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INVITED REVIEW

The endocannabinoid system: a revolving plate in neuro-immune interaction in health and disease

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Abstract Studies of the last 40 years have brought to light an important physiological network, the endocannabinoid system. Endogenous and exogenous cannabinoids mediate their effects through activation of specific cannabinoid receptors. This modulatory homoeostatic system operates in the regulation of brain function and also in the periphery. The cannabinoid system has been shown to be involved in regulating the immune system. Studies examining the effect of cannabinoid-based drugs on immunity have shown that many cellular and cytokine mechanisms are modulated by these agents, thus raising the hypothesis that these compounds may be of value in the management of chronic inflammatory diseases. The special properties of endocannabinoids as neurotransmitters, their pleiotropic effects and the impact on immune function show that the endocannabinoid system represents a revolving plate of neural and immune interactions. In this paper, we outline current information on immune effects of cannabinoids in health and disease.

Keywords Endocannabinoid system · Immune cells · Cannabinoids · Immunomodulation

Abbreviations

AC	Adenylate cyclase
AD	Alzheimer disease
AEA	Anandamide
AG	Arachidonoyl-glycerol
BM	Bone marrow
CB	Cannabinoid
CB1R	Cannabinoid receptor 1
CB2R	Cannabinoid receptor 2
CBC	Cannabichromene
CBD	Cannabidiol
CBG	Cannabigerol
CBR	Cannabinoid receptors
COX	Cyclooxygenase
DC	Dendritic cells
ERK	Extracellular signal-regulated kinase
FAAH	Fatty acid amide hydrolase
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GPCR	G *protein*-coupled *receptor*
HPA	Hypothalamic–pituitary–adrenal
HSPC	Hematopoietic stem and progenitor cells
IFN-γ	Interferon gamma
IL	Interleukin
LG	Linoleoyl glycerol
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MC	Mast cell
NAAA	*N*-acylethanolamine-hydrolysing acid amidase
NGF	Nerve growth factor
OA	Ostheoarthritis
OEA	Oleoylethanolamide
PBMC	Peripheral blood mononuclear cells
PEA	Palmitoylethanolamide
PKA	cAMP-Dependent protein kinase
PPAR	Peroxisome proliferator-activated receptors
RA	Rheumatoid arthritis
THC	Tetrahydrocannabinol
THCV	Tetrahydrocannabivarin

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TNF Tumor necrosis factor
TRPV Vanilloid receptor-type

Introduction

The endocannabinoid system is a complex endogenous signalling network, which includes cannabinoid receptors and ligands.

It has pro-homoeostatic actions in the brain and the periphery (immune system, autonomic nervous system, endocrine network, gastrointestinal tract, reproductive system and microcirculation). Evolutionarily, the endocannabinoid system has been preserved from coelenterates to man, and proven to be a successful biological network with adaptability and enhancement of function through increasing biological complexity.

Endocannabinoids share the defining characters of neurotransmitters, but have particularities in terms of their synthesis, storage, transmission and removal. A neurotransmitter is mainly synthesized in neurons (Levite 2008); however, endocannabinoids can also be released, from non-neuronal cells, including immune cells. Due to their hydrophobicity and tendency to diffuse across membranes, they cannot be stored within synaptic vesicles, but are released in a phospholipid precursor form following calcium-dependent activation of appropriate enzymes or ion channels. A classical neurotransmitter is present in the presynaptic terminal and released to act on the postsynaptic neuron or effector organs. However, endocannabinoids show retrograde transmission, being released by the postsynaptic neuron and acting on the presynaptic neuron, modulating its activity. Moreover, exogenous administration of a neurotransmitter should mimic the action of the endogenously released transmitter. Endocannabinoids act in orchestration with other endogenous molecules and transmitting pathways, which may lead to a variety of biochemical consequences when agonists are administered exogenously. Finally, since the site of action of cannabinoids (CB) is not only the synaptic cleft, but also the pericellular space near immune or other cells, there is no uniform removal mechanism.

Exogenous or endogenous CB regulates the function of both immune and nervous systems. In neurons, endocannabinoids regulate synaptic transmission through pre- and postsynaptic mechanisms. In immune cells, the activation of cannabinoid receptors (CBR) alters the metabolic activity and responses during inflammation. The distribution of the two main CBR subtypes, type 1 (CB1R) and 2 (CB2R), underlines this relationship. CB1R is found mainly in the brain, while CB2R is mainly in immune cells. The endocannabinoid system seems to be a revolving plate of neural–immune interactions.

The endocannabinoid system: general principles

The endocannabinoid system is a pleiotropic, locally acting signalling system activated 'on demand' following perturbation of cell homoeostasis (De Petrocellis and Di Marzo 2009). It includes: (1) at least two CBR, CB1R and CB2R; (2) endogenous cannabinoid ligands comprising at least two families of lipid signalling molecules, the *N*-acyl-ethanolamines (the main representative being *N*-arachidonyl-ethanolamine or anandamide, AEA) and the monoacyl-glycerols such as 2-arachidonoyl-glycerol (2-AG); (3) enzymes and proteins for the regulation of endocannabinoid levels and action at receptors (De Petrocellis and Di Marzo 2009).

CB1R and CB2R are single polypeptides with an extracellular N-terminus, an intracellular C-terminus and seven transmembrane helices. They are activated endogenously by the lipid-type signalling CB molecules such as AEA and 2-AG (Pertwee et al. 2010). CB1R and CB2R activate Gi/o proteins inhibitory to adenylate cyclase (AC) (Howlett and Mukhopadhyay 2000), but can also activate AC through stimulating G_s proteins (Glass and Northup 1999). Both are positively coupled to mitogen-activated protein kinase (MAPK) (Woelkart et al. 2008).

CB1R is located mainly in the hippocampus and basal ganglia (Mackie 2005) and may be involved in neuroplasticity (Chevaleyre et al. 2006). In peripheral tissues, CB1R is found in adipocytes, liver, pancreas and skeletal muscle. Activated somatic CB1R can induce neuronal hyperpolarization (Cavuoto et al. 2007). CB1R are also expressed by immune cells (Howlett et al. 2002). CB1R may exist as homo- or heteromultimers (Milligan 2004). CB1R form heteromers with other GPCR and this affects the response to agonists, possibly by influencing ligand selectivity or relative intrinsic activity. (Ferre et al. 2009). CB2R receptors are expressed on immune cells and neurons (Galiegue et al. 1995). CB2R is also found on peripheral nerve terminals and in the retina (Griffin et al. 1997; Lu et al. 2000). In the brain, CB2R is present on astrocytes, microglia, neural subpopulations and oligodendroglial progenitors (Onaivi et al. 2006a). CB2R expression on microglia is related to the cell activation status, i.e. induced by local inflammation, infection or stress (Carlisle et al. 2002b). The CB2R activation status is linked to modulatory properties on immune cell migration and cytokine release (Cabral and Staab 2005).

As an ancestral biological network, the endocannabinoid system interacts with other endogenous systems, including the endovanilloid and opioid systems. Some classical effects of CB such as anti-emesis may not be mediated only by the CB1R–CB2R receptor system (Parker et al. 2004), but by additional CBR subtypes. Moreover, some of the CB effects may be the result of simultaneous action on classical and non-classical receptor pathways. Endocannabinoids

interact with the vanilloid receptor-type 1 (TRPV-1), K+ channels, 5-HT3 receptors and α7 nicotinic receptors (Oz 2006; Szallasi and Di Marzo 2000), peroxisome proliferator-activated receptors (PPAR) (Michalik et al. 2006) or other GPCR such as GPR55 (Ryberg et al. 2007). It is not clear if these interactions are relevant for the physiologic effects of CB, or if these are just a consequence of their lipophilic properties (Mackie 2008). Lipophilicity is also implicated in the direct effects of CB agonists on mitochondrial function, which may explain their metabolic and anti-cancer effects (Athanasiou et al. 2007a, b). Another CBR-independent mechanism potentially important for immune-cell function involves effects on lipid-raft structure and function (Vogt et al. 2002). Current evidence suggests that CBR can be regulated by the rate of interlayer exchange and lateral diffusion of endocannabinoid/cholesterol complexes within lipid bilayers (Oddi et al. 2007). CBR pharmacology is discussed in more detail in recent reviews (Pertwee 2008b; Pertwee et al. 2010; Ashton et al. 2008; Hanus and Mechoulam 2010).

Cannabinoid ligands and analogues

The term 'cannabinoid' denotes, in the broader sense, any ligand or related compound acting on the CBR (Fig. 1). However, it was commonly used for plant CB. Phytocannabinoids may be psychoactive [D9-THC, D8-THC, cannabichromene (CBC), cannabigerol (CBG) and tetrahydrocannabivarin (D9-THCV)] or non-psychoactive [cannabinol and cannabidiol (CBD)]. The pharmacology of plant-derived ligands was recently reviewed (Pertwee 2008a; Pertwee et al. 2010). Phytocannabinoids, like D9-THC, can stimulate the CB system via CB1R or CB2R, but CBD can exert anti-inflammatory effects despite low affinity for CBR (Malfait et al. 2000b). D9-THC is a partial agonist that can block activation by other ligands of both CBR, but also induce stimulatory effects, depending on the receptor expression level, coupling efficiency and endogenous CB release (Pertwee 2008a). D9-THC has modulatory effects on both cell-mediated and humoral immunity. It may suppress T-cell proliferation and inhibit IFN-γ production via a CB2R-mediated mechanism (Yuan et al. 2002). CBD, by antagonizing CB1R/CB2R agonists, can inhibit immune cell migration and thus induce anti-inflammatory effects (Walter et al. 2003). Ajulemic acid, a derivative of THC-11-oic acid, has low affinity for CB2R but exerts anti-inflammatory activity, which might be through disruption of the arachidonic acid cascade or through activation of PPAR (Klein 2005). Alkamides from *Echinacea* sp. have structural similarities with AEA and affinity for CB2R (Raduner et al. 2006). At low nanomolar concentrations, they affect cytokine and chemokine

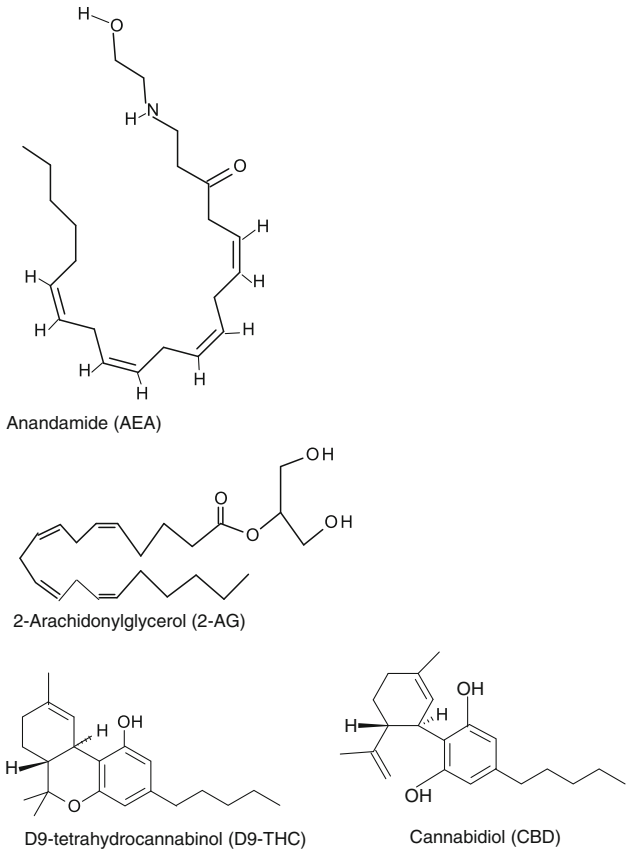

Fig. 1 Chemical structures of main representatives of phytocannabinoids (D9-THC and CBD) and endocannabinoids (AEA and 2-AG)

expression in human blood (Woelkart et al. 2006). IL-6 production by B cells or macrophages can be increased by alkamides and AEA in a CB2R-dependent manner (Woelkart et al. 2008).

Endocannabinoids include arachidonic acid metabolites AEA, 2-AG, palmitoylethanolamide (PEA), 2-arachidonylglycerylether (noladin ether), 2-linoleoyl glycerol (2-LG), *O*-arachidonyl ethanolamine (virodhamine) (Porter et al. 2002) and oleoylethanolamide (OEA).

AEA is produced by immune cells and neurons (Yang et al. 1999). It is more selective for CB1R than CB2R, but can activate TRPV-1 receptors as well (Pertwee 2005). AEA is highly produced in brain areas where CB1R is highly expressed (striatum, hippocampus, cerebellum). Inside the cell, AEA signalling is inactivated by fatty acid amide hydrolases 1 and 2 (FAAH1, FAAH2) or *N*-acylethanolamine-hydrolysing acid amidase (NAAA)-mediated hydrolysis, into arachidonic acid, or by COX2 oxidation into prostaglandin E2-ethanolamide, which can be further transformed into other bioactive lipids such as prostaglandins. FAAH1 is the principal contributor to AEA hydrolysis in the CNS. NAAA is highly expressed in macrophages (Tsuboi et al. 2007). Interestingly, the preferred substrate of NAAA is PEA, which is increased

during inflammation. Microglia respond to PEA (Stella 2009), and NAAA may be an interesting target in inflammatory states. In addition to being lipophilic, AEA may be shuttled by binding proteins to PPAR, TRPV1 (Maccarrone et al. 2010) or adiposomes (Weibel et al. 2009). 2-AG is present in higher quantities than AEA in the immune system and has lower affinity for CB1R. It influences, via CB2R, the chemotactic response of microglia. Exogenous CB (D9-THC, CP55940) may antagonize these effects (Cabral et al. 2008). Interestingly, some effects of endogenously released AEA and 2-AG may be enhanced through an "entourage effect" that relies on the co-release of other endogenous fatty acid derivatives (Garcia Mdel et al. 2009).

PEA is generated by neurons and immune cells. It is produced during inflammation and inhibits mast cells via CB2R (Facci et al. 1995a). However, although CB2R antagonists can counteract its CB-like effects, PEA may not bind either CB1R or CB2R (Facci et al. 1995a) and may be more of an 'entourage' molecule for AEA and 2-AG (Muccioli 2010).

'Classical' synthetic cannabinoids are those that retain the natural cannabinoid ring structures and their oxygen atoms (nabilone, HU-210, HU-211), while 'non-classical' have either rearrangements, deletions or additions to the natural structures, or isosteric replacement of an atomic constituent (levonantrol, CP-55,940, WIN55,212, AM-404). Their pharmacology has been reviewed (Pertwee et al. 2010).

Cannabinoid effects on immune cells

Expression of CBR by immune cells

Both CBR are expressed by immune cells and are activated after infection or immune stimulation. T lymphocytes in the basal state express CB1R, albeit at low levels. Expression is up-regulated by CB themselves, an effect mediated by IL-4, which may enable CB1R-mediated communication to neuronal cells (Börner et al. 2008). We have observed that expression of both CB1R and CB2R is induced in human peripheral blood mononuclear cells (PBMC) and T cells, by proinflammatory cytokines TNF-alpha, IL-1 and IL-6 (Jean-Gilles et al. unpublished observations). It was suggested that CB1R may be involved in CB-induced T-helper cell subset differentiation (Börner et al. 2008).

CB2R expression within the immune system is usually higher than that of CB1R (Massi et al. 2006), and CB2R mRNA is found in decreasing amounts in human B cells, NK cells, monocytes, polymorphonuclear neutrophils and T cells (CD8 > CD4) (Galiegue et al. 1995). In immune organs, CB2R is expressed in thymus, spleen, cortex of lymph nodes and nodular corona of Peyer's patches (Lynn and Herkenham 1994). Recently, an analysis of CB2R protein levels expressed by blood-derived immune cells from healthy human donors showed that NK cells, B cells and monocytes expressed higher levels of CB2R than CD4+, CD8+ T cells or neutrophils (Graham et al. 2010). Interestingly, NK cells have the greatest variation in CB2R expression levels, whereas for all other cell types these were similar between subjects. CB2R is present on resting T cells at low abundance in some healthy subjects (Graham et al. 2010). Also, dendritic cells (DC) can express CB2R, suggesting a role in modulating antigen presentation (Matias 2002). The expression of CBR depends on the cell activation state (Carlisle et al. 2002a). The human Jurkat T-cell line and mouse macrophages express more CB1R when they are activated (Daaka et al. 1996). Splenocyte CB2R mRNA expression is reduced by LPS stimulation and increased by anti-CD40 co-stimulation (Lee et al. 2001). Marijuana use and anti-CD40 co-stimulation can increase the expression of both CB1R and CB2R (Klein 2003). CBR is expressed by microglia in the brain (Carrier et al. 2004). CB2R expression is higher in activated ('primed' and 'responsive') microglia (Carlisle et al. 2002a; Cabral and Staab 2005). A CB2R-dependent time window for functional modulation of microglial actions seems to exist, and synthetic and endogenous CB analogues have different modulatory effects in this setting (Cabral et al. 2008; Walter et al. 2003). Studies of mice with targeted disruption of CB1R and CB2R have produced various and sometimes discordant results. Targeted disruption of CBR did not produce profound effects on immune competence, as assessed by well-established and widely used immune function assays. Also, no profound differences between $CB1R^{-/-}/CB2R^{-/-}$ and wild-type mice were observed in the percentages of major leukocyte subpopulations or in responses to mitogenic stimuli, the mixed lymphocyte response and the production of IL-2 and IFN-γ (Springs et al. 2008a). However, CBR involvement was observed, in that humoral responses required CD40-initiated signalling for suppression by D9-THC (Springs et al. 2008a).

General principles of CB effects on immune cells

CB immune effects have been reviewed over the years (Berdyshev 2000; Croxford and Yamamura 2005; Massi et al. 2006; Tanasescu and Constantinescu 2010). CB can have opposing actions on immune cells, depending on three key factors: (1) type of CB, (2) dose of CB and (3) type of cell that the CB is acting on. The degree of CBR expression may also play a role, and receptor-independent actions may be present.

Immune effects of CB are concentration dependent. There is a biphasic response in vitro: a CB ligand can be stimulatory in nanomolar concentration and inhibitory in micromolar concentration (Croxford and Yamamura 2005; Eisenstein et al. 2007a). Differential sensitivity to endocannabinoids and promiscuous activation of several classes of receptor appear to be involved in these effects as well (Alexander and Kendall 2007). Indeed, the interactions between the different CB ligands makes their immune actions very complex (e.g. the partial agonist effect of phytocannabinoid D9-THC is antagonistic for the endocannabinoid 2-AG). Moreover, activation or inhibition in vitro may vary according to cell lineage, medium conditions and concentration, which can explain the contradictory results found in the literature. Endocannabinoid signalling may provide a tonic control of immune cell activation and limit spontaneous activation of immune cell function (Pandey et al. 2009). The effect of CB on immune functions appears to be transient, allowing the inhibitory effects to be overcome when the immune system needs to be activated during infections. As a consequence, the adverse effects of therapies targeting the endocannabinoid system may be low (Pandey et al. 2009).

CB effects on T cells

Nanomolar concentrations of D9-THC can be stimulatory and micromolar concentrations inhibitory (Patrini et al. 1997). Several days of exposure to D9-THC but not acute treatment inhibits ConA-induced splenocyte proliferation (Patrini et al. 1997). However, only acute treatment with CB CP55,940 can inhibit PHA-induced splenocyte proliferation (Massi et al. 1997).

CB usually suppresses T-cell proliferation and has important effects on T helper 1- and 2-specific cytokines and TGF-β secretion (Croxford and Yamamura 2005; Borner et al. 2009).

The evidence that major effects of CB are through CBR is supported by their lack of effect in CB2R-deficient T-helper cells (Buckley et al. 2000). However, CB1R also participates in CB immune effects. Activation can up-regulate CB1R transcription in Jurkat cells (Börner et al. 2007). CB1R expression can be up-regulated by IL-4 in T cells (Börner et al. 2008). Non-CBR mechanisms may also be involved (Tashkin et al. 2002).

Early reports on CB inhibitory effects on T cells such as decreases in number or sensitivity (Nahas et al. 1977; El-Gohary and Eid 2004) were not corroborated by other studies (White et al. 1975; Lau et al. 1976). Different parameters regarding marijuana intake (routes of administration, type, quantity, frequency) can account for this. Lymphocyte recruitment to airways is decreased in D9-THC-treated mice challenged with influenza virus A/PR/8/34 (PR8) and CBR-dependent and -independent mechanisms are suggested (Buchweitz et al. 2008). Chronic exposure to CB may result in modulation of CBR expression, decreased T-cell number and increased incidence of infection and squamous cell carcinoma of the head and neck (Zhang et al. 1999; El-Gohary and Eid 2004). D9-THC treatment in immune cell cultures has shown a suppressive effect on functions in T and B cells, NK cells or macrophages (Nahas et al. 1977).

CD8 cells may be more sensitive to CB action than CD4 cells (Klein et al. 1991). CB suppresses their cytolytic activity (Fischer-Stenger et al. 1992). This also occurs indirectly by reducing the expression of MHC molecules on DC via CB1R (Wacnik et al. 2008). Encephalitogenic T-cell adhesion to inflamed brain venules is controlled by inverse agonism of CB1 which blocks PKA-dependent signal (Rossi et al. 2011).

CB suppresses Th1 and enhances Th2 responses, via both CBR (Yuan 2002) and by modulation of cytokines produced by DC (Lu et al. 2006). They also directly induce B-cell class switch from IgM to IgE via CB2R (Agudelo et al. 2008). D9-THC increases Th2 and Th2-promoting cytokines and decreases IFN-γ, IL-12 and IL-12 receptors (Tanasescu and Constantinescu 2010). Induction of Th2-associated cytokines can inhibit Th1 cells (Croxford and Yamamura 2005). CBD, via CBR, suppresses IL-2 production by activated murine splenocytes (Kaplan et al. 2008) and may regulate the production of IL-2 in T cells (Borner et al. 2009).

CBR ligands can suppress the expression of inflammatory cytokines (TNF-α, IL-1, IL-2, IL-6, IL-12) (Croxford and Yamamura 2005). CB1R on T cells may mediate the decrease in IFN-γ and IL-12Rβ2 (Newton et al. 2009), while D9-THC increases IL-4 and GATA-3 (Newton et al. 2009) and inhibits IFN-γ secretion (Yuan 2002) via CB2R.

AEA dose-dependently inhibits mitogen-induced human T- and B-cell proliferation, presumably by CBR-independent mechanisms (Schwarz et al. 1994; Derocq et al. 1998). AEA also has unique pro-proliferative effect on hematopoietic cell lines (not seen for other natural or synthetic CB), acting synergistically with other growth stimuli (Valk et al. 1997). 2-AG has strong modulatory activity on mitogen-induced T-cell proliferation (Lee et al. 1995). AEA suppresses proliferation and release of cytokines like IL-2, TNF-α and IFN-γ from activated human peripheral T lymphocytes in a CB2R-dependent manner. Furthermore, AEA suppresses IL-17 production (Cencioni et al. 2010). AEA enhances LPS/IFN-γ-induced IL-10 production in activated microglia in vitro, by activating ERK1/2 and JNK MAPK via CB2R (Correa et al. 2010). In addition, AEA inhibits IL-12p70/IL-23 axis in microglia via CB2R (Correa et al. 2009). This could contribute to the accumulation of anti-inflammatory microglia at the lesion sites, for example in MS (Correa et al. 2010).

On the other hand, low-dose AEA (0.1 mg/kg) given immediately prior to sensitization had a stimulatory effect on Th1-mediated immunity in vivo, by increasing DC activation and IFN-γ production. These effects are concentration dependent: AEA at nanomolar concentrations increases IFN-γ and decreases it at the micromolar range (Ribeiro et al. 2010).

CB effects on natural killer cells (NK)

Both proliferation and cytolytic activity of NK cells can be influenced by CB treatment through CBR-mediated mechanisms in animal studies (Massi et al. 2006). In vitro investigations indicate that D9-THC may suppress human NK activity and the constitutive expression of proinflammatory TNF-α, GM-CSF and IFN-γ (Specter et al. 1986). "Bhang"—a form of marijuana that is drunk or smoked—can lower NK cell number (El-Gohary and Eid 2004).

Systemic administration of CBD, repeated for 14 days at relatively low doses, produces bidirectional effects on lymphocyte subset distribution in peripheral blood of rats (Ignatowska-Jankowska et al. 2009). Since circulating NK cell number may be important in cancer patients' prognosis (Terabe and Berzofsky 2007), further study is needed to clarify if this may explain the antitumor effects of CBD (Ignatowska-Jankowska et al. 2009).

CB effects on macrophages

Macrophages express both CBR, although predominantly CB2R (Sinha et al. 1998). CB modulates 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 (Cabral et al. 1995; Berdyshev et al. 2001). CB may inhibit antigen presentation and phagocytic capacity (Sacerdote et al. 2005). In turn, macrophages can synthesize endocannabinoids, which modulate immune responses through CBR-dependent and -independent mechanisms.

CB1R is overexpressed in macrophages in coronary atheroma and its blockade exhibits anti-inflammatory effects, thus providing potential beneficial effects on atherogenesis (Sugamura et al. 2009).

CB effects on neutrophils

CB inhibits human neutrophil migration, possibly through CBR-independent mechanisms. However, low doses of D9-THC do not have such effects on neutrophils from healthy humans (Deusch et al. 2003). Synthetic CB such as CP55940, but not AEA, inhibits neutrophil lysosomal enzyme release independently of CBR activation (Kraft et al. 2004). AEA levels correlate with adhesive and phagocytic function of neutrophils in patients with fibromyalgia. These effects are the opposite of those of endogenous glucocorticoids (Kaufmann et al. 2008).

CB effects on mast cells (MC)

Both CBR 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. 2008a). Agonists of both CBR prevent mast cell-dependent angiogenesis during granuloma formation (De Filippis et al. 2008c).

PEA reduces MC activation in vitro in a rat model, an effect antagonized by AEA (Facci et al. 1995b). On the other hand, independently of CBR but still in a Gi/o-protein-dependent manner, only CB containing a benzopyran ring (D9-THC; D8-THC; and AEA—only in high concentrations), but not PEA or PEA derivatives induces an energy and concentration-dependent histamine release from peritoneal MC (Bueb et al. 2001). In contrast, 2-AG-mediated suppression of histamine release from guinea pig mast cells can be reversed by a CB2R antagonist or a nitric oxide synthase inhibitor (Vannacci et al. 2004). PEA shows anti-inflammatory actions in several MC-mediated models of inflammation (Jonsson et al. 2006). Drugs containing PEA could be efficacious in the treatment of dermatitis symptoms via inhibition of nerve growth factor (NGF) release from MC (Pulvirenti et al. 2007).

CB effects on dendritic cells (DC)

DC expresses both CBR. AEA, 2-AG and PEA are found in lipid extracts from immature DC (Matias et al. 2002). LPS can increase the levels of 2-AG in DC, without increased CBR or FAAH expression (Maestroni 2004). In turn, 2-AG may act as a chemotactic molecule, recruiting DC during innate immune responses (Maestroni 2004). Both exogenous and endogenous CBs induce apoptosis in DC (Do et al. 2004). AEA apoptotic activity is concentration dependent and may be linked to rapid AEA hydrolysis by FAAH (Do et al. 2004). Moreover, apoptosis seems to be CBR mediated, since antagonists of CB1R (SR141716A) or CB2R (SR144528) reverse the AEA effects (Do et al. 2004).

CB effects on hematopoietic stem and progenitor cells (HSPC)

Endocannabinoids can be positive or negative factors in hematopoietic cell migration and differentiation (Randall 2007). AEA and 2AG, whose structural differences lie in the nature of the end-group alone, act in opposite

directions, by reducing or enhancing, respectively, bone marrow cell migration. These effects are partially independent of CBR (Patinkin et al. 2008). Both AEA and 2AG stimulation leads to roughly doubling granulocyte, erythrocyte, macrophage and megakaryocyte colony forming units (Patinkin et al. 2008). CB2R mediates the retention of immature B cells in bone marrow sinusoids (Pereira et al. 2009) and physiological levels of endocannabinoids are important for retention of HSPC in the BM niches (Jiang et al. 2011). CB1R and CB2R are expressed in human and murine HSPCs, and BM stromal cells express AEA and 2AG. Endocannabinoid-mediated mobilization of HSPCs may be stimulated by inflammatory cytokines, CXCR4 signalling or integrin interactions. Therefore, CB has potential applications in bone marrow transplantation (Jiang et al. 2011).

CB effects on B cells and humoral immunity

CB may affect B-cell number, proliferation, migration and function (Ig production, isotype switching) (Croxford and Yamamura 2005). Antibody production is suppressed by synthetic or plant CBR ligands (Kaminski et al. 1994). Both D9-THC and AEA may induce dose-related suppression of antibody formation, via CB2R (Eisenstein et al. 2007b). In mice, 2-AG preferentially attracts unstimulated naive B cells, thus influencing the structure of B-cell compartments in secondary lymphoid tissues (Tanikawa et al. 2007). In ovalbumin-sensitized mice, CBD suppression of humoral immunity is due to impaired function of splenocytes (Jan 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 marijuana smokers' blood is influenced by CB ingestion (Nahas and Osserman 1991). A biphasic effect is seen on B-cell proliferation and migration, with low doses acting as proliferation inducers (Croxford and Yamamura 2005). In mice, D9-THC can suppress the humoral immune responses involving CD40 at low micromolar concentrations, raising questions about why relatively high concentrations of CB are required to suppress in vitro immune responses (Springs et al. 2008b). This phenomenon may be related to the lipophilic properties of CB, which promote nonspecific binding with serum lipids and proteins (Springs et al. 2008b), but we suggest that this may be linked to endocannabinoid signalling to the CBR, as recently discussed (Howlett et al. 2011).

Non-CBR-mediated pathways are involved in CB antioxidant actions which modulate cell survival and growth of B cells (Chen and Buck 2000). Human peripheral blood B cells express one, while mouse splenic B cells express three CB2R transcripts, with specific transcript selection during B-cell activation by LPS (Sherwood et al. 2009). The extent to which transcript selection changes during B-cell activation is unclear.

CB and cytokines

The relation between the endocannabinoid system and cytokines is bidirectional: CB modulates cytokine secretion, which can in turn have particular effects on CBR (Jean-Gilles et al. 2010). CB may induce a shift in cytokine profile from proinflammatory to anti-inflammatory. Synthetic low affinity ligands and plant CB may inhibit TNF-α and other acute phase cytokines. However, in some conditions, some of these ligands may increase the expression of TNF-α and other inflammatory cytokines and chemokines (Klein et al. 2000).

Cytokines may also affect the endocannabinoid system by regulating enzymes involved in endocannabinoid degradation. IL-10 and IL-4 stimulate FAAH, whereas IFN-γ and IL-12 decrease FAAH activity and protein expression (Maccarrone et al. 2001b). TGF-β actively regulates lymphocyte CB2R expression in an autocrine and paracrine manner (Gardner et al. 2002). IFN-γ increases CB2R mRNA and protein in rat macrophages (Carlisle et al. 2002a) and microglia (Racz et al. 2008). CB2R up-regulation in a mouse model of MS highly correlates with the production of pro-inflammatory cytokines (Loría et al. 2008). CB1R is up-regulated by Th2 cytokine IL-4 and by CB themselves in human T lymphocytes (Börner et al. 2008). We investigated the regulation of CB1R and CB2R by cytokines in T cells, other immune cell types, PBMCs and whole blood collected from healthy human subjects and patients with MS. Stimulation of these different cell populations with pro-inflammatory cytokines, especially TNF-α, increased CB1R and CB2R mRNA and protein levels (Jean-Gilles et al. unpublished observations).

Production and metabolism of cannabinoids in immune cells

Immune cells secrete endocannabinoids and have functional transport and breakdown mechanisms for CB (Pestonjamasp and Burstein 1998). Immune cells increase the production of endocannabinoids in response to LPS and other stimuli (Jiang et al. 2011). Uptake and degradation of endocannabinoids in immune cells have been shown for macrophages and leukocytes (Bisogno et al. 1997). These cells can synthesize AEA and PEA, as well as take up these molecules, thereby regulating inflammation and vascular tone (Pandey et al. 2009).

CB production by CNS and peripheral immune cells is part of a homoeostatic immunomodulatory function. Thus, activation of the inflammatory response to infection involves the release of pro-inflammatory cytokines,

chemokines and other metabolic products of immune cells. Activated immune cells can release arachidonic acid and other fatty acids or chemically similar metabolites such as AEA (Di Marzo et al. 1996). As-yet-uncharacterized endocannabinoid membrane transporters may be involved both in the release and in the subsequent uptake of endocannabinoids by neurons and glial cells (Klein 2005). LPS increases the production of AEA and 2-AG by macrophages, PBMC, DC and platelets (Klein 2005; Varga et al. 1998) and reduces the expression of FAAH (Maccarrone et al. 2001a). Once released, endocannabinoids act as chemotactic agents, triggering an influx of lymphoid and myeloid cells from the blood to sites of infection/inflammation in conjunction with cytokines and chemokines (Moser et al. 2004). 2-AG can attract immune cells in vitro (Klein 2005) and induce migration of myeloid leukaemic cells, which overexpress CB2R (Jordà et al. 2004).

Microglia also produce 2-AG and AEA. 2-AG is found at 200-fold higher concentrations in brain tissue during neuronal damage and neuroinflammation, being produced in response to intracellular Ca^{2+} and stimulation of glutamate receptors. 2-AG is produced by microglia and astrocytes in response to ATP released by injured neurons, by stimulation of purinergic receptors (Pandey et al. 2009). In turn, released 2-AG stimulates microglial proliferation via CB2R (Carrier et al. 2004).

Cannabinoids in inflammation and stress

CBs exert their immune modulating properties in five main ways: inhibition of cell proliferation, inhibition of cytokine and chemokine production, inhibition of bone marrow-derived myeloid cell recruitment, induction of regulatory T cells and induction of apoptosis.

CB can increase the production of TNF, IL-1, IL-6 and IL-10 when administered alone or together with bacteria or other antigens (Klein et al. 1993). In mice primed by *Corynebacterium parvum* and injected with LPS, then treated with the synthetic CB HU-210, TNF and IL-12 were decreased in serum, while IL-10 was increased, probably protecting against the lethal effects of LPS (Smith et al. 2000). In rats with closed head injury, treatment with CB HU-211 was followed by suppression of TNF production in the brain, independently of CBR, but acting via NMDA receptors, thereby preventing excitotoxicity and neuronal death (Shohami et al. 1997). Recently, protective effects of CBD in a rat model of cardiac ischaemia were also described (Walsh et al. 2010).

CB2R-dependent inhibition of rolling and adhesion of venous leukocytes (Ni et al. 2004) may result from the inhibition of IFN-γ, a cytokine that facilitates transendothelial cell trafficking (Klein 2005).

A simplistic view of the therapeutic implications may assume that compounds that function either by binding CB2R or by CBR-independent mechanisms would be of benefit as anti-inflammatory drugs, since CB1R-related psychoactive side effects would be bypassed. However, this view would imply that: psychoactive effects of CB are strictly CB1R mediated; CBR-independent effects are necessarily positive [this is not always the case, for example, CB can inhibit mitochondrial function with potentially negative consequences (Athanasiou et al. 2007a)]; and CBR-dependent and independent effects occur at similar concentrations of CB. Nevertheless, the selective suppression of Th1 and possibly Th17 immunity by CB drugs supports their potential use in the treatment of chronic inflammatory diseases.

Another way of alleviating inflammation is apoptosis. Damage to membranes releases endocannabinoids that transmit stress signals via redox modulation (Rieder et al. 2010; Nunn et al. 2010). CB may protect or induce apoptosis of individual cells, depending on disposability. At certain concentrations, CB may induce apoptosis in immune cells, and thus have a beneficial effect when there is a need for immune modulation (Rieder et al. 2010). In conditions where disease is caused by activated immune cells, like MS, lupus, arthritis or septic shock, targeting immune cells via CB2R agonists may trigger apoptosis and anti-inflammatory effects (Rieder et al. 2010). In other instances, e.g. in patients with breast cancer in which CBR may not be expressed by the cancer cells, CB may worsen the disease, since the immune system is weakened and the breast cancer cells are resistant to CB-induced apoptosis (Rieder et al. 2010).

The endocannabinoid system can interact with the immune system via the HPA axis (Tasker 2004). Endogenous CB signalling is essential for stress adaptation, and differential regulation of AEA and 2-AG are associated with distinct HPA axis habituation (Hill et al. 2010). CB signalling constrains HPA axis activity, facilitates adaptation or habituation of the HPA axis and behavioural responses to stress, reduces anxiety- and depressive-like behaviour and mediates analgesic responses to stress (Patel et al. 2004; Finn 2010). Lack of CB1R causes HPA axis dysregulation and exacerbates stress-induced excitotoxic and neuroinflammatory responses (Zoppi et al. 2010). Stress-induced suppression of endocannabinoid signalling in amygdala contributes to HPA axis activation (Hill et al. 2009).

The endocannabinoid system modulates the function of all of the major types of immune cells. These cells release chemokines and cytokines, which directly modulate the HPA axis (Jara et al. 2006). Several studies demonstrate a role for the endocannabinoid system in regulating cytokine responses to immune stress in vivo (Smith et al. 2000,

2001; Roche et al. 2006). It has, therefore, been hypothesized that modulation of cytokine signalling may mediate both the effects of endocannabinoids on HPA axis and behavioural reactions to stress (e.g. anxiety, despair, analgesia) (Finn 2010). This mechanism may be added to modulation of classical neurotransmitters or neuropeptides and has been suggested for other psychotropic drugs like antidepressants (Leonard 2006; Griebel et al. 2005). Supporting this idea, CB2R has been linked to psycho-behavioural conditions such as anxiety, depression and stress (Onaivi et al. 2006b, 2008).

Neural and immune effects of cannabinoids in the CNS

In the brain, the expression of CBR or of enzymes controlling endocannabinoid levels undergo time and brain region-specific changes during neurodegenerative and neuroinflammatory disorders. Endocannabinoids may play a modulating role between neurogenesis and neurodegeneration, via the immune system or independent pathways (Wolf and Ullrich 2008b). Most studies support the notion that endocannabinoids are neuroprotective and that a loss of this neuroprotective tonic activity facilitates neurodegeneration.

Neural progenitor cell proliferation and differentiation is reduced in conditions associated with brain inflammation (Rossi et al. 2010). Conversely, newly formed neurons may survive despite chronic inflammation and even specifically arise within an inflammatory environment. Brain CB might regulate neurogenesis. (Wolf and Ullrich 2008a). For example, the endocannabinoid system may induce neural stem cell proliferation via a TNF pathway (Rubio-Araiz et al. 2008). Therefore, in MS and other neurodegenerative diseases, neuroinflammation may be targeted by therapeutic approaches involving CB. For example, in Parkinson's disease (PD), CB might provide protection against the progression of neuronal injury and influence local inflammatory events associated with the characteristic pathology (Lastres-Becker and Fernández-Ruiz 2006). In Alzheimer's disease (AD), CB2R expression is strongly up-regulated, particularly in the microglial cells surrounding beta-amyloid plaques (Ramirez et al. 2005). Most of the studies in AD suggest that changes in endocannabinoid system are induced by the inflammatory CNS environment. CB2R activation is an attempt to halt microglial activation, but this innate compensation is insufficient to prevent the inflammatory damage to neurons, which may also be more vulnerable due to CB1R down-regulation. Some data demonstrate that CB stimuli may have therapeutic benefit by augmenting the brain's innate response (Scotter et al. 2010).

The discussion above is based upon the assumption that endocannabinoids are by nature protective. This may be an oversimplification. Novel CB neuroprotective drugs that show a promising profile in experimental animals have not produced breakthroughs in clinical settings. There are several explanations for this paradox. For acute conditions like stroke, the window of opportunity for CB treatment may be missed. In chronic conditions like AD, an important determinant of clinical outcome is the degree to which the target receptors are functional. In AD, impaired G protein signalling can reduce the efficacy of compounds targeting GPCR (Rossi et al. 2010). Moreover, CB may also be neurotoxic. For example, CB1R activation may have neurodegenerative, apoptotic effects in neurons by activating JNK and caspase-3, and increasing Bax expression (Downer et al. 2003). In vivo data show that neuroprotective and harmful effects of endocannabinoid system manipulation are difficult to separate and often coexist. While direct or indirect activation of CB1R on glutamatergic nerve terminals decreases excitotoxicity, direct or indirect activation of CB1R on GABAergic nerve terminals can decrease GABA release and inhibitory signalling in pathological excitotoxic conditions (Rossi et al. 2010). Moreover, effects due to the blockade of endocannabinoid metabolism via CBR-independent mechanisms by increased levels of AEA can be both detrimental (via TRPV1) and beneficial (via PPARα). As already mentioned, CB can influence mitochondrial metabolism, promoting apoptosis (Rossi et al. 2010). This can be beneficial or harmful, depending on the context. Also, selective activation of CB2R to target inflammatory processes may be beneficial, but strictly related to a time window for treatment (Rossi et al. 2010).

The context-dependent effects of CB have different consequences on immune interactions. Endogenous CBs are released following various types of injury to the brain. The "immune economy" is different depending on the type of injury (Tanasescu and Constantinescu 2010). Immune effects of CB will be different for inflammation, stroke or infections, making it more difficult to predict the net impact of CBR activation on complex pathological events.

Cannabinoids and pathological conditions involving immune system

Multiple sclerosis

MS is a neuroinflammatory and neurodegenerative disease. Although primarily used for the control of symptoms such as spasticity, pain or bladder dysfunction, CBs have the potential to exert immunomodulatory and neuroprotective effects in MS. EAE is a CD4 + T lymphocyte-mediated autoimmune disease that serves as an animal model of MS (Constantinescu et al. 2011). Effects of CB in EAE have

recently been reviewed (Kubajewska and Constantinescu 2010). CB may regulate Toll-like receptor signalling and IFN-β expression leading to protection from inflammatory demyelination in EAE (Downer et al. 2011). Interestingly, immune cells from MS patients may be more susceptible to cannabinoid-induced potentiation of IFN-β expression (Downer et al. 2011). Moreover, immunomodulation by CB was associated with reduced myelin-specific T-cell responses and reduced clinical disease (Croxford et al. 2008). This implies indirect mechanisms by CB1R nerve signalling pathways controlling the systemic release of immunomodulatory molecules, and direct actions by CB2R-mediated inhibition of immune cells (Baker et al. 2007). However, the practical relevance of these actions is unclear, since these effects only occur at high doses. On the other hand, the expression of both CBR and its up-regulation by inflammatory cytokines on immune cells may be higher in MS than in EAE, and thus immunomodulatory effects of CB at therapeutic doses are not excluded. Moreover, it is suggested that lower doses of CB, can slow the accumulation of axonal loss and disability, acting on the glial response implicated in the neurodegenerative component of the disease. Evidence exists for the presence of functional cannabinoid receptors (CB1 and CB2 receptors) in both adult oligodendrocytes and in oligodendrocyte progenitor cells, promoting their survival (Molina-Holgado et al. 2002). Also, potentiation of the endogenous CB signalling could be a substitute to the use of exogenously administered CB (Loría et al. 2008). This may involve interleukin-1 receptor antagonist (a naturally occurring antagonist for the inflammatory actions of IL-1 beta in the brain) as the critical mediator for the neuroprotective and anti-inflammatory actions of the endocannabinoid system in the CNS (Molina-Holgado et al. 2003).

CB may have different effects depending on the phase of the disease. Very recently, it was shown that D9THC, CBD and non-psychoactive flavonoids from *Cannabis sativa* may exert heterogeneous effects on chronic relapsing EAE-induced motor deficits, depending on the type of the extract and the moment of administration (Buccellato et al. 2011).

Therefore, CB can influence both pathological aspects of MS, neuroinflammation and neurodegeneration. CB2R activation can exert an anti-inflammatory effect by inhibiting the production of proinflammatory cytokines in microglial cells and by directly suppressing T-cell effectors. CB1R-mediated immunomodulatory effects, as well as CB2R-mediated neurobiological effects, are also possible. The stimulation of CB1R located on presynaptic glutamatergic terminals leads to inhibition of glutamate release, limiting excitotoxic damage and thus exerting a direct neuroprotective effect (Rossi et al. 2010). A role for postsynaptic CB1R signalling cannot be ruled out, since CB1R activation blocks the TNFα-induced increase in surface AMPA receptors and protects hippocampal neurons from excitotoxicity (Zhao et al. 2010). Moreover, pharmacological inhibition of endocannabinoid uptake can protect against AMPA-induced excitotoxicity by enhancing endocannabinoid levels and activating CBR and PPARγ (Loría et al. 2010). Other anti-neurodegenerative actions of CB can target mitochondrial dysfunction and Ca^{++} dysregulation occurring under pathological conditions (Ryan et al. 2009). Moreover, CBs allow initiation of repair mechanisms and synaptic plasticity (Hashimotodani et al. 2007; Kano et al. 2009).

The endocannabinoid system is altered in MS, but the results of studies on these changes are contradictory. CB ligands were found to have either increased or decreased levels. We found altered endocannabinoid levels in the blood of MS patients, differing between MS subtypes or when compared with normals (Jean-Gilles et al. 2009). Selective glial expression of CBR and FAAH is induced in MS, thus supporting a role for the endocannabinoid system in the pathogenesis and/or evolution of this disease (Benito et al. 2007).

Atherosclerosis

Increasing evidence suggests that endocannabinoid signalling plays a critical role in atherogenesis. CB2R activation by D9-THC inhibits atherosclerotic plaque progression in mice by inhibiting macrophage recruitment, and AEA inhibits inflammatory gene expression in endothelial cells and consequently monocyte adhesion (Mach and Steffens 2008). CB2R may influence atherosclerosis by modulating lesional macrophage apoptosis (Freeman-Anderson et al. 2008). Endocannabinoids may also mediate pro-atherosclerotic effects by inducing platelet activation (Mach and Steffens 2008). Recently, it was demonstrated that 2-AG, PEA and OAE levels were altered in the aorta and visceral adipose tissue in a mouse model of atherosclerosis (Montecucco et al. 2009). The increase of endocannabinoids in the atherosclerotic plaque may provide a molecular mechanism for the plaque reducing effect of a CB1R antagonist reported in another model of atherosclerosis (Dol-Gleizes et al. 2009).

Rheumatic disease

CBR have become therapeutic targets for 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 of the articular CB system. In an experimental model of arthritis, CBD had anti-arthritis effects (Malfait et al. 2000a) and in patients with RA the drug combination of D9-THC and CBD reduced disease activity (Blake et al. 2006). Non-

steroidal anti-inflammatory drugs (NSAIDs), which inhibit cyclooxygenase, inhibit FAAH, thus interfering with the degradation of endocannabinoids (Fowler et al. 2003). CB1R and CB2R, AEA 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). CB1R and TRPV-1 seem to be important targets in controlling OA pain (Schuelert and McDougall 2008). The attenuation of CB2R-mediated vasodilatation in acutely and chronically inflamed rat joints suggests an alteration in CB2R expression or sensitivity following an arthritic insult (McDougall et al. 2008).

Ajulemic acid has several effects that make it attractive for future therapies in RA, systemic lupus erythematosus and osteoporosis. It suppresses 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).

Inflammatory bowel disease (IBD)

Studies show that endocannabinoid signalling is increased in the inflamed intestine (Izzo and Sharkey 2010). Current data highlight the importance of both CBR in modulating inflammatory processes: CB1R promotes epithelial wound healing (Wright et al. 2005) and CB2R inhibits IL-8 release in human colonic epithelial cells (Ihenetu et al. 2003). Endocannabinoids may limit intestinal inflammation via CBR, as shown in rodent models of IBD (Smid 2008). Genetic ablation of CBR or treatment with a CBR antagonist rendered mice more sensitive to induced colitis (Massa et al. 2004), and CBR agonists reduced experimental intestinal inflammation (Storr et al. 2008). Moreover, FAAH-deficient mice, which have higher levels of AEA, showed significant protection against intestinal inflammation (Massa et al. 2004). The CB effect on gastrointestinal motility in sepsis has recently been reviewed (De ?tul?> Winter and De Man 2010). Both CBR play a role in motility in inflammatory conditions (Izzo and Sharkey 2010). Septic ileus in mice is associated with up-regulation of intestinal CB1R but not CB2R. CBD decreases LPS-induced motility disturbances in vivo (De Filippis et al. 2008b). More recently, it was shown that CBD treatment abrogates LPS-induced sepsis and the associated hyperactivation of glial cells, MC, and macrophages and TNF expression in the intestine (De Filippis et al. 2009).

In summary, the endocannabinoid system mediates protective effects in the inflamed gut, via CB1R and/or CB2R activation through suppression of inflammatory mediators, intestinal motility and diarrhoea, and attenuation of visceral sensitivity (Izzo and Camilleri 2009).

Transplantation

CB may suppress the T-cell-mediated immune response against engrafted organs. Data on tolerance to allografts in $FAAH^{-/-}$ mice on levels of endocannabinoid modulation during allograft rejection and endocannabinoid roles in the function of endothelial cells at allograft sites will soon help clarify the involvement of the endocannabinoid system in allograft rejection (Nagarkatti et al. 2010).

Diabetes and lipid metabolism

In diabetes, CB may protect against islet destruction by suppressing insulitis and IFN-γ, TNFα and IL-12 mRNA expression (Li et al. 2001); CBs may also treat neuropathic pain in diabetic patients, mainly via the CB2R pathway (Toth et al. 2010). Rimonabant (SR141716), the CB1R-selective inverse agonist, can inhibit adipocyte function and was used in the treatment of obesity. However, it has psychiatric side effects (Van Diepen et al. 2008).

Liver disease

Exogenous or endogenous CB, targeting CBR and the use of FAAH inhibitors, may become therapeutic modalities for immune-mediated liver inflammation (Hegde et al. 2008), hepatic fibrosis and hepatic neoplastic disease (Izzo and Camilleri 2008). In murine ConA-induced hepatitis, D9-THC induces apoptosis in effector T cells, up-regulates Treg function and suppresses inflammatory cytokines, thus preventing T-cell-mediated liver injury. AEA ameliorates ConA-induced hepatitis, while FAAH reduction increases resistance to the disease (Hegde et al. 2008).

Allergic asthma

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

In conclusion, the complexity of global CB actions and relations with the immune system is far more than the simplified paradigm of immunosuppression and CBR separation in ‘brain versus immune’. Advances in the understanding of the interplay between this non-conventional neurotransmitter system and the immune network may provide the basis for future treatments for conditions insufficiently alleviated by current therapies.

Conflict of interest The authors declare that they have no conflict of interest.

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