synthesis of anandamide or with the MAG lipase catalyzed breakdown of 2-AG made the study of endocannabinoid effects difficult (Fowler et al., 2005). To date, abundant information suggest that cannabinoid effects on cytokine-dependent pathways correlate with a shift in cytokine expression profile from that of proinflammatory Th1 to that of anti-inflammatory Th2, as discussed above (Klein and Cabral, 2006). Secondly, immune cells with modified cytokine pattern of secretion after cannabinoid treatment can also express various humoral mediators, thus increasing the complexity and reinforcing the bidirectionality of the relationship between cannabinoids and cytokines.

Therapeutic implications

The immune effects of cannabinoids and endocannabinoid system provide promising therapeutic implications in a variety of conditions.

Multiple sclerosis: Used for symptom control such as spasticity and pain in MS patients (discussed further in this special issue, see Rog et al., 2005; Consroe et al., 1997; Notcutt et al., 2004; Pertwee, 2002; Zajicek et al., 2003; Rog et al., 2005; Wade et al., 2004), cannabinoid agonists can exert both immunomodulatory and neuroprotective effects. In study models, immunomodulation was associated with reduced myelin-specific T cell responses and reduced clinical disease (Croxford et al., 2008). This implies indirect mechanisms by CB1 nerve signaling pathways controlling the systemic release of immunomodulatory molecules, and direct actions by CB2R-mediated inhibition of macrophages, microglia and lymphocyte function (Baker et al., 2007). In clinical practice, however, the relevance of these actions is unclear, since these effects only occur at high doses. On the other hand, it is suggested that lower doses of cannabinoids, non-immunosuppressive, can slow the accumulation of axonal loss and disability, acting on the glial response implicated in the neurodegenerative component of the disease. Also, potentiation of the endogenous cannabinoid signaling could represent a substitute to the use of exogenously administrated cannabinoid ligands (Loria et al., 2008).

Other neurodegenerative diseases with immune connections may be targeted by therapeutic approaches in the future, since neurogenesis might be regulated by brain cannabinoids, either directly or indirectly via the immune system. For example, in Parkinson's disease (PD), cannabinoid-based compounds might provide protection against the progression of neuronal injury and influence local inflammatory events associated with the characteristic pathogenesis of this disease (Lastres-Becker and Fernandez-Ruiz, 2006).

Atherosclerosis: A growing body of evidence suggests that endocannabinoid signaling plays a critical role in the pathogenesis of atherogenesis and its clinical manifestations (Steffens et al., 2005; Mach and Steffens, 2008). CB2R activation by THC inhibits atherosclerotic plaque progression in mice by inhibiting macrophage recruitment and anandamide inhibits inflammatory gene expression in endothelial cells, and consequently monocyte adhesion (Mach and Steffens, 2008). CB2 may influence atherosclerosis by modulating lesional macrophage apoptosis (Freeman-Anderson et al., 2008). Endocannabinoids might also mediate pro-atherosclerotic effects by inducing platelet activation (Mach and Steffens, 2008). Further understanding of whether increased endocannabinoid signaling is associated with disease progression and increased risk of acute thrombotic events may result in potential pharmacological approach in order to decrease atherosclerosis process.

Rheumatic disease: The cannabinoid receptor system may become an important therapeutic target for the treatment of pain and inflammation associated with ostheoarthritis (OA) and rheumatoid arthritis (RA). The basis of this approach could be the reduction in Th1 immunity, or triggering the articular cannabinoid system. This has been demonstrated in an experimental model of arthritis, where cannabidiol had anti-arthritis effects (Malfait et al., 2000) and in patients with RA where the drug Sativex, a combination of D9-THC and cannabidiol reduced disease activity (Blake et al., 2006). Non-steroidal anti-inflammatory drugs (NSAIDs), which act via the inhibition of cyclooxygenase, have been shown to inhibit FAAH, an essential enzyme in the synthesis of endocannabinoids (Fowler et al., 2003). CB1R and CB2R system, anandamide and 2-AG are present in the synovia of patients with OA and RA, whereas PEA levels are higher in the synovial fluid of normal volunteers (Richardson et al., 2008). This suggests that the loss of PEA may contribute to arthritic disease and support the important functional role of the endocannabinoid receptor system in these conditions. Also, CB1R and TRPV-1 receptors, but not CB2R, seem to be important targets in controlling OA pain (Schuelert and McDougall, 2008).

The cannabinoid ajulemic acid has several effects that make it attractive for future therapies in rheumatoid arthritis, systemic lupus erythematosus and osteoporosis. It suppresses human macrophage IL-6 (Parker et al., 2008), inhibits osteoclastogenesis in mononuclear precursor cells and induces apoptosis in mature osteoclast-like cells (George et al., 2008).

Diabetes and lipid metabolism: In diabetes, cannabinoids may protect against islet destruction by suppressing insulitis and IFN-γ, TNFα and IL-12 mRNA expression (Li et al., 2001), but also treating neuropathic pain in diabetic patients via CB2R pathway (Croxford and Yamamura, 2005). Rimonabant (SR141716) is a CB1R-selective inverse agonist of CBR. Rimonabant can inhibit adipocyte function and was used in the treatment of obesity. However it has psychiatric side-effects (van Diepen et al., 2008).

Allergic asthma: Cannabinoids may be beneficial in the treatment of asthma, by ameliorating of cytokine profiles, decreasing overproduction of mucus in the lungs and by playing a role in bronchodilation (Croxford and Yamamura, 2005).

Gut and liver disease: Cannabinoids may reduce gut inflammation via CB1R and/or CB2R activation by direct suppression of proinflammatory mediators, inhibition of intestinal motility and diarrhoea, and attenuation of visceral sensitivity (Izzo and Camilleri, 2008). Exogenous or endogenous cannabinoids targeting cannabinoid receptors and use of FAAH inhibitors may constitute novel therapeutic modalities for immune-mediated liver inflammation (Hegde et al., 2008), hepatic fibrosis and hepatic and intestinal neoplastic disease (Izzo and Camilleri, 2008). Also, CB2R activation is a promising therapeutic target in gastrointestinal inflammatory states where there is immune activation and motility dysfunction (Wright et al., 2008).

Finally, we emphasize the context-dependent effects of cannabinoid ligands, with different consequences on immune interactions. Endogenous cannabinoids are released following various types of injury to the brain. The "immune economy" is different depending on the type of injury (Herrera et al., 2008). Consequently, immune effects of cannabinoids will be different for conditions as inflammation, stroke or various infections, making it more difficult to predict the net impact of CBR activation on complex pathological events. Further study is necessary to clarify how and when to enhance the positive anti-inflammatory and tissue protective potential of cannabinoids, without deleterious effects.

References

Agudelo, M., Newton, C., Widen, R., Sherwood, T., Nong, L., Friedman, H., Klein, T.W., 2008. Cannabinoid receptor 2 (CB2) mediates immunoglobulin class switching from IgM to IgE in cultures of murine-purified B lymphocytes. J. Neuroimmune Pharmacol. 3, 35–42.

Arends, J., 1997. Do antioxidants inhibit immune response? Med. Monatsschr. Pharm. 20, 47–48.

Bacci, A., Huguenard, J.R., Prince, D.A., 2004. Long-lasting self-inhibition of neocortical interneurons mediated by endocannabinoids. Nature 431, 312–316.

Baker, D., Jackson, S.J., Pryce, G., 2007. Cannabinoid control of neuroinflammation related to multiple sclerosis. Br. J. Pharmacol. 152, 649–654.

Baldwin, G.C., Tashkin, D.P., Buckley, D.M., Park, A.N., Dubinett, S.M., Roth, M.D., 1997. Marijuana and cocaine impair alveolar macrophage function and cytokine production. Am. J. Respir. Crit. Care Med. 156, 1606–1613.

Bayewitch, M., Rhee, M.H., Avidor-Reiss, T., Breuer, A., Mechoulam, R., Vogel, Z., 1996. (-)-Delta9-tetrahydrocannabinol antagonizes the peripheral cannabinoid receptor-mediated inhibition of adenylyl cyclase. J. Biol. Chem. 271, 9902–9905.

Beltramo, M., Bernardini, N., Bertorelli, R., Campanella, M., Nicolussi, E., Fredduzzi, S., Reggiani, A., 2006. CB2 receptor-mediated antihyperalgesia: possible direct involvement of neural mechanisms. Eur. J. Neurosci. 23 1530–1538

Berdyshev, E.V., Schmid, P.C., Krebsbach, R.J., Kuwae, T., Huang, C., Ma, W.Y., Dong, Z., Schmid, H.H., 2001. Role of N-acylethanolamines in cell signaling. World Rev. Nutr. Diet 88, 207–214.

Blake, D.R., Robson, P., Ho, M., Jubb, R.W., McCabe, C.S., 2006. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford) 45, 50–52.

Bodor, A.L., Katona, I., Nyiri, G., Mackie, K., Ledent, C., Hajos, N., Freund, T.F., 2005. Endocannabinoid signaling in rat somatosensory cortex: laminar differences and involvement of specific interneuron types. J. Neurosci. 25, 6845–6856.

Borner, C., Bedini, A., Hollt, V., Kraus, J., 2008. Analysis of promoter regions regulating basal and interleukin-4-inducible expression of the human CB1 receptor gene in T lymphocytes. Mol. Pharmacol. 73, 1013–1019.

Borner, C., Hollt, V., Kraus, J., 2007. Activation of human T cells induces upregulation of cannabinoid receptor type 1 transcription. Neuroimmunomodulation 14, 281–286.

Breivogel, C.S., Griffin, G., Di Marzo, V., Martin, B.R., 2001. Evidence for a new G protein-coupled cannabinoid receptor in mouse brain. Mol. Pharmacol. 60, 155–163.

Buchweitz, J.P., Karmaus, P.W., Williams, K.J., Harkema, J.R., Kaminski, N.E., 2008. 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. 83, 785–796.

Buckley, N.E., McCoy, K.L., Mezey, E., Bonner, T., Zimmer, A., Felder, C.C., Glass, M., Zimmer, A., 2000. Immunomodulation by cannabinoids is absent in mice deficient for the cannabinoid CB(2) receptor. Eur. J. Pharmacol. 396, 141–149.

Bueb, J.L., Lambert, D.M., Tschirhart, E.J., 2001. Receptor-independent effects of natural cannabinoids in rat peritoneal mast cells in vitro. Biochim. Biophys. Acta 1538, 252–259.

Cabral, G.A., Dove Pettit, D.A., 1998. Drugs and immunity: cannabinoids and their role in decreased resistance to infectious disease. J. Neuroimmunol. 83 116–123

Cabral, G.A., Raborn, E.S., Griffin, L., Dennis, J., Marciano-Cabral, F., 2008. CB2 receptors in the brain: role in central immune function. Br. J. Pharmacol. 153, 240–251.

Cabral, G.A., Staab, A., 2005. Effects on the immune system. Handb. Exp. Pharmacol., 385–423.

Cabral, G.A., Toney, D.M., Fischer-Stenger, K., Harrison, M.P., Marciano-Cabral, F., 1995. Anandamide inhibits macrophage-mediated killing of tumor necrosis factor-sensitive cells. Life Sci. 56, 2065–2072.

Calignano, A., La Rana, G., Giuffrida, A., Piomelli, D., 1998. Control of pain initiation by endogenous cannabinoids. Nature 394, 277–281.

Carlisle, S.J., Marciano-Cabral, F., Staab, A., Ludwick, C., Cabral, G.A., 2002. Differential expression of the CB2 cannabinoid receptor by rodent macrophages and macrophage-like cells in relation to cell activation. Int. Immunopharmacol. 2, 69–82.

Carracedo, A., Lorente, M., Egia, A., Blazquez, C., Garcia, S., Giroux, V., Malicet, C., Villuendas, R., Gironella, M., Gonzalez-Feria, L., Piris, M.A., Iovanna, J.L., Guzman, M., Velasco, G., 2006. The stress-regulated protein p8 mediates cannabinoid-induced apoptosis of tumor cells. Cancer Cell 9, 301–312.

Carrier, E.J., Kearn, C.S., Barkmeier, A.J., Breese, N.M., Yang, W., Nithipatikom, K., Pfister, S.L., Campbell, W.B., Hillard, C.J., 2004. Cultured rat microglial cells synthesize the endocannabinoid 2-arachidonylglycerol, which increases proliferation via a CB2 receptor-dependent mechanism. Mol. Pharmacol. 65, 999–1007.

Carrier, E.J., Patel, S., Hillard, C.J., 2005. Endocannabinoids in neuroimmunology and stress. Curr Drug Targets CNS Neurol Disord 4, 657–665.

Cavuoto, P., McAinch, A.J., Hatzinikolas, G., Janovska, A., Game, P., Wittert, G.A., 2007. The expression of receptors for endocannabinoids in human and rodent skeletal muscle. Biochem. Biophys. Res. Commun. 364, 105–110.

Chevaleyre, V., Takahashi, K.A., Castillo, P.E., 2006. Endocannabinoid-mediated synaptic plasticity in the CNS. Annu Rev Neurosci 29, 37–76.

Condie, R., Herring, A., Koh, W.S., Lee, M., Kaminski, N.E., 1996. Cannabinoid inhibition of adenylate cyclase-mediated signal transduction and interleukin 2 (IL-2) expression in the murine T-cell line, EL4.IL-2. J. Biol. Chem. 271, 13175–13183.

Consroe, P., Musty, R., Rein, J., Tillery, W., Pertwee, R., 1997. The perceived effects of smoked cannabis on patients with multiple sclerosis. Eur. Neurol. 38, 44–48.

Cota, D., 2007. CB1 receptors: emerging evidence for central and peripheral mechanisms that regulate energy balance, metabolism, and cardiovascular health. Diabetes Metab. Res. Rev. 23, 507–517.

Croxford, J.L., 2003. Therapeutic potential of cannabinoids in CNS disease. CNS Drugs 17, 179–202.

Croxford, J.L., Miller, S.D., 2003. Immunoregulation of a viral model of multiple sclerosis using the synthetic cannabinoid R+WIN55,212. J. Clin. Invest. 111, 1231–1240.

Croxford, J.L., Pryce, G., Jackson, S.J., Ledent, C., Giovannoni, G., Pertwee, R.G., Yamamura, T., Baker, D., 2008. Cannabinoid-mediated neuroprotection, not immunosuppression, may be more relevant to multiple sclerosis. J. Neuroimmunol. 193, 120–129.

Croxford, J.L., Yamamura, T., 2005. Cannabinoids and the immune system: potential for the treatment of inflammatory diseases? J. Neuroimmunol. 166, 3–18.

Daaka, Y., Friedman, H., Klein, T.W., 1996. Cannabinoid receptor proteins are increased in Jurkat, human T-cell line after mitogen activation. J. Pharmacol. Exp. Ther. 276, 776–783.

De Filippis, D., D'Amico, A., Iuvone, T., 2008. Cannabinomimetic control of mast cell mediator release: new perspective in chronic inflammation. J. Neuroendocrinol. 20 (Suppl. 1), 20–25.

Derocq, J.M., Bouaboula, M., Marchand, J., Rinaldi-Carmona, M., Segui, M., Casellas, P., 1998. The endogenous cannabinoid anandamide is a lipid messenger activating cell growth via a cannabinoid receptor-independent pathway in hematopoietic cell lines. FEBS Lett. 425, 419–425.

Deusch, E., Kraft, B., Nahlik, G., Weigl, L., Hohenegger, M., Kress, H.G., 2003. No evidence for direct modulatory effects of delta 9-tetrahydrocannabinol on human polymorphonuclear leukocytes. J. Neuroimmunol. 141, 99–103.

Devane, W.A., Hanus, L., Breuer, A., Pertwee, R.G., Stevenson, L.A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A., Mechoulam, R., 1992. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258, 1946–1949.

Eisenstein, T.K., Meissler, J.J., Wilson, Q., Gaughan, J.P., Adler, M.W., 2007. Anandamide and Delta9-tetrahydrocannabinol directly inhibit cells of the immune system via CB2 receptors. J. Neuroimmunol. 189, 17–22.

El-Gohary, M., Eid, M.A., 2004. Effect of cannabinoid ingestion (in the form of bhang) on the immune system of high school and university students. Hum. Exp. Toxicol. 23, 149–156.

Facci, L., Dal Toso, R., Romanello, S., Buriani, A., Skaper, S.D., Leon, A., 1995. Mast cells express a peripheral cannabinoid receptor with differential sensitivity to anandamide and palmitoylethanolamide. Proc. Natl. Acad. Sci. U S A 92, 3376–3380.

Fernandez-Ruiz, J., Romero, J., Velasco, G., Tolon, R.M., Ramos, J.A., Guzman, M., 2007. Cannabinoid CB2 receptor: a new target for controlling neural cell survival? Trends Pharmacol. Sci. 28, 39–45.
Fischer-Stenger, K., Updegrove, A.W., Cabral, G.A., 1992. Delta 9-tetrahydrocannabinol decreases cytotoxic T lymphocyte activity to herpes simplex virus type 1-infected cells. Proc. Soc. Exp. Biol. Med. 200, 422–430.
Fowler, C.J., Holt, S., Nilsson, O., Jonsson, K.O., Tiger, G., Jacobsson, S.O., 2005. The endocannabinoid signaling system: pharmacological and therapeutic aspects. Pharmacol. Biochem. Behav. 81, 248–262.
Fowler, C.J., Holt, S., Tiger, G., 2003. Acidic nonsteroidal anti-inflammatory drugs inhibit rat brain fatty acid amide hydrolase in a pH-dependent manner. J. Enzyme Inhib. Med. Chem. 18, 55–58.
Freeman-Anderson, N.E., Pickle, T.G., Netherland, C.D., Bales, A., Buckley, N.E., Thewke, D.P., 2008. Cannabinoid (CB2) receptor deficiency reduces the susceptibility of macrophages to oxidized LDL/oxysterol-induced apoptosis. J. Lipid Res. 49, 2338–2346.
Galiegue, S., Mary, S., Marchand, J., Dussossoy, D., Carriere, D., Carayon, P., Bouaboula, M., Shire, D., Le Fur, G., Casellas, P., 1995. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. Eur. J. Biochem. 232, 54–61.
Gaoni, Y., Mechoulam, R., 1964. Isolation, structure, and partial synthesis of an active constituent of hashish. J. Am. Chem. Soc. 86, 1646–1647.
George, K.L., Saltman, L.H., Stein, G.S., Lian, J.B., Zurier, R.B., 2008. Ajulemic acid, a nonpsychoactive cannabinoid acid, suppresses osteoclastogenesis in mononuclear precursor cells and induces apoptosis in mature osteoclast-like cells. J. Cell Physiol. 214, 714–720.
Giudice, E.D., Rinaldi, L., Passarotto, M., Facchinetti, F., D'Arrigo, A., Guiotto, A., Carbonare, M.D., Battistin, L., Leon, A., 2007. Cannabidiol, unlike synthetic cannabinoids, triggers activation of RBL-2H3 mast cells. J. Leukoc. Biol. 81, 1512–1522.
Glass, M., Northup, J.K., 1999. Agonist selective regulation of G proteins by cannabinoid CB(1) and CB(2) receptors. Mol. Pharmacol. 56, 1362–1369.
Gong, J.P., Onaivi, E.S., Ishiguro, H., Liu, Q.R., Tagliaferro, P.A., Brusco, A., Uhl, G.R., 2006. Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. Brain Res. 1071, 10–23.
Griffin, G., Fernando, S.R., Ross, R.A., McKay, N.G., Ashford, M.L., Shire, D., Huffman, J.W., Yu, S., Lainton, J.A., Pertwee, R.G., 1997. Evidence for the presence of CB2-like cannabinoid receptors on peripheral nerve terminals. Eur. J. Pharmacol. 339, 53–61.
Hegde, V.L., Hegde, S., Cravatt, B.F., Hofseth, L.J., Nagarkatti, M., Nagarkatti, P.S., 2008. Attenuation of experimental autoimmune hepatitis by exogenous and endogenous cannabinoids: involvement of regulatory T cells. Mol. Pharmacol. 74, 20–33.
Herrera, R.A., Oved, J.H., Reiss, C.S., 2008. Disruption of IFN-gamma-mediated antiviral activity in neurons: the role of cannabinoids. Viral Immunol. 21 141–152
Herring, A.C., Kaminski, N.E., 1999. Cannabinol-mediated inhibition of nuclear factor-kappaB, cAMP response element-binding protein, and interleukin-2 secretion by activated thymocytes. J. Pharmacol. Exp. Ther. 291, 1156–1163.
Herring, A.C., Koh, W.S., Kaminski, N.E., 1998. Inhibition of the cyclic AMP signaling cascade and nuclear factor binding to CRE and kappaB elements by cannabinol, a minimally CNS-active cannabinoid. Biochem. Pharmacol. 55, 1013–1023.
Hollister, L.E., 1986. Health aspects of cannabis. Pharmacol. Rev. 38, 1–20.
Howlett, A.C., Barth, F., Bonner, T.I., Cabral, G., Casellas, P., Devane, W.A., Felder, C.C., Herkenham, M., Mackie, K., Martin, B.R., Mechoulam, R., Pertwee, R.G., 2002. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol. Rev. 54, 161–202.
Howlett, A.C., Mukhopadhyay, S., 2000. Cellular signal transduction by anandamide and 2-arachidonoylglycerol. Chem. Phys. Lipids 108, 53–70.
Izzo, A.A., Camilleri, M., 2008. Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects. Gut 57, 1140–1155.
Jan, T.R., Farraj, A.K., Harkema, J.R., Kaminski, N.E., 2003. Attenuation of the ovalbumin-induced allergic airway response by cannabinoid treatment in A/J mice. Toxicol. Appl. Pharmacol. 188, 24–35.
Jan, T.R., Su, S.T., Wu, H.Y., Liao, M.H., 2007. Suppressive effects of cannabidiol on antigen-specific antibody production and functional activity of splenocytes in ovalbumin-sensitized BALB/c mice. Int. Immunopharmacol. 7, 773–780.
Jeon, Y.J., Yang, K.H., Pulaski, J.T., Kaminski, N.E., 1996. Attenuation of inducible nitric oxide synthase gene expression by delta 9-tetrahydrocannabinol is mediated through the inhibition of nuclear factor- kappa B/Rel activation. Mol. Pharmacol. 50, 334–341.
Jones, S.A., 2005. Directing transition from innate to acquired immunity: defining a role for IL-6. J. Immunol. 175, 3463–3468.
Jorda, M.A., Verbakel, S.E., Valk, P.J., Vankan-Berkhoudt, Y.V., Maccarrone, M., Finazzi-Agro, A., Lowenberg, B., Delwel, R., 2002. Hematopoietic cells expressing the peripheral cannabinoid receptor migrate in response to the endocannabinoid 2-arachidonoylglycerol. Blood 99, 2786–2793.
Kaminski, N.E., Abood, M.E., Kessler, F.K., Martin, B.R., Schatz, A.R., 1992. Identification of a functionally relevant cannabinoid receptor on mouse spleen cells that is involved in cannabinoid-mediated immune modulation. Mol. Pharmacol. 42, 736–742.
Kaminski, N.E., Koh, W.S., Yang, K.H., Lee, M., Kessler, F.K., 1994. Suppression of the humoral immune response by cannabinoids is partially mediated through inhibition of adenylate cyclase by a pertussis toxin-sensitive G-protein coupled mechanism. Biochem. Pharmacol. 48, 1899–1908.
Kaplan, B.L., Springs, A.E., Kaminski, N.E., 2008. The profile of immune modulation by cannabidiol (CBD) involves deregulation of nuclear factor of activated T cells (NFAT). Biochem. Pharmacol. 76, 726–737.
Kenakin, T., 2001. Inverse, protean, and ligand-selective agonism: matters of receptor conformation. Faseb J. 15, 598–611.
Klein, T.W., Cabral, G.A., 2006. Cannabinoid-induced immune suppression and modulation of antigen-presenting cells. J. Neuroimmune Pharmacol. 1, 50–64.
Klein, T.W., Friedman, H., Specter, S., 1998. Marijuana, immunity and infection. J. Neuroimmunol. 83, 102–115.
Klein, T.W., Kawakami, Y., Newton, C., Friedman, H., 1991. Marijuana components suppress induction and cytolytic function of murine cytotoxic T cells in vitro and in vivo. J. Toxicol. Environ. Health 32, 465–477.
Klein, T.W., Lane, B., Newton, C.A., Friedman, H., 2000. The cannabinoid system and cytokine network. Proc. Soc. Exp. Biol. Med. 225, 1–8.
Klein, T.W., Newton, C., Friedman, H., 1998. Cannabinoid receptors and immunity. Immunol. Today 19, 373–381.
Klein, T.W., Newton, C., Larsen, K., Lu, L., Perkins, I., Nong, L., Friedman, H., 2003. The cannabinoid system and immune modulation. J. Leukoc. Biol. 74, 486–496.
Kobayashi, Y., Arai, S., Waku, K., Sugiura, T., 2001. Activation by 2-arachidonoylglycerol, an endogenous cannabinoid receptor ligand, of p42/44 mitogen-activated protein kinase in HL-60 cells. J. Biochem. 129, 665–669.
Koh, W.S., Jeon, Y.J., Herring, A.C., Kaminski, N.E., 1997. Transient CRE- and kappa B site-binding is cross-regulated by cAMP-dependent protein kinase and a protein phosphatase in mouse splenocytes. Life Sci. 60, 425–432.
Koh, W.S., Yang, K.H., Kaminski, N.E., 1995. Cyclic AMP is an essential factor in immune responses. Biochem. Biophys. Res. Commun. 206, 703–709.
Kraft, B., Wintersberger, W., Kress, H.G., 2004. Cannabinoid receptor-independent suppression of the superoxide generation of human neutrophils (PMN) by CP55 940, but not by anandamide. Life Sci. 75, 969–977.
Lastres-Becker, I., Fernandez-Ruiz, J., 2006. An overview of Parkinson's disease and the cannabinoid system and possible benefits of cannabinoid-based treatments. Curr. Med. Chem. 13, 3705–3718.
Lau, R.J., Tubergen, D.G., Barr Jr., M., Domino, E.F., Benowitz, N., Jones, R.T., 1976. Phytohemagglutinin-induced lymphocyte transformation in humans receiving delta9-tetrahydrocannabinol. Science 192, 805–807.
Lee, M., Yang, K.H., Kaminski, N.E., 1995. Effects of putative cannabinoid receptor ligands, anandamide and 2-arachidonyl-glycerol, on immune function in B6C3F1 mouse splenocytes. J. Pharmacol. Exp. Ther. 275, 529–536.
Lee, S.F., Newton, C., Widen, R., Friedman, H., Klein, T.W., 2001. Differential expression of cannabinoid CB(2) receptor mRNA in mouse immune cell subpopulations and following B cell stimulation. Eur. J. Pharmacol. 423, 235–241.
Li, X., Kaminski, N.E., Fischer, L.J., 2001. Examination of the immunosuppressive effect of delta9-tetrahydrocannabinol in streptozotocin-induced autoimmune diabetes. Int. Immunopharmacol. 1, 699–712.
Loria, F., Petrosino, S., Mestre, L., Spagnolo, A., Correa, F., Hernangomez, M., Guaza, C., Di Marzo, V., Docagne, F., 2008. Study of the regulation of the endocannabinoid system in a virus model of multiple sclerosis reveals a therapeutic effect of palmitoylethanolamide. Eur. J. Neurosci. 28, 633–641.
Lu, Q., Straiker, A., Lu, Q., Maguire, G., 2000. Expression of CB2 cannabinoid receptor mRNA in adult rat retina. Vis. Neurosci. 17, 91–95.
Lu, T., Newton, C., Perkins, I., Friedman, H., Klein, T.W., 2006. Cannabinoid treatment suppresses the T-helper cell-polarizing function of mouse dendritic cells stimulated with Legionella pneumophila infection. J. Pharmacol. Exp. Ther. 319, 269–276.
Lunn, C.A., Fine, J.S., Rojas-Triana, A., Jackson, J.V., Fan, X., Kung, T.T., Gonsiorek, W., Schwarz, M.A., Lavey, B., Kozlowski, J.A., Narula, S.K., Lundell, D.J., Hipkin, R.W., Bober, L.A., 2006. A novel cannabinoid peripheral cannabinoid receptor-selective inverse agonist blocks leukocyte recruitment in vivo. J. Pharmacol. Exp. Ther. 316, 780–788.
Mach, F., Steffens, S., 2008. The role of the endocannabinoid system in atherosclerosis. J. Neuroendocrinol. 20 (Suppl 1), 53–57.
Mackie, K., 2005. Distribution of cannabinoid receptors in the central and peripheral nervous system. Handb. Exp. Pharmacol., 299–325.
Mackie, K., 2008. Cannabinoid receptors: where they are and what they do. J. Neuroendocrinol. 20 (Suppl. 1), 10–14.
Mageed, R.A., Adams, G., Woodrow, D., Podhajcer, O.L., Chernajovsky, Y., 1998. Prevention of collagen-induced arthritis by gene delivery of soluble p75 tumour necrosis factor receptor. Gene Ther 5, 1584–1592.
Malfait, A.M., Gallily, R., Sumariwalla, P.F., Malik, A.S., Andreakos, E., Mechoulam, R., Feldmann, M., 2000. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc. Natl. Acad. Sci. U S A 97, 9561–9566.
Mallat, A., Teixeira-Clerc, F., Deveaux, V., Lotersztajn, S., 2007. Cannabinoid receptors as new targets of antifibrosing strategies during chronic liver diseases. Expert Opin. Ther. Targets 11, 403–409.
Marciano-Cabral F., Ferguson T., Bradley S.G., Cabral G. 2001. Delta-9-tetrahydrocannabinol (THC), the major psychoactive component of marijuana, exacerbates brain infection by Acanthamoeba. J. Eukaryot. Microbiol. Suppl.:4S-5S.
Maresz, K., Carrier, E.J., Ponomarev, E.D., Hillard, C.J., Dittel, B.N., 2005. Modulation of the cannabinoid CB2 receptor in microglial cells in response to inflammatory stimuli. J. Neurochem. 95, 437–445.
Massi, P., Patrini, G., Rubino, T., Fuzio, D., Parolaro, D., 1997. Changes in rat spleen cannabinoid receptors after chronic CP-55,940: an autoradiographic study. Pharmacol. Biochem. Behav. 58, 73–78.

Massi, P., Sacerdote, P., Ponti, W., Fuzio, D., Manfredi, B., Vigano, D., Rubino, T., Bardotti, M., Parolaro, D., 1998. Immune function alterations in mice tolerant to delta9-tetrahydrocannabinol: functional and biochemical parameters. J. Neuroimmunol. 92, 60–66.
Massi, P., Vaccani, A., Parolaro, D., 2006. Cannabinoids, immune system and cytokine network. Curr. Pharm. Des. 12, 3135–3146.
Matias, I., Pochard, P., Orlando, P., Salzet, M., Pestel, J., Di Marzo, V., 2002. Presence and regulation of the endocannabinoid system in human dendritic cells. Eur. J. Biochem. 269, 3771–3778.
Mechoulam, R., Ben-Shabat, S., Hanus, L., Ligumsky, M., Kaminski, N.E., Schatz, A.R., Gopher, A., Almog, S., Martin, B.R., Compton, D.R., et al., 1995. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem. Pharmacol. 50, 83–90.
Milligan, G., 2004. G protein-coupled receptor dimerization: function and ligand pharmacology. Mol. Pharmacol. 66, 1–7.
Molina-Holgado, E., Vela, J.M., Arevalo-Martin, A., Almazan, G., Molina-Holgado, F., Borrell, J., Guaza, C., 2002. Cannabinoids promote oligodendrocyte progenitor survival: involvement of cannabinoid receptors and phosphatidylinositol-3 kinase/Akt signaling. J. Neurosci. 22, 9742–9753.
Munro, S., Thomas, K.L., Abu-Shaar, M., 1993. Molecular characterization of a peripheral receptor for cannabinoids. Nature 365, 61–65.
Nahas, G.G., Morishima, A., Desoize, B., 1977. Effects of cannabinoids on macromolecular synthesis and replication of cultured lymphocytes. Fed. Proc. 36, 1748–1752.
Nahas, G.G., Osserman, E.F., 1991. Altered serum immunoglobulin concentration in chronic marijuana smokers. Adv. Exp. Med. Biol. 288, 25–32.
Noe, S.N., Newton, C., Widen, R., Friedman, H., Klein, T.W., 2000. Anti-CD40, anti-CD3, and IL-2 stimulation induce contrasting changes in CB1 mRNA expression in mouse splenocytes. J. Neuroimmunol. 110, 161–167.
Nong, L., Newton, C., Cheng, Q., Friedman, H., Roth, M.D., Klein, T.W., 2002. Altered cannabinoid receptor mRNA expression in peripheral blood mononuclear cells from marijuana smokers. J. Neuroimmunol. 127, 169–176.
Notcutt, W., Price, M., Miller, R., Newport, S., Phillips, C., Simmons, S., Sansom, C., 2004. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. Anaesthesia 59, 440–452.
Nyiri, G., Cserep, C., Szabadits, E., Mackie, K., Freund, T.F., 2005. CB1 cannabinoid receptors are enriched in the perisynaptic annulus and on preterminal segments of hippocampal GABAergic axons. Neuroscience 136, 811–822.
Ofek, O., Karsak, M., Leclerc, N., Fogel, M., Frenkel, B., Wright, K., Tam, J., Attar-Namdar, M., Kram, V., Shohami, E., Mechoulam, R., Zimmer, A., Bab, I., 2006. Peripheral cannabinoid receptor, CB2, regulates bone mass. Proc. Natl. Acad. Sci. U S A 103, 696–701.
Onaivi, E.S., Ishiguro, H., Gong, J.P., Patel, S., Perchuk, A., Meozzi, P.A., Myers, L., Mora, Z., Tagliaferro, P., Gardner, E., Brusco, A., Akinshola, B.E., Liu, Q.R., Hope, B., Iwasaki, S., Arinami, T., Teasenfitz, L., Uhl, G.R., 2006. Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain. Ann. N Y Acad. Sci. 1074, 514–536.
Oz, M., 2006. Receptor-independent effects of endocannabinoids on ion channels. Curr. Pharm. Des. 12, 227–239.
Palazuelos, J., Aguado, T., Egia, A., Mechoulam, R., Guzman, M., Galve-Roperh, I., 2006. Non-psychoactive CB2 cannabinoid agonists stimulate neural progenitor proliferation. Faseb J. 20, 2405–2407.
Parker, J., Atez, F., Rossetti, R.G., Skulas, A., Patel, R., Zurier, R.B., 2008. Suppression of human macrophage interleukin-6 by a nonpsychoactive cannabinoid acid. Rheumatol. Int. 28, 631–635.
Parker, L.A., Kwiatkowska, M., Burton, P., Mechoulam, R., 2004. Effect of cannabinoids on lithium-induced vomiting in the Suncus murinus (house musk shrew). Psychopharmacology (Berl.) 171, 156–161.
Patel, S., Hillard, C.J., 2006. Pharmacological evaluation of cannabinoid receptor ligands in a mouse model of anxiety: further evidence for an anxiolytic role for endogenous cannabinoid signaling. J. Pharmacol. Exp. Ther. 318, 304–311.
Patrini, G., Sacerdote, P., Fuzio, D., Manfredi, B., Parolaro, D., 1997. Regulation of immune functions in rat splenocytes after acute and chronic in vivo treatment with CP-55,940, a synthetic cannabinoid compound. J. Neuroimmunol. 80, 143–148.
Pertwee, R.G., 2002. Cannabinoids and multiple sclerosis. Pharmacol. Ther. 95, 165–174.
Pertwee, R.G., 2005. Pharmacological actions of cannabinoids. Handb. Exp. Pharmacol., 1–51.
Pertwee, R.G., 2006. The pharmacology of cannabinoid receptors and their ligands: an overview. Int. J. Obes. (Lond.) 30 (Suppl. 1), S13–S18.
Pertwee, R.G., 2008. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br. J. Pharmacol. 153, 199–215.
Porter, A.C., Sauer, J.M., Knierman, M.D., Becker, G.W., Berna, M.J., Bao, J., Nomikos, G.G., Carter, P., Bymaster, F.P., Leese, A.B., Felder, C.C., 2002. Characterization of a novel endocannabinoid, virodhamine, with antagonist activity at the CB1 receptor. J. Pharmacol. Exp. Ther. 301, 1020–1024.
Raborn, E.S., Marciano-Cabral, F., Buckley, N.E., Martin, B.R., Cabral, G.A., 2008. The cannabinoid delta-9-tetrahydrocannabinol mediates inhibition of macrophage chemotaxis to RANTES/CCL5: linkage to the CB2 receptor. J. Neuroimmune Pharmacol. 3, 117–129.
Rachelefsky, G.S., Opelz, G., Mickey, M.R., Lessin, P., Kiuchi, M., Silverstein, M.J., Stiehm, E.R., 1976. Intact humoral and cell-mediated immunity in chronic marijuana smoking. J. Allergy Clin. Immunol. 58, 483–490.
Racke, M.K., Dhib-Jalbut, S., Cannella, B., Albert, P.S., Raine, C.S., McFarlin, D.E., 1991. Prevention and treatment of chronic relapsing experimental allergic encephalomyelitis by transforming growth factor-beta 1. J. Immunol. 146, 3012–3017.
Raduner, S., Majewska, A., Chen, J.Z., Xie, X.Q., Hamon, J., Faller, B., Altmann, K.H., Gertsch, J., 2006. Alkylamides from Echinacea are a new class of cannabinomimetics. Cannabinoid type 2 receptor-dependent and -independent immunomodulatory effects. J. Biol. Chem. 281, 14192–14206.
Richardson, D., Pearson, R.G., Kurian, N., Latif, M.L., Garle, M.J., Barrett, D.A., Kendall, D.A., Scammell, B.E., Reeve, A.J., Chapman, V., 2008. Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. Arthritis Res. Ther. 10, R43.
Rog, D.J., Nurmikko, T.J., Friede, T., Young, C.A., 2005. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 65, 812–819.
Ross, R.A., Brockie, H.C., Pertwee, R.G., 2000. Inhibition of nitric oxide production in RAW264.7 macrophages by cannabinoids and palmitoylethanolamide. Eur. J. Pharmacol. 401, 121–130.
Roth, M.D., Baldwin, G.C., Tashkin, D.P., 2002. Effects of delta-9-tetrahydrocannabinol on human immune function and host defense. Chem. Phys. Lipids 121, 229–239.
Ryberg, E., Larsson, N., Sjogren, S., Hjorth, S., Hermansson, N.O., Leonova, J., Elebring, T., Nilsson, K., Drmota, T., Greasley, P.J., 2007. The orphan receptor GPR55 is a novel cannabinoid receptor. Br. J. Pharmacol. 152, 1092–1101.
Sacerdote, P., Martucci, C., Vaccani, A., Bariselli, F., Panerai, A.E., Colombo, A., Parolaro, D., Massi, P., 2005. The nonpsychoactive component of marijuana cannabidiol modulates chemotaxis and IL-10 and IL-12 production of murine macrophages both in vivo and in vitro. J. Neuroimmunol. 159, 97–105.
Salzet, M., Breton, C., Bisogno, T., Di Marzo, V., 2000. Comparative biology of the endocannabinoid system possible role in the immune response. Eur. J. Biochem. 267, 4917–4927.
Schuelert, N., McDougall, J.J., 2008. Cannabinoid-mediated antinociception is enhanced in rat osteoarthritic knees. Arthritis Rheum. 58, 145–153.
Schwarz, H., Blanco, F.J., Lotz, M., 1994. Anadamide, an endogenous cannabinoid receptor agonist inhibits lymphocyte proliferation and induces apoptosis. J. Neuroimmunol. 55, 107–115.
Shay, A.H., Choi, R., Whittaker, K., Salehi, K., Kitchen, C.M., Tashkin, D.P., Roth, M.D., Baldwin, G.C., 2003. Impairment of antimicrobial activity and nitric oxide production in alveolar macrophages from smokers of marijuana and cocaine. J. Infect. Dis. 187, 700–704.
Sidney, S., Beck, J.E., Tekawa, I.S., Quesenberry, C.P., Friedman, G.D., 1997. Marijuana use and mortality. Am. J. Public Health 87, 585–590.
Sinha, D., Bonner, T.I., Bhat, N.R., Matsuda, L.A., 1998. Expression of the CB1 cannabinoid receptor in macrophage-like cells from brain tissue: immunochemical characterization by fusion protein antibodies. J. Neuroimmunol. 82, 13–21.
Steffens, S., Veillard, N.R., Arnaud, C., Pelli, G., Burger, F., Staub, C., Karsak, M., Zimmer, A., Frossard, J.L., Mach, F., 2005. Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. Nature 434, 782–786.
Stella, N., 2004. Cannabinoid signaling in glial cells. Glia 48, 267–277.
Straiker, A., Mackie, K., 2006. Cannabinoids, electrophysiology, and retrograde messengers: challenges for the next 5 years. Aaps J. 8, E272–E276.
Szallasi, A., Di Marzo, V., 2000. New perspectives on enigmatic vanilloid receptors. Trends Neurosci. 23, 491–497.
Tanikawa, T., Kurohane, K., Imai, Y., 2007. Induction of preferential chemotaxis of unstimulated B-lymphocytes by 2-arachidonoylglycerol in immunized mice. Microbiol. Immunol. 51, 1013–1019.
Tashkin, D.P., Baldwin, G.C., Sarafian, T., Dubinett, S., Roth, M.D., 2002. Respiratory and immunologic consequences of marijuana smoking. J. Clin. Pharmacol. 42, 71S–81S.
Triantaphyllopoulos, K.A., Williams, R.O., Tailor, H., Chernajovsky, Y., 1999. Amelioration of collagen-induced arthritis and suppression of interferon-gamma, interleukin-12, and tumor necrosis factor alpha production by interferon-beta gene therapy. Arthritis Rheum. 42, 90–99.
Valk, P., Verbakel, S., Vankan, Y., Hol, S., Mancham, S., Ploemacher, R., Mayen, A., Lowenberg, B., Delwel, R., 1997. Anandamide, a natural ligand for the peripheral cannabinoid receptor is a novel synergistic growth factor for hematopoietic cells. Blood 90, 1448–1457.
van Diepen, H., Schlicker, E., Michel, M.C., 2008. Prejunctional and peripheral effects of the cannabinoid CB(1) receptor inverse agonist rimonabant (SR 141716). Naunyn Schmiedebergs Arch. Pharmacol. 378, 345–369.
Van Sickle, M.D., Duncan, M., Kingsley, P.J., Mouihate, A., Urbani, P., Mackie, K., Stella, N., Makriyannis, A., Piomelli, D., Davison, J.S., Marnett, L.J., Di Marzo, V., Pittman, Q.J., Patel, K.D., Sharkey, K.A., 2005. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 310, 329–332.
Wacnik, P.W., Luhr, K.M., Hill, R.H., Ljunggren, H.G., Kristensson, K., Svensson, M., 2008. Cannabinoids affect dendritic cell (DC) potassium channel function and modulate DC T cell stimulatory capacity. J. Immunol. 181, 3057–3066.
Wade, D.T., Makela, P., Robson, P., House, H., Bateman, C., 2004. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult. Scler. 10, 434–441.
Walter, L., Franklin, A., Witting, A., Wade, C., Xie, Y., Kunos, G., Mackie, K., Stella, N., 2003. Nonpsychotropic cannabinoid receptors regulate microglial cell migration. J. Neurosci. 23, 1398–1405.
White, S.C., Brin, S.C., Janicki, B.W., 1975. Mitogen-induced blastogenic responses of lymphocytes from marihuana smokers. Science 188, 71–72.

Woelkart, K., Marth, E., Suter, A., Schoop, R., Raggam, R.B., Koidl, C., Kleinhappl, B., Bauer, R., 2006. Bioavailability and pharmacokinetics of Echinacea purpurea preparations and their interaction with the immune system. Int. J. Clin. Pharmacol. Ther. 44, 401–408.

Woelkart, K., Salo-Ahen, O.M., Bauer, R., 2008. CB receptor ligands from plants. Curr. Top. Med. Chem. 8, 173–186.

Wolf, S.A., Ullrich, O., 2008. Endocannabinoids and the brain immune system: new neurones at the horizon? J. Neuroendocrinol. 20 (Suppl. 1), 15–19.

Wotherspoon, G., Fox, A., McIntyre, P., Colley, S., Bevan, S., Winter, J., 2005. Peripheral nerve injury induces cannabinoid receptor 2 protein expression in rat sensory neurons. Neuroscience 135, 235–245.

Wright, K.L., Duncan, M., Sharkey, K.A., 2008. Cannabinoid CB2 receptors in the gastrointestinal tract: a regulatory system in states of inflammation. Br. J. Pharmacol. 153, 263–270.

Yang, H.Y., Karoum, F., Felder, C., Badger, H., Wang, T.C., Markey, S.P., 1999. GC/MS analysis of anandamide and quantification of N-arachidonoylphosphatidylethanolamides in various brain regions, spinal cord, testis, and spleen of the rat. J. Neurochem. 72, 1959–1968.

Yao, B.B., Mukherjee, S., Fan, Y., Garrison, T.R., Daza, A.V., Grayson, G.K., Hooker, B.A., Dart, M.J., Sullivan, J.P., Meyer, M.D., 2006. In vitro pharmacological characterization of AM1241: a protean agonist at the cannabinoid CB2 receptor? Br. J. Pharmacol. 149, 145–154.

Yea, S.S., Yang, K.H., Kaminski, N.E., 2000. Role of nuclear factor of activated T-cells and activator protein-1 in the inhibition of interleukin-2 gene transcription by cannabinol in EL4 T-cells. J. Pharmacol. Exp. Ther. 292, 597–605.

Yuan, M., Kiertscher, S.M., Cheng, Q., Zoumalan, R., Tashkin, D.P., Roth, M.D., 2002. Delta 9-Tetrahydrocannabinol regulates Th1/Th2 cytokine balance in activated human T cells. J. Neuroimmunol. 133, 124–131.

Zajicek, J., Fox, P., Sanders, H., Wright, D., Vickery, J., Nunn, A., Thompson, A., 2003. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 362, 1517–1526.

Zhang, Z.F., Morgenstern, H., Spitz, M.R., Tashkin, D.P., Yu, G.P., Marshall, J.R., Hsu, T.C., Schantz, S.P., 1999. Marijuana use and increased risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol. Biomarkers Prev. 8, 1071–1078.

Ziring, D., Wei, B., Velazquez, P., Schrage, M., Buckley, N.E., Braun, J., 2006. Formation of B and T cell subsets require the cannabinoid receptor CB2. Immunogenetics 58, 714–725.