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The Role of Cannabinoids in Allergic Diseases: Collegium Internationale Allergologicum (CIA) Update 2020

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Keywords
Cannabinoids · Cannabinoid receptors · Allergy · Asthma · Atopic dermatitis · Immunosuppression · Immunomodulation

Abstract
The human endocannabinoid system (ECS) is a complex signalling network involved in many key physiological processes. The ECS includes the cannabinoid receptors, the endocannabinoid ligands, and the enzymes related to their synthesis and degradation. Other cannabinoids encompass the phytocannabinoids from *Cannabis sativa* L. (marijuana) and the synthetic cannabinoids. Alterations in the ECS are associated with different diseases, including inflammatory and immune-mediated disorders such as allergy. Allergy is a global health problem of increasing prevalence with high socioeconomic impact. Different studies have convincingly demonstrated that cannabinoids play a role in allergy, but their actual contribution is still controversial. It has been shown that cannabinoids exert anti-inflammatory properties in the airways and the skin of allergic patients. Other studies reported that cannabinoids might exacerbate asthma and atopic dermatitis mainly depending on CB2-mediated signalling pathways. A better understanding of the molecular mechanisms involved in the mode of action of specific cannabinoids and cannabinoid receptors on relevant immune cells under different biological contexts might well contribute to the design of novel strategies for the prevention and treatment of allergic diseases. Future research in this promising emerging field in the context of allergy is warranted for the upcoming years.
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Introduction

The cannabis plant *Cannabis sativa* L. (marijuana) has been used for both therapeutic and recreational effects for many centuries. However, the purification and the chemical characterization of its unique active components, the so-called cannabinoids, were not carried out until the 1960s [1]. In the early 1990s, specific cannabinoid receptors (CBRs) were cloned and their endogenous ligands were characterized, uncovering the mechanism of action

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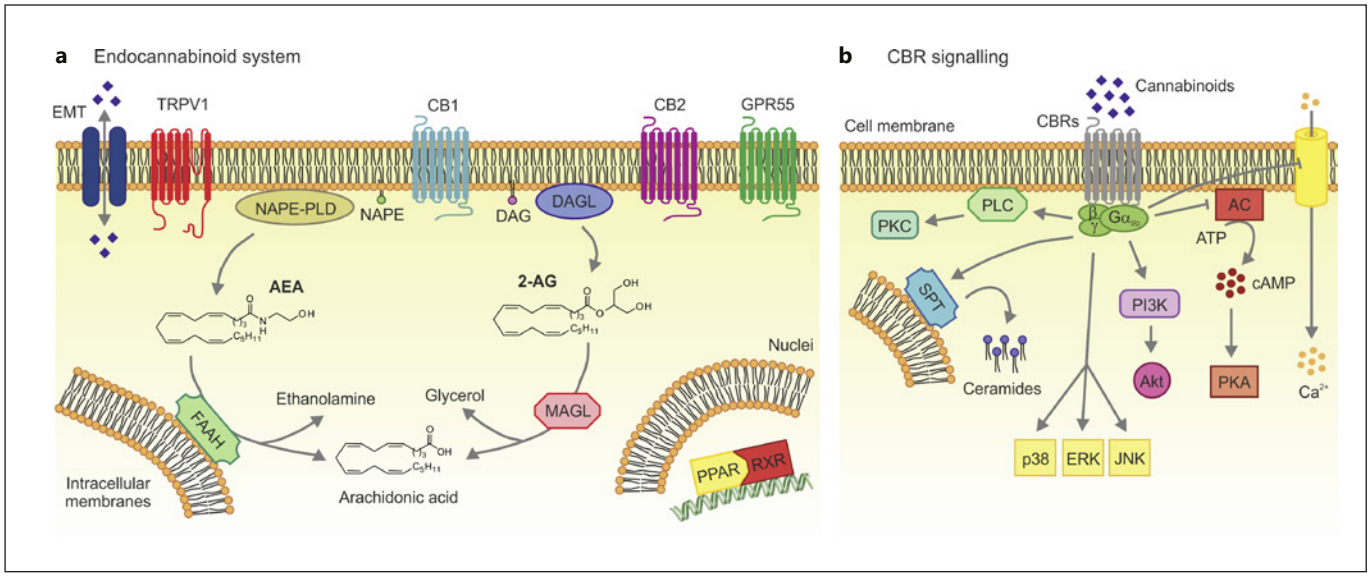

Fig. 1. a Main components of the endocannabinoid system (ECS). Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are synthesized on demand from membrane lipids by *N*-acyl-phosphatidylethanolamine-hydrolysing phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL), respectively. AEA and 2-AG move across the cell membrane through a purported endocannabinoid membrane transporter (EMT). Cannabinoid receptor 1 (CB1), cannabinoid receptor 2 (CB2), transient receptor potential vanilloid 1 (TRPV1), G-protein-coupled receptor 55 (GPR55), and PPARs are the main receptor targets of AEA and 2-AG. AEA and 2-AG are hydrolysed by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively, releasing arachidonic acid. **b** Cannabinoid receptor (CBR)-induced signalling. After cannabinoid binding, CBRs signal several cellular pathways including inhibition of protein kinase A (PKA) pathway, activation of mitogen-activated protein kinase cascades (p38, JNK, and ERK), activation of protein kinase B (Akt) pathway, inhibition of calcium channels, activation of protein kinase C (PKC), and generation of ceramides.

of cannabinoids [2, 3]. These findings boosted basic and clinical research to better understand the molecular pathways involved in the mode of action of cannabinoids and to explore potential novel therapeutic applications. The human endocannabinoid system (ECS) encompasses the CBRs, the endocannabinoid ligands, and the group of enzymes responsible for their synthesis, transport, and degradation [4]. The ECS is involved in a large number of vital physiological processes in the body, such as the control of neuronal activity, energy metabolism, cardiovascular tone, and immunity. Alterations in the ECS have been associated with different diseases, including inflammatory and immune-mediated disorders, which suggests the ECS components as promising novel therapeutic targets [5, 6]. Cannabinoids regulate immune responses by promoting anti-inflammatory properties in brain injury, inflammatory bowel diseases, sepsis, multiple sclerosis, airway inflammation, and allergy [7].

Allergy represents a global health problem of increasing prevalence, affecting almost one billion patients worldwide. The main clinical manifestations of allergy include allergic rhinitis, allergic asthma, atopic dermatitis (AD) and other skin diseases, food allergy, and anaphylaxis. Allergic diseases can be generally considered as type 2-mediated diseases characterized by the production of high levels of IgE against innocuous substances called allergens [8, 9]. Allergic disorders significantly affect patients' quality of life, decrease productivity at work, and enhance sanitary costs of health care systems, thus representing a significant health problem with high socio-economic impact [10, 11]. Therapeutic strategies that not only treat allergic symptoms but also might prevent or modify the course of the disease are highly demanded. Currently, allergen-specific immunotherapy (AIT) remains as the only treatment with potential long-term disease-modifying capacity for allergic disorders [12, 13]. AIT consists of the administration of high doses of the causative allergens to induce a state of permanent tolerance upon treatment discontinuation. AIT is a successful treatment strategy for many patients, but it displays some important drawbacks related to efficacy, safety, and duration. Therefore, the design and development of novel therapeutic approaches for the prevention and treatment of allergic diseases is fully demanded.

Several studies have demonstrated the participation of the ECS in the development and maintenance of allergic

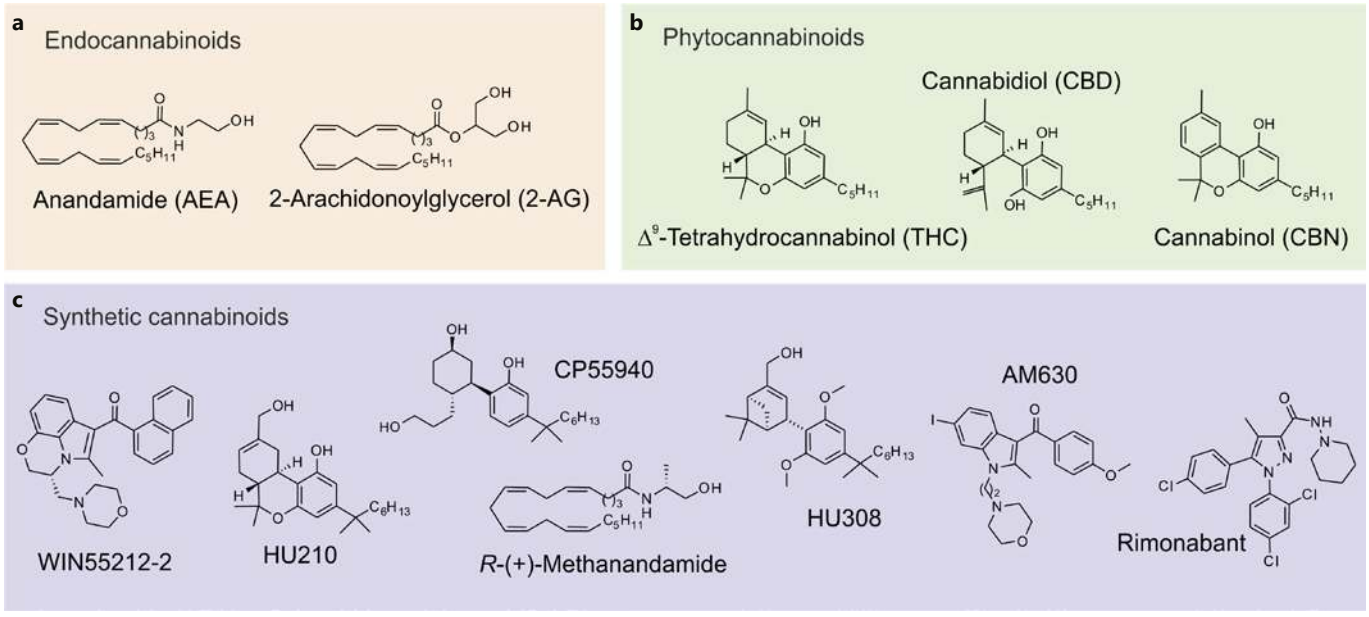

Fig. 2. Cannabinoid ligands. **a** Endocannabinoids. **b** Plant-derived cannabinoids or phytocannabinoids. **c** Synthetic cannabinoid including non-selective agonists, CB1- and CB2-selective agonists, and CB1- and CB2-selective antagonists.

diseases, but the data related to the actual role of cannabinoids in allergy are still controversial. The capacity of the ECS to suppress inflammation in mouse models of allergen-induced airway inflammation, AD, and contact allergy has been well documented [14, 15]. In contrast, other studies have shown that CBR 2 (CB2)-mediated signalling contributes to the exacerbation of asthma and AD [16, 17]. Future basic and clinical research will help to delineate the detailed molecular mechanisms by which cannabinoids might exert their functions on different immune cells in the context of allergy as well as their potential clinical implications. The development of novel chemical probes is enabling a better understanding of these pathways, which will be of outmost value to firmly confirm how cannabinoids can modulate allergic responses. In this article, we will comprehensively review our current knowledge on the role played by the ECS and the potential therapeutic applications of cannabinoid-based drugs in the context of the main allergic diseases.

The Human ECS

The human ECS is a complex and essential signalling pathway involved in many physiological processes. The ECS is involved in the control of many relevant physiological processes such as neuronal development, brain plasticity, learning and memory, regulation of appetite, stress and emotions, proliferation, differentiation, cell survival, metabolism, and immunity. Alterations in the ECS have been associated with a plethora of diseases, and preclinical and clinical studies have indicated cannabinoids as novel potential therapeutic tools in cancer, neurological, inflammatory, and immune-mediated diseases [6, 18, 19]. The main components of the ECS include the endocannabinoid ligands, the enzymes related to their synthesis and degradation, and the CBRs (Fig. 1).

Endocannabinoids are lipid-derived signalling molecules that are endogenously synthesized and can bind and activate CBRs. Anandamide (arachidonoylethanolamide, AEA) and 2-arachidonoylglycerol (2-AG) are the most widely investigated. However, other biochemically and structurally related endocannabinoids such as *N*-palmitoylethanolamine (PEA), 2-arachidonoylglyceryl ether (noladin ether, 2-AGE), O-arachidonoylethanolamine (virodhamine), and N-arachidonoyldopamine (NADA) have also been recognised [20]. AEA is a high-affinity partial agonist of the G-protein-coupled receptors (GPCRs) CBR 1 (CB1) and a low-affinity ligand of the GPCR CB2, whereas 2-AG acts as a full agonist with moderate affinity for both CBRs [20, 21]. AEA and 2-AG can also interact with other receptors or ion channels, including

different GPCRs, peroxisome proliferator-activated receptors (PPARs), and transient receptor potential channels (TRPVs) [22]. Other cannabinoid compounds encompass the phytocannabinoids derived from the plant *Cannabis sativa* L. (marijuana) and the synthetic cannabinoids (Fig. 2). The most abundant and well-characterized phytocannabinoid is Δ^9-tetrahydrocannabinol (THC), which was isolated and structurally characterized in the 1960s [1]. THC is the major psychoactive component of marijuana and exerts a wide variety of biological effects by activation of CB1 and CB2 [23]. The potential therapeutic effects of THC have been studied in several diseases, including cancer, multiple sclerosis, epilepsy, Alzheimer disease, Parkinson disease, and pain treatment [23]. Currently, THC and its synthetic analogue nabilone (Marinol and Cesamet, respectively) are approved for inhibiting chemotherapy-induced nausea and vomiting [6]. Cannabidiol (CBD) and cannabinol (CBN) are other plant-derived cannabinoids produced in significant amounts. CBD is the main non-psychoactive phytocannabinoid and its therapeutic interest is due to its analgesic, antipsychotic, antioxidant, and anti-inflammatory properties [24]. A mixture of equal doses of THC and CBD, known as Sativex, is marketed for the treatment of spasticity in patients with multiple sclerosis [6, 24]. Since the identification of the ECS, a large number of synthetic cannabinoids have been developed in order to mimic some of the beneficial properties of THC, while avoiding its negative effects. They include agonists with similar affinity for CB1 and CB2 but greater potency than THC, such as WIN55212-2 (from the aminoalkylindole family), HU210 (synthesized at the Hebrew University; HU series), and CP55940. Compounds with specific selectivity have also been described: R(+)-methanandamide (CB1-selective agonist) and HU308 (CB2-selective agonist). In addition, selective antagonists have been generated such as Rimonabant and AM630, CB1- and CB2-selective antagonists, respectively [25, 26] (Fig. 2). Numerous cannabinoids, including phytocannabinoids and synthetic cannabinoids, have been included in clinical trials [5].

Endocannabinoids are synthesized and released on demand from membrane precursors, but it is suggested that they could also be accumulated in storage organelles within the cell [27, 28]. As shown in Figure 1, synthesis of AEA starts with the hydrolysis of *N*-acyl-phosphatidylethanolamine (NAPE) by NAPE-hydrolysing phospholipase D (NAPE-PLD). Alternative pathways involving other NAPE phospholipases and enzymes are also described [4, 28]. The synthesis of 2-AG consists of the sequential hydrolysis of arachidonoyl-containing phosphatidylinositol 4,5-bisphosphate by phospholipase C (PLC) followed by hydrolysis of the resulting diacylglycerol by diacylglycerol lipase (DAGL) [4]. Endocannabinoids are rapidly inactivated by a two-step process: cellular uptake and intracellular hydrolysis. Cellular uptake of endocannabinoids from extracellular space is mediated by putative endocannabinoid membrane transporters, the existence of which is only based on indirect evidence as it has not been cloned yet [29]. Degradation of AEA is mediated by the fatty acid amide hydrolase (FAAH), whereas the degradation of 2-AG is primarily due to monoacylglycerol lipase (MAGL). The resulting products of AEA and 2-AG degradation are arachidonic acid, which is required for prostaglandin synthesis, and ethanolamine and glycerol, respectively [4] (Fig. 1). FAAH and MAGL represent promising therapeutic targets for the treatment of different disorders, and pharmacological inhibitors have been developed. Pharmacological or genetic inhibition of FAAH and MAGL increases AEA and 2-AG levels, prolonging their anti-inflammatory and analgesic effects via CBRs [30]. Remarkably, FAAH and MAGL inhibition also reduces arachidonic acid, a key precursor of pro-inflammatory prostaglandins and thromboxanes. FAAH and MAGL inhibitors may have a large number of therapeutic applications, including pain, nausea, neurodegenerative pathologies, inflammation, metabolic disorders, and cancer [31, 32].

The effects of endocannabinoids are mainly mediated by CB1 and CB2 but other receptors acting as CBRs have been proposed. CB1 and CB2 share 44% sequence identity [3]. Both receptors consist of a single polypeptide chain with 7 transmembrane α-helices inserted in the cell membrane, as well as an extracellular N-terminus and intracellular C-terminus domain. Their high-resolution crystal structure in humans has been recently reported [33–35]. CB1 and CB2 are generally coupled to inhibitory $G\alpha_{i/o}$ proteins, thus inhibiting adenylate cyclase and the conversion of ATP to cyclic AMP and protein kinase A activation, a positive regulatory signalling pathway of immune response. CB1 can also activate adenylate cyclase through $G\alpha_s$ protein stimulation [36]. Gβγ subunits coupled to CBRs activate mitogen-activated protein kinases (MAPKs) and protein kinase B (Akt) with important consequences in the maintenance of cellular homeostasis. Other CBR-mediated signalling pathways include modulation of ion channels, ceramide biosynthesis, and activation of PLCβ (Fig. 1) [37, 38]. CB1 is highly expressed in the central nervous system (CNS) where it regulates diverse neuronal functions and behaviours. Far from being restricted to the CNS, CB1 expression is also observed in

peripheral tissues including immune cells, liver, pancreas, skeletal muscle, and peripheral nervous system, where it has been implicated in other key physiologic processes such us control of immunity, metabolism, etc. [6]. For a long time it was thought that CB2 was only expressed in peripheral immune system cells, but it has been shown that CB2 is also expressed in different cell subsets in the CNS, muscle, pancreas, intestine, and testis [39, 40]. Interestingly, CB1 and CB2 expression can be increased in pathologic or injury conditions. CB1 is significantly increased in murine models of colitis inflammation or lipopolysaccharide-stimulated macrophages [41, 42]. CB1 gene expression is also increased in human immune system cells from patients with allergic diseases [43]. CB2 expression is upregulated in chronic inflammation of the immune system, as well as in brain injury [44, 45].

Other receptors including orphan GPCRs (GPR55, GPR19), TRPV1, and PPARs are also involved in the cannabinoid-induced signalling pathways. GPR55 was initially described as a putative "CB3," but the low sequence similarity with conventional CBRs does not fully endorse this concept [46, 47]. GPR55 is widely expressed in the immune system, CNS, and peripheral tissues [47]. It is coupled to Gα12/13, signalling through RhoA and controlling several physiological processes [48]. Unlike CB1 and CB2 that mainly trigger inhibitory effects, GPR55 mostly exerts excitatory and stimulatory effects [49, 50]. AEA, 2-AG, THC, and HU210 have been described as GPR55 ligands [51]. Other orphan GPCRs such as GPR18, GPR19, and GPR110 have also been described as cannabinoid targets [5]. TRPV1, also known as capsaicin receptor, is a non-selective channel expressed in the CNS and periphery tissues, including liver, skin, intestine, and immune system cells. Upon activation, the pore allows the flux of ions across the membrane. TRPV1 can be activated by heat, capsaicin, arachidonic acid derivatives, protons, and cannabinoids [52]. AEA shows a similar affinity for TRPV1 as capsaicin, but less potency [53]. CBD has also been described as TRPV1 activator, whereas THC does not modulate this channel [22, 54]. Some synthetic cannabinoids such as WIN55212-2 or AM1241 are also TRPV1 ligands [22]. Several studies demonstrated the activation of PPARs by some cannabinoids [55, 56]. PPARs are nuclear hormone receptors with 3 isoforms (α, β, and γ) highly expressed on metabolically active tissues. Upon ligand binding, PPARs heterodimerize with retinoic acid receptor and bind to the PPAR response element DNA sequences, regulating the transcription of genes involved in metabolism, cell differentiation, and inflammation [57]. AEA and 2-AG bind and activate both PPARα and PPARγ, and phytocannabinoids can mainly bind to PPARγ. Although the detailed mechanisms of cannabinoid-PPAR interaction are not clear, activation of PPARs by cannabinoids exerts anti-inflammatory and neuroprotective effects in several disease models [58, 59].

The ECS and the Immune System

The ECS play an important role in the regulation of both innate and adaptive immune responses. Immune cells are not only influenced by cannabinoids, but also produce and secrete endocannabinoids themselves, which in turn modulates the functional features of immune cells [60]. CB2 is the most expressed CBR in immune cells and its activation usually mediates immunosuppressive responses, but other CBRs such as CB1, GPR55, and PPARs are also involved in immune cell regulation. In a broad perspective, the anti-inflammatory effects of cannabinoids are a consequence of some specific effects on immune cells such as their capacity to modulate cytokine production, cell migration, T-cell responses, cell proliferation, and apoptosis [7, 60].

Regulation of Immune Cells by Cannabinoids

AEA, 2-AG, THC, and CBD control macrophage function by inhibiting cytokine production, nitric oxide release, and phagocytosis [61–63]. In human monocyte-derived dendritic cells (DCs), the expression of all the components of the ECS has been described [64] and several inflammatory models showed the capacity of cannabinoids to modulate DC function. AEA and THC inhibit pro-inflammatory cytokine production and the capacity of DCs to polarize Th1 and Th17 responses [65–67]. THC induces apoptosis in murine DCs, providing a potential immunosuppression mechanism of immune cells [68].

The contribution of ECS signalling in the regulation of neutrophils and natural killer (NK) cell function is still controversial. Neutrophils express low levels of CBRs, but the lack of CB2 enhances their migration [69, 70]. In contrast, 2-AG induces neutrophil activation and the release of antimicrobial mediators [71]. NK cells express high levels of CB1, CB2, and GPR55, but controversial results are reported. THC treatment impairs the cytolytic activity of NK cells [72], but GPR55 activation induces the release of cytokines and cytolytic activity [49]. Although there is scarce data about the effect of cannabinoids on eosinophils, AEA inhibits the activation, maturation, and degranulation of mast cells [73]. Mice lacking CB2 display a low number of type 2 innate lymphoid cells (ILC2s),

Table 1. Main effects of cannabinoids in immune cells

Cell type	CBR expression	Role of cannabinoid ligands
Monocytes/ macrophages	CB1 and CB2 [184, 185]	AEA, 2-AG, THC, and CBD inhibit cytokine production [61, 81, 186, 187] AEA and PEA stimulate phagocytosis [188, 189] 2-AG, THC, and WIN55212-2 modulate ROS production [187, 190] CBD induces apoptosis [191]
Dendritic cells (DCs)	CB1 and CB2 [43, 64]	AEA, THC, JWH-015, and JWH-133 inhibit inflammatory cytokine production [65, 66] AEA and THC inhibit the capacity to induce Th1 and Th17 responses [65, 67] THC induces apoptosis [68] THC impairs human monocyte-derived DC differentiation [192]
Neutrophils	CB1 and CB2 [70, 193]	AEA, CBD, and CB2 signalling reduce cell migration [69, 70] AEA and 2-AG induce cell activation and the release of antimicrobial effectors [70, 71, 194]
NK cells	CB1 and CB2 [60]	2-AG and THC inhibit cytolytic activity [72, 74] CB2 signalling reduces cell migration [74] O-1602 induces high cytolytic activity and cytokine production [49]
Eosinophils	CB1 and CB2 [195]	2-AG increases cell recruitment [195, 196] WIN55212-2 reduces cell recruitment [197]
Mast cells	CB1 and CB2 [73, 103, 198]	AEA and AEA-derived compounds inhibit cell maturation and degranulation [73, 141, 199] AM251 induces cell maturation and degranulation [103]
Innate lymphoid cells (ILCs)	CB2 [200]	CBD promotes ILC2 induction [200] CB2 signalling induces high numbers of ILC2 [74]
T lymphocytes	CB1 and CB2 [76, 201]	AEA, THC and JWH-133 inhibit T-cell proliferation [201–203] AEA and THC supress T-cell responses [201] CBD and JTE907 induce functional Treg generation [77, 204] HU210 and HU308 inhibit cytokine production [76]
B cells	CB1 and CB2 [76, 205]	THC and WI55212-2 increase B-cell proliferation [206] CP55940 induces IgE class switching [207] CB2 signalling promotes B-cell retention in bone marrow or splenic marginal zones [78, 79]

suggesting the role of CB2 signalling in the induction of ILC2s [74].

Cannabinoids mainly suppress adaptive T-cell responses by inhibiting proliferation and cytokine production [75, 76]. CBD has been shown to induce tolerogenic responses by favouring the generation of regulatory T (Treg) cells [77]. B cells express the highest levels of CB2, which is essential for mouse B-cell subset formation and for retention of immature B cells in bone marrow and splenic marginal zones [78, 79]. A more detailed summary of the main effects of cannabinoids on the different immune cells is presented in Table 1.

Anti-Inflammatory Mechanisms of Cannabinoids

Compelling experimental evidence supports that cannabinoids exert powerful anti-inflammatory effects on immune cells, but the mechanisms by which they exert such effects need to be better understood [7]. Toll-like receptor (TLR) activation leads to NF-κB and MAPK signalling pathway activation, inducing the expression of pro-inflammatory genes [80]. Cannabinoids impair pro-inflammatory cytokine and nitric oxide production by LPS-stimulated monocyte, macrophages, and microglia due to NF-κB signalling pathway inhibition [62, 81]. In vivo models of LPS-induced inflammation support the capacity of cannabinoids to interfere in TLR signalling [82, 83]. TLR activation enhances CBR expression and endocannabinoid production, suggesting an important role of the ECS in the modulation of TLR-mediated immune responses [42, 82].

Novel findings indicate that cannabinoids might also mediate their anti-inflammatory effects by rewiring the metabolic pathways in immune cells [84]. Metabolic reprogramming can govern the function of T cells, macrophages, and DCs. Immune activation is mainly linked to a glycolysis-driven upregulation of anabolic processes,

whereas the tolerance state is characterized by increased catabolic processes [85–87]. AMP kinase (AMPK) is a master regulator of catabolism promoting mitochondrial biogenesis, oxidative phosphorylation, and autophagy. Simultaneously, AMPK also downregulates anabolic processes, antagonising immune cell activation [88, 89]. In pancreatic cancer cells, cannabinoid agonists induce AMPK activation depending on ROS-mediated increase of AMP/ATP ratio [90]. Similarly, THC and JWH015 activate AMPK through CB2 and inhibit energetic metabolism [91]. In these studies, AMPK activation leads to autophagy induction, a catabolic process involved in cellular homeostasis [88, 90, 91]. Autophagy has also been involved in immune system control by clearance of intracellular bacteria, control of inflammatory cytokine secretion and inflammation, antigen presentation, and lymphocyte development [92, 93]. CBD and AEA attenuate inflammation in an autophagy-dependent manner [94]. Considering all these aspects, cannabinoid-based treatment demonstrated anti-inflammatory and beneficial effects in brain injury, inflammatory bowel diseases, vascular inflammation, sepsis, rheumatic disease, multiple sclerosis, airway inflammation, and allergy [7, 95].

Cannabinoids in Allergic Diseases

Allergy is a type 2 helper T cell (Th2)-mediated disease of increasing prevalence affecting around 30% of the population worldwide. Allergic diseases constitute a public health problem with a high socio-economic impact. The main allergic diseases include allergic rhinitis, allergic asthma, food allergy, AD, and anaphylaxis [9]. The immunological mechanisms underlying allergic diseases can be divided into two main phases: (i) sensitization and memory and (ii) effector phase. The sensitization phase occurs during the first contact with the allergen and leads to the generation of allergen-specific $CD4^+$ Th2 cells and allergen-specific IgE antibodies that diffuse and bind to the IgE high-affinity receptor (FcεRI) on the surface of mast cells and basophils, thus leading to patient sensitization. Upon new allergen encounters, allergen-dependent cross-linking of the IgE-FcεRI complexes on sensitized mast cells and basophils triggers the release of a plethora of anaphylactogenic mediators, responsible for the immediate clinical symptoms. Late-phase reactions are initiated by the accumulation of mediators and by the activation of allergen-specific memory Th2 via mechanisms depending on IgE-facilitated presentation by DCs and B cells. Th2 cells in cooperation with ILC2s activated by epithelial cell-derived alarmins (TSLP, IL-33, or IL-25) produce large amounts of IL-4, IL-5, IL-9, and IL-13 that contribute to maintain allergen-specific IgE levels, eosinophilia, mucus production, inflammatory cell recruitment, and tissue inflammation, leading to chronicity and the most severe clinical manifestation of allergy [8, 9, 96].

Allergen-specific Treg and regulatory B (Breg) cell generation is essential in the induction and maintenance of allergen tolerance in healthy responses and successful AIT [9, 97]. Although AIT, the single treatment with the capacity to induce long-term modifying effects upon discontinuation, is effective in many cases, it displays several important drawbacks in terms of efficacy, safety, and duration. Therefore, the development of novel prophylactic and therapeutic interventions is highly demanded in the field of allergy. In this regard, a better understanding of the role of ECS in the context of allergy might well contribute to open new avenues for the design of novel preventive and curative strategies. To date, the data on the effect of cannabinoids in the context of allergic diseases are still a bit controversial. Some studies reported a potential protective role of ECS in allergen-induced airway inflammation and contact allergy [14, 15, 98, 99]. In contrast, other studies in mice showed that CB2 signalling contributes to allergic exacerbation in OVA-asthma models or AD models [16, 17, 100]. Our group has previously shown that the gene expression of CB1 is significantly increased in peripheral blood and tonsils of atopic patients, but the functional significance of these findings remains to be fully elucidated [43]. In the next sections, we will comprehensively review our current knowledge on the role of the ECS and cannabinoid-based drugs in the context of different allergic diseases.

Allergic Rhinitis

Allergic rhinitis is a highly prevalent disorder in western countries, especially in children. It is defined by chronic inflammation of the nasal mucosa that promotes the appearance of its main clinical symptoms: sneezing, itch, nasal congestion, and rhinorrhoea [101, 102]. The pathophysiology of allergic rhinitis is mediated by a type 2 immune response where Th2 cells, ILC2s, B cells, mast cells, basophils, and eosinophils together with structural cells from the nasal mucosa interact and release a range of mediators that end up in the development of classical features of rhinitis [8, 9]. Several pathophysiological mechanisms of allergic rhinitis are also present in the lower respiratory tract of asthmatic patients. In fact, both diseases coexist in many patients and the diagnosis of al-

lergic rhinitis is an important risk factor for the future development of asthma [101, 102].

Studies addressing the role of the ECS in allergic rhinitis are scarce. As mentioned above, we previously showed that the expression of CB1 was significantly upregulated in tonsils from allergic rhinitis patients compared to non-atopic donors [43]. CB1 limits mucosal mast cell activation and maturation from nasal polyps [103], indicating a protective role in allergen-induced airway diseases. Conversely, in patients with allergic rhinitis, nasal stimulation of TRPV1 by capsaicin or olvanil during the pollen season resulted in an increased perception of itch compared to placebo-treated controls [104]. Intriguingly, no effects were found when TRPV1 was activated by AEA, possibly due to a high degradation rate of AEA in the nasal mucosa [104]. These findings suggest that the ECS may contribute to some extent to the pathophysiology of allergic rhinitis, but future research is required.

Allergic Asthma

Asthma is a heterogeneous syndrome characterized by chronic inflammation of the conducting airways affecting up to 358 million people worldwide. It encompasses several phenotypes with different pathophysiological mechanisms that share common clinical symptoms such as bronchial hyperreactivity (BHR), reversible airflow obstruction, and intermittent periods of wheezing, cough, and chest tightness as well as airway remodelling and exacerbations in the most severe manifestations [105–107]. Allergic asthma represents one of the most common and well-studied asthma phenotypes [108]. It is associated with an early age onset, increased levels of total and allergen-specific serum IgE, and type 2 immune responses [8, 108]. Corticosteroids and bronchodilators are the mainstay treatment for asthma and many patients are properly controlled with them. However, in patients with severe asthma, the treatment of the disease is still challenging [106, 107]. Over the last years, biologicals have significantly improved the asthma control and quality of life of many severe asthma patients, but novel safe and cost-effectiveness treatments are still demanded [109–111].

First evidence on the therapeutic potential of cannabinoids in the airways dates back to the 1970s when several studies pointed out the bronchodilatory properties of marijuana smoke and oral administration of THC [112]. However, its therapeutic exploitation was hampered due to concerns of its psychotropic effects at the CNS and the paradoxical bronchoconstrictory responses reported in some asthmatic patients [113]. Since then, different studies have addressed the potential involvement of the ECS in asthma. Increased levels of AEA have been reported in the bronchoalveolar lavage fluid of allergic asthma patients upon allergen challenge and the mRNA levels of CB1 are increased in asthmatics [43, 114]. The expression of CB2 is enhanced in peripheral blood eosinophils from allergic patients with seasonal respiratory symptoms compared to healthy controls [16]. These data, together with findings in mice showing decreased levels of PEA and upregulation of CB2 and GPR55 receptors after OVA sensitization [115], suggest a potential role of the ECS in the pathophysiology of asthma. However, whether they are a cause or consequence of the ongoing disease needs to be considered carefully.

AEA might play a dual role in the pathogenesis of asthma as it promotes an increase in airway epithelial cell permeability while it also reduces prostaglandin D4-induced bronchospasm in guinea pigs [33, 116]. Besides, AEA controls capsaicin-induced BHR via CB1 in axon terminals of airway nerves, but it also promotes bronchospasm when the vagus nerve constricting tone is removed [117]. This could explain the above-mentioned paradoxical bronchoconstriction in some asthmatic patients treated with cannabinoid compounds [113, 118]. PEA significantly inhibited BHR as well as inflammatory cell recruitment to the airways [115]. In addition to the role of CB1 as a suppressor of mast cell degranulation in the airways, CB1 activation prevented BHR through a modulatory control of nerve-mediated cholinergic contractions in mice and humans, confirming a probable protective role in asthma [119, 120]. In contrast, CB2-mediated signalling strongly potentiates eosinophil chemotaxis and responsiveness, leading to worsening of airway hyperreactivity in mice [16]. Supporting this data, CB2 knockout animals developed a significantly attenuated allergic airway inflammation after house dust mite exposure compared to wild-type mice [74]. This result correlated with increased levels of NK cells and reduced numbers of ILC2s in the lungs of mice lacking CB2, which led to the discovery that NK cells are key negative regulators of ILC2s. However, CB2 activation may also play a protective role in asthma since stimulation of CB2 inhibited antigen-induced plasma extravasation and electrical field-induced contraction of bronchial smooth cells by acting on C-fibres in guinea pig airways [121, 122].

The pleiotropic functions exerted by different ECS components highlight the complexity of the system and its therapeutic potential in the pathogenesis of asthma [123]. In mice, THC attenuated allergic inflammation

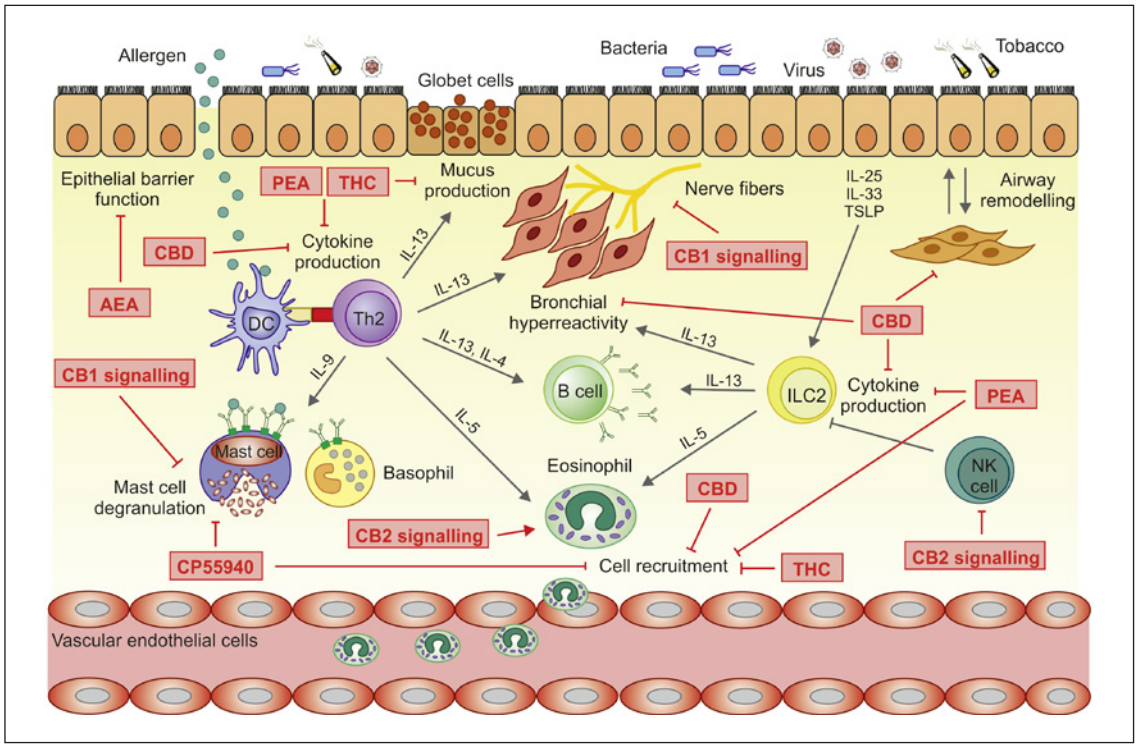

Fig. 3. Modulatory pathways of the ECS in asthma pathophysiology. In allergen-sensitized patients, antigen exposure results in IgE-FcεRI cross-linking in the surface of mast cells and basophils that lead to the release of their anaphylactogenic mediators, causing increased vascular permeability, bronchoconstriction, and/or mucus production. Following this early process, APC-activated Th2 cells and alarmin-activated ILC2s produce large amounts of Th2 cytokines (IL-4, IL-13, IL-5, and IL-9) that contribute to the activation and recruitment of eosinophils and other inflammatory cells, contraction of smooth muscle, and bronchial hyperreactivity. If the inflammatory environment persists, it may trigger the remodelling of the airways. The contribution of the ECS to the different asthma pathways is highlighted with the corresponding arrow.

in the airways by reducing Th2 cytokine production, total cell infiltration, mucus secretion, and serum IgE levels in a CB1- and CB2-independent manner [14, 124]. In an antigen-induced asthma model in guinea pigs, CP55940 decreased respiratory clinical abnormalities, histological changes in the lung, mast cell degranulation, and airway cell recruitment [125]. Furthermore, the non-psychotropic cannabinoid CBD improved lung function and reduced airway inflammation in a murine model of LPS-induced acute lung injury [126]. Supporting these findings, CBD ameliorated the outcomes of a murine model of experimental allergic asthma by decreasing cytokine production, airway hyperresponsiveness and remodelling, and restoring lung function [99]. Finally, the potential application of manipulating endocannabinoid levels by using inhibitors of the cannabinoid degrading enzymes has also been assessed in the airways. Both MAGL and FAAH inhibitors, after intraperitoneal administration, prevented BHR and lung inflammation in a murine model of LPS-induced airway inflammation [127].

In summary, the ECS seems to be clearly involved in the pathophysiology of asthma by acting in structural cells and by regulating immune responses (Fig. 3). Different strategies targeting immune cells with different types of immunomodulators have been previously shown as promising therapies for allergic diseases [128–130]. Thus, the rational design of novel immunomodulatory drugs targeting the ECS may be of potential interest for the development of new therapies for allergic asthma treatment.

Allergic Skin Diseases

Despite their low mortality rates, allergic skin disorders such as AD and allergic contact dermatitis (ACD) have a great impact on patients' quality of life. Skin allergies are complex diseases initiated by allergens and multiple environmental factors on genetically susceptible individuals that rely on the communication be-

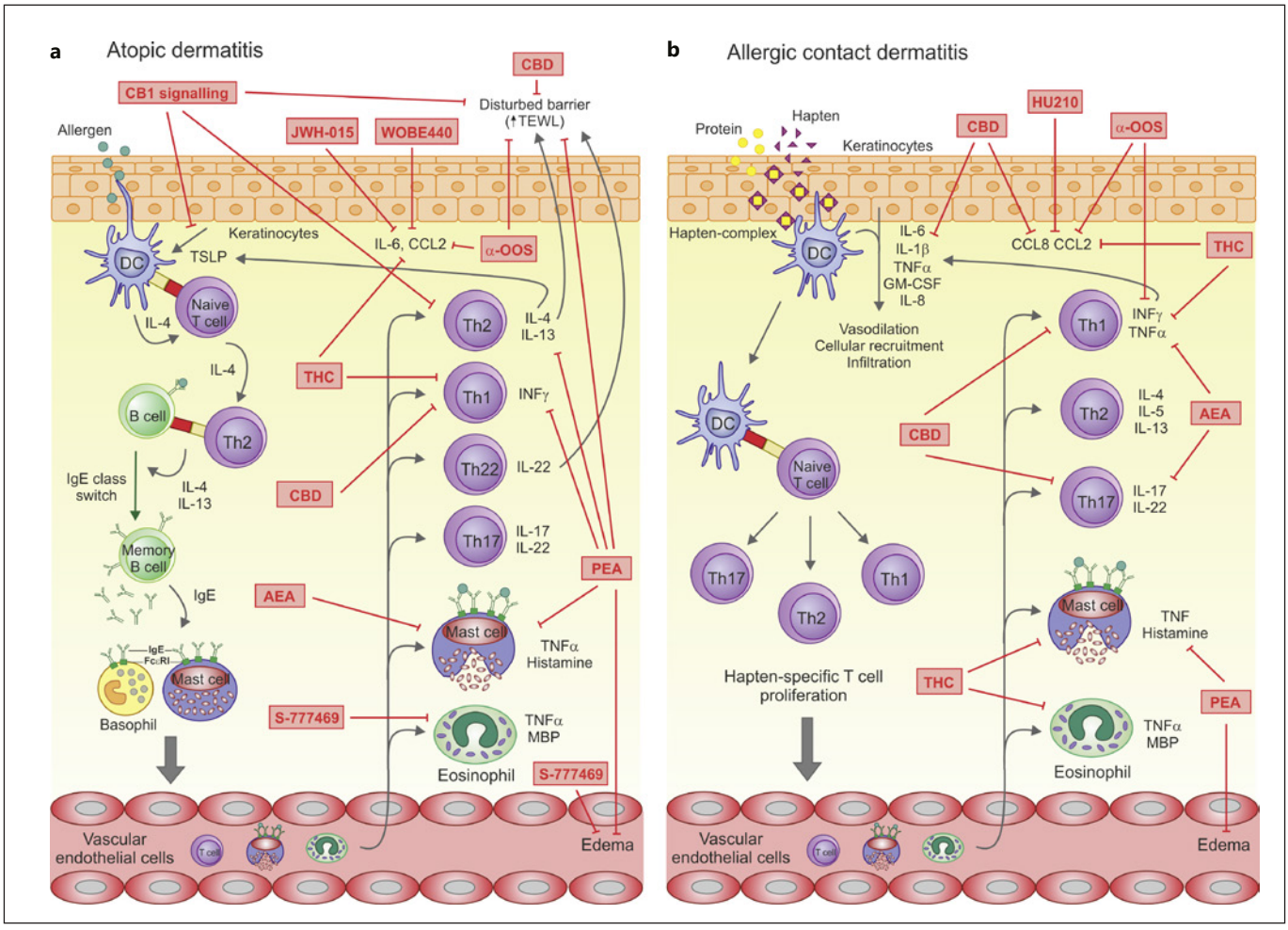

Fig. 4. Modulatory pathways of the ECS in the pathogenesis of atopic dermatitis (AD) and allergic contact dermatitis (ACD). **a** In the early phase of AD, allergen encounter and presentation to naïve T cells lead to a Th2 inflammatory response. In this context, cytokines and chemokines drive the infiltration of inflammatory cells to the skin. In the chronic phase of AD, bacterial colonization of the skin promotes a Th1, Th2, Th17, and Th22 effector response. Th2 and Th22 during the early and late phase of AD contribute to epithelial barrier impairment and transepithelial water loss (TEWL). **b** The sensitization phase of ACD is hallmarked by the hapten-induced secretion of pro-inflammatory mediators leading to vasodilation, recruitment, and infiltration of immune cells. During the effector phase, hapten-specific T cells are recruited into the skin, activating keratinocytes and endothelial cells that secrete pro-inflammatory mediators that further amplify the immune response. The contribution of the ECS to every process in AD and ACD is highlighted with the corresponding arrow. TNFα, tumour necrosis factor α; GM-CSF, granulocyte macrophage colony stimulating factor.

tween immune cells and other cell types such as keratinocytes and fibroblasts [8]. Regardless of the triggering factor, allergic skin disorders involve increased interleukins and chemokines, leading to the expansion of different T-helper subsets and activation of effector cells that may cause the chronicity of the disease [131]. Nevertheless, the cells residing in the skin are also able to secrete anti-inflammatory cytokines and chemokines, responsible for the regulation of local immune responses [9, 97, 132].

Different studies demonstrated that the ECS and endocannabinoids are expressed in the skin [15]. Cannabinoids have various effects over different skin cell types, ranging from activation or inhibition of keratinocyte proliferation to anti-inflammatory and anti-pruritic properties [133, 134]. Topical cannabinoids have shown high safety profiles, and their local application as oils, emollients, or creams have not been related to any adverse systemic effects, rendering them as an attractive therapeutic option [135].

AD is a chronic inflammatory skin disease where a number of polymorphisms associated with IL-4 secretion/signalling and structural proteins such as claudin and filaggrin compromise epidermal integrity [136, 137]. Initial disruption of the epidermis caused by scratching, microbial toxins, or allergens triggers the release of inflammatory mediators, including alarmins (TSLP, IL33, or IL-25), GM-CSF, TNFα, or IL-1β, by epidermal keratinocytes, mast cells, or DCs. These mediators play an important role in the infiltration of inflammatory cells into the skin, being Th2 cells and their secreted cytokines the cornerstones of the early phase of AD inflammation [8]. In the chronic phase, Th2 cells but also Th1, Th17, and Th22 predominate in the skin together with epidermal hyperplasia and bacterial colonization.

CB1 in keratinocytes is essential to preserve repair responses and membrane integrity, and prevent transepithelial water loss as shown in AD-like $CB1^{-/-}$ mouse models [138, 139]. Mice with $CB1^{-/-}$ keratinocytes presented higher skin inflammation, eosinophil infiltration, and expression levels of IL-4, TSLP, and CCL8 when challenged with fluorescein isothiocyanate [138]. Topical administration of AEA and α-oleoyl oleylamine serinol (α-OOS), a synthetic CB1 agonist, accelerated barrier recovery and reduced chemokines in both oxazolone- and tetradecanoylphorbol acetate-induced AD models [140, 141]. CB1 activation also showed anti-inflammatory functions, reduced mast cell recruitment, proliferation, and degranulation, and decreased Th2 cytokines [73, 141, 142]. PEA, another CB1 agonist, reduced the secretion of pro-inflammatory chemokines in human keratinocytes in vitro and showed relieving effects in acute dermatitis and pruritus in clinical studies [143, 144]. Supporting these findings, FAAH and NAAA inhibitors decreased pro-inflammatory cytokine secretion in keratinocytes, reduced oedema in AD mouse models, and also had an impact systemically, normalizing serum IL-4, IL-5, IFNγ, and IgE levels [145, 146]. CBD inhibited Th1, Th2, and Th17 responses and suppressed B cells [147–150]. In clinical studies, CBD ameliorated transepithelial water loss and improved skin barrier by restoring the IFNγ-mediated inhibition of skin ceramide synthesis [151, 152]. Preclinical studies have shown that the synthetic CB2 antagonist S-777469 suppressed swelling, epidermal thickness, and mast cell and eosinophil infiltration in 2,4-dinitrofluorobenzene (DNFB) and house dust mite-induced AD models [153]. The effects of cannabinoids in AD are summarized in Figure 4.

ACD is an inflammatory response of the skin after contact with certain chemicals (haptens) whose characteristics and low molecular weight render them as highly reactive and capable of penetrating the skin barrier. During sensitization, chemicals react with epidermal proteins generating hapten carrier complexes that stimulate innate immune cells via TLRs [154–156]. The secretion of pro-inflammatory mediators (IL-1β, IL-18, TNFα) by innate cells leads to the activation of DCs, which uptake encountered hapten complexes and migrate to lymph nodes where they prime antigen-specific naïve T cells to differentiate into Th1 and Th17 cells. During the effector phase, repeated hapten complex exposure induces the recruitment of allergen-specific IFNγ- and IL-17-producing T-effector cells into the skin, which activate keratinocytes and endothelial cells to produce pro-inflammatory cytokines and mediators. This promotes vasodilation and the infiltration of macrophages and neutrophils, which in turn further amplify the recruitment of effector cells [157–159].

The protective role of CB1 in ACD has been extensively studied. In a mouse model with $CB1^{-/-}$ keratinocytes, myeloid immune cell skin infiltration and CCL8 expression were increased [98]. Moreover, CB1 agonists alone have proven strong anti-inflammatory effects in vitro and in vivo. AEA pre-treatment of HaCaT keratinocytes prevented the secretion of Th1 and Th17 polarizing cytokines in an IFNγ-induced pro-inflammatory context [63]. AEA levels may be increased by other cannabinoids such as CBD, which suppressed the inflammation in poly-(I:C)-induced ACD in human keratinocyte cells [160]. The systemic and local administration of THC significantly reduced inflammation and myeloid immune cell infiltration in DNFB-induced contact hypersensitivity mouse models [15, 134]. THC not only decreased ear swelling in vivo, but also inhibited the production of IFNγ by T cells and the secretion of the pro-inflammatory mediators CCL2, CCL8, and CXCL10 by keratinocytes in vitro. Other synthetic cannabinoids and endocannabinoids displayed potent CB2-mediated anti-inflammatory effects both in vitro and in vivo. PEA decreased ear swelling, mast cell number, and the angiogenic factor VEGF in a contact dermatitis mouse model [161]. However, there is also conflicting evidence regarding the role of CB2, which might show either an exacerbation or suppression of inflammatory responses depending on the context and assayed conditions [15, 134]. The effects of cannabinoids in ACD are summarized in Figure 4.

The complexity of cannabinoids and the role of ECS in skin homeostasis and pathology are evident. Cannabinoids may play different roles depending on the origin of disease and pre-clinical studies have unveiled some of

their possible mechanisms of action. However, limitations such as the low number of double-blinded clinical trials and the high variation of cannabinoids tested, as well as their delivery routes, hinder the interpretation of clinical data. Further investigation is needed to understand the potential therapeutic role of cannabinoids in allergic skin diseases.

Food Allergy

The prevalence of food allergy is increasing in westernized countries, affecting up to 8% of children and 5% of adults. Even though oral tolerance is the physiological response to ingested antigens, the breakdown of this tolerance triggers the development of allergic sensitization. Such sensitization can occur in the gastrointestinal tract, oral cavity, skin, and occasionally in the respiratory tract. Re-exposure to food allergens induces the release of the anaphylactogenic mediators responsible of the clinical symptoms, including anaphylaxis [162]. The current standard treatment for food allergy is the strict and causative avoidance of the causative food and the use of epinephrine in the case of accidental ingestion. Although increasing research studies focus on the study of oral (OIT), sublingual (SLIT) and epicutaneous (EPIT) immunotherapy for the treatment of food allergy, only an OIT product for peanut allergy has been recently approved by the FDA [163, 164]. Therefore, the development of novel therapeutic approaches that improve the current strategies of immunotherapy for food allergy are needed. To date, there are no available data associated with the potential role of cannabinoids in food allergy models. The role played by ECS in other allergic diseases suggests that cannabinoids could also modulate food allergic reactions, but further research is warranted. Interestingly, we previously reported that the mRNA levels of CB1 are significantly higher in PBMCs from peanut-allergic children than healthy controls, suggesting that CB1 might well also play an immune regulatory role in food allergy [43].

Chemical Probes for ECS Research

The development of multiple cannabinoid agonists and antagonists has marked a milestone in the understanding of the effects of ECS signalling at the molecular level. However, the poor translational outcomes shown in clinical trials and their adverse side effects [165, 166] indicate that further validation and characterization of the receptors triggering the observed effects is necessary. In this context, the lack of suitable antibodies due to drawbacks in specificity and reliability [167, 168] prompted scientists to develop chemical probes to address the issue. In recent years, various probes have been validated for the assessment of CBR expression (Table 2). Biotinylated probes overcame the drawbacks shown in previous attempts to design high-affinity CBR tools [169]. Their ability to bind different streptavidin tags made them suitable to study and visualize CBRs in native systems [170]. Moreover, several CB2-specific probes based on photoaffinity and fluorescent labelling have also been developed [171–175]. Their capacity to track CB2 in various cell types and settings may be of quite some interest in studies monitoring the expression of CB2 and its interactions in biological systems (Table 2). Regarding CB1, the conjugation of HU210, a dual agonist of CB1 and CB2, with the fluorescent tag Alexa Fluor 488 resulted in a high-affinity CB1-specific probe [76]. The probe was suitable for use in common biochemical and immunological techniques such as confocal microscopy and flow cytometry. It was also validated for the visualization of CB1 in different immune cell subsets [76], suggesting it to be a promising implement for future ECS research in immune-related diseases such as allergy. Besides, novel probes that provide reliable information on the allosteric motifs of CB1 have been designed. These probes could be useful for drug discovery, thus helping to overcome the limited translational potential of the orthosteric ligands [176]. These advances, together with the generation of compounds such as the recently developed THC-based photoaffinity probe allowing the identification of cannabinoid off-targets [173], might well contribute to widen the knowledge on the molecular mechanisms and receptors involved in cannabinoid-induced effects.

Other strategies to overcome the limitations displayed by drugs based on cannabinoid agonists and antagonists have focused on the manipulation of the enzymes involved in endocannabinoid metabolism [5]. Consequently, various chemical probes have been developed and used for the discovery and validation of novel inhibitors of the ECS metabolic enzymes [177] (Table 2). In this way, the generation of a photoaffinity probe that binds to the endocannabinoid membrane transport has been a remarkable finding that may help with the identification of the proteins involved in endocannabinoid membrane trafficking and the investigation of novel modulators of this process [178]. Furthermore, activity-based protein profiling (ABPP) probes have been used to evaluate the activity of hydrolase inhibitors and visualize additional targets in human leukocytes [179]. In fact, the use of tailored ABPP probes has provided important information on the

Table 2. Main small molecules and probes developed and used for ECS research

Type of compound	Targets	Validated uses	Potential use in ECS research	Ref.
Fluorescent probe	CB1	Identification and quantification of CB1 expression in different human immune cell subsets	Monitoring CB1 expression and function in biological systems	[76]
Electrophilic/ photoaffinity probes	CB1	Covalent binding to CB1 allosteric site and negative allosteric modulation	Characterization and mapping of CB1 ligand binding sites	[176]
Biotinylated probes	CB1/CB2	Visualization of CBRs in native cell systems	Functional and imaging studies of CBRs	[170]
Photoaffinity probe	CB2	Monitorization of CB2 expression in human immune cells	Monitoring CB2 expression and ligand occupancy	[208]
Fluorescent probe	CB2	Assessment of CB2 expression in mice immune cells	Monitoring CB2 expression and ligand interactions	[171]
Fluorescent probe	CB2	Visualization of CB2 in human cell line	Monitoring CB2 expression	[174]
Fluorescent probe	CB2	High-affinity binding to CB2	Monitoring CB2 expression	[172]
Fluorescent probe	CB2	Imaging of CB2 in human tumour cell line	Monitoring CB2 expression and function	[175]
Photoaffinity probe	–	Identification of additional targets of THC in mouse neural cell line	Elucidation of novel THC off-targets as a tool for new drug discovery	[173]
ABPP probe	DAGL	Evaluation of inhibitor activity in biological systems	Development of novel inhibitors of endocannabinoid biosynthesis	[209]
ABPP probe	DAGL	Development of selective inhibitors of DAGLα	Development of novel inhibitors of endocannabinoid biosynthesis	[210]
Fluorescent probe	MAGL	High-throughput assessment of MAGL activity in vitro	Studying MAGL activity and development of new MAGL inhibitors	[211]
ABPP probes	Serine hydrolases	Tracking the dynamic expression and function of the serine hydrolases family	Monitoring serine hydrolase expression and development of novel inhibitors of endocannabinoid degradation pathways	[212]
ABPP Probe	Serine hydrolases	Visualization of endocannabinoid hydrolases and assessment of compound inhibitor activities on biological systems	Monitoring serine hydrolase expression and development of novel inhibitors of endocannabinoid degradation pathways	[213]
Photoaffinity probe	-	Irreversible blockage of endocannabinoid membrane transport	Identification of membrane proteins involved in endocannabinoid trafficking and generation of pharmacological modulators of EC transport	[178]

endogenous activity of MAGL in macrophages and DCs, leading to the identification of DAGLβ as a potential target for chronic inflammation [180, 181]. However, targeting the endocannabinoid metabolism has also shown relevant side effects [5, 182]. Future perspectives in ECS research include multitargeted therapies and a better clinical study of plant-derived cannabinoids and allosteric modulators of CBRs [5]. The use of small molecules and probes has provided reliable information on CBR expression and imaging, the identification of novel off-targets, and the expression and activity assessment of the ECS enzymes in biological systems. Therefore, their thoughtful design may help in achieving future goals in this field of research. Particularly, in the context of allergic diseases, it is of note that despite the huge amount of preclinical studies confirming a role for the ECS in allergy, to our knowledge, only one drug for AD has reached clinical trials [183]. This information highlights the need of ECS research tools to improve the translational potential of preclinical studies in allergic diseases and underlines their relevance in the future of this area.

Conclusions and Future Perspectives

Our knowledge on the underlying molecular mechanisms by which the ECS and cannabinoids regulate vital physiological processes in diverse biological contexts has significantly improved over the last years. These advances have led to the development of different cannabinoid-

based strategies for therapeutic interventions in several pathologic conditions, such as cancer and neurological disorders. The participation of the ECS and cannabinoids in allergy is still controversial. Different studies have convincingly demonstrated the anti-inflammatory properties exerted by cannabinoids in the airways and the skin in the context of allergic diseases both in mice and humans. On the other hand, other studies reported that cannabinoids might exacerbate asthma and AD via mechanisms depending on CB2-mediated signalling pathways. It seems evident that much more basic and clinical research is needed to better understand the role of cannabinoids in the pathophysiology of allergic diseases. In this regard, the rational design of small molecules and chemical probes targeting specific components of the ECS might well represent outstanding tools for its manipulation. Similarly, a deeper knowledge on how the specific endocannabinoids, phytocannabinoids, and synthetic cannabinoids contribute to immunomodulate the functional features of relevant immune cells involved in the orchestration of innate and adaptive immune responses, as well as on their receptor target profiling, will be of utmost importance to delineate future novel strategies for the prevention and treatment of allergic diseases.

Disclosure Statement

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Author Contributions

O.P. conceived and designed the review. A.A., M.P.-D., J.L.-A., and O.P. wrote the manuscript. All authors approved the final version of the paper.

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