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REVIEW ARTICLE

The Endocannabinoid System in Allergic Airway Diseases: Mechanisms and Therapeutic Potential

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The Endocannabinoid System in Allergic Airway Diseases: Mechanisms and Therapeutic Potential

SUMMARY

Allergic airway diseases, including allergic asthma and rhinitis, are characterised by airway inflammation and altered responses to inhaled allergens. The endocannabinoid system (ECS) significantly contributes to the regulation of airway tone and immune system activity. Experimental studies indicate that cannabinoid receptor ligands and inhibitors of endocannabinoid metabolism can modify airway hyperreactivity, inflammatory cell recruitment, and allergic inflammation. However, these effects are not uniform. CB1 and CB2 receptor signalling may produce different outcomes depending on the ligand, responding cell population, tissue, and experimental model. Endocannabinoid-related lipids may likewise exert protective or pro-inflammatory effects through different pathways. Evidence for therapeutic targeting of the ECS is more extensive in allergic asthma, where improvements in airway function or inflammation have been reported. In allergic rhinitis, pharmacological evidence remains limited, and the available clinical findings are insufficient to draw definitive conclusions. The established data suggest the ECS as a potential target in allergic airway diseases while underscoring the need to clarify receptor-dependent and receptor-independent mechanisms mediating their effects and establish efficacy and safety in well-characterized human populations. This review focuses on the role of the ECS in allergic airway diseases and evaluates its potential as a therapeutic target.

Keywords: *Endocannabinoid, airway, allergy, asthma, rhinitis, inflammation.*

Alerjik Solunum Yolu Hastalıklarında Endokannabinoid Sistem: Mekanizmalar ve Terapötik Potansiyel

ÖZ

Alerjik astım ve rinitin de dahil olduğu alerjik solunum yolu hastalıkları, solunum yolu inflamasyonu ve solunan alerjenlere karşı artmış yanıtlar ile karakterizedir. Endokannabinoid sistem (EKS), hava yolu tonusunun ve bağışıklık sistemi aktivitesinin düzenlenmesine önemli ölçüde katkıda bulunur. Deneysel çalışmalar, kannabinoid reseptör ligandlarının ve endokannabinoid metabolizması inhibitörlerinin hava yolu aşırı duyarlılığını, inflamatuvar hücrelerin infiltrasyonunu ve alerjik inflamasyonu değiştirebildiğini göstermektedir. Ancak bu etkiler tek yönlü değildir. CB1 ve CB2 reseptör sinyalizasyonu; liganda, yanıt veren hücre popülasyonuna, dokuya ve deneysel modele bağlı olarak farklı sonuçlar doğurabilir. Endokannabinoidlerle ilişkili lipidler de benzer şekilde farklı yolaklar aracılığıyla koruyucu veya proinflamatuvar etkiler gösterebilir. EKS'nin terapötik olarak hedeflenmesine ilişkin kanıtlar, özellikle alerjik astımda, hava yolu fonksiyonunda veya inflamasyonundaki iyileşmelerin bildirildiği çalışmalar ile daha ön plana çıkmıştır. Alerjik rinitte ise farmakolojik kanıtlar sınırlı kalmakta olup mevcut klinik bulgular kesin sonuçlara varmak için yetersizdir. Mevcut veriler, EKS'yi alerjik hava yolu hastalıklarında potansiyel bir hedef olarak öne çıkarmakla birlikte, bu etkilere aracılık eden reseptör-bağımlı ve reseptörden bağımsız mekanizmaların aydınlatılması ve etkinlik ile güvenliliğin iyi tanımlanmış insan çalışmaları ile ortaya konması gerektiğini göstermektedir. Bu derleme, EKS'nin alerjik hava yolu hastalıklarındaki rolüne ve bu hastalıklarda terapötik bir hedef olarak potansiyelinin değerlendirilmesine odaklanmıştır.

Anahtar Kelimeler: *Endokannabinoid, solunum yolu, alerji, astım, rinit, inflamasyon*

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INTRODUCTION

Following the isolation of bioactive constituents obtained from the plant cannabis, endogenous cannabinoid-binding sites, termed cannabinoid receptors, were discovered and identified in the 1990s (Di Marzo & Fontana, 1995). Then, endogenous compounds naturally synthesized in the body, which can act as Δ9-tetrahydrocannabinol (THC), the primary compound responsible for the effects of cannabis sativa, were discovered and defined as endocannabinoids (Gui, Tong, Qu, Mao, & Dai, 2015). Endocannabinoids, their binding sites, receptors, and metabolic pathways constitute the "Endocannabinoid System" (Di Marzo & Fontana, 1995). The endocannabinoid system (ECS) is involved in numerous vital physiological processes, including neuronal activity, energy metabolism, regulation of cardiovascular tone, and the immune response. Alterations in the function of the ECS have been shown to be associated with various inflammatory and immune-mediated diseases (Di Marzo, 2018; Velasco, Sanchez, & Guzman, 2012). Cannabinoids modulate immune responses by possessing anti-inflammatory effects in various conditions such as multiple sclerosis, sepsis, airway inflammation, inflammatory bowel disease, and allergy (Klein, 2005).

Endocannabinoids are endogenously synthesized, lipid-derived signalling molecules that can bind to and activate cannabinoid receptors (CBRs) (Toczek & Malinowska, 2018). Anandamide (arachidonoylethanolamide [AEA]) was the first endocannabinoid to be isolated from the porcine brain (Devane et al., 1992), followed by the identification of 2-arachidonoylglycerol (2-AG) in the canine gut (Mechoulam et al., 1995). AEA is a high-affinity partial agonist of the CB1 receptor and a low-affinity ligand of the CB2 receptor. On the other hand, 2-AG is a full agonist with moderate affinity for both CB1 and CB2 receptors (Pertwee, 2015; Toczek & Malinowska, 2018). Although AEA and 2-AG are the most extensively studied endocannabinoids, other endocannabinoids with similar biochemical and structural properties have also been identified, including 2-arachidonoylglyceryl ether (noladin ether, 2-AGE), N-palmitoylethanolamine (PEA), O-arachidonoylethanolamine (virodhamine), and N-arachidonoyldopamine (NADA) (Toczek & Malinowska, 2018).

Endocannabinoids are synthesized through the enzymatic breakdown of phospholipids in the cell membrane. Following their synthesis and release, endocannabinoid ligands diffuse locally, and their effects occur through retrograde signalling, regulating the release of presynaptic mediators. After being taken up into cells, endocannabinoid ligands are rapidly removed from the synaptic cleft and are catabolized and inactivated by specific intracellular enzymes (Burstein & Zurier, 2009). This inactivation is catalysed by intracellular enzymes specific to each endocannabinoid. Fatty acid amide hydrolase (FAAH) is mainly responsible for the degradation of AEA, whereas monoacylglycerol lipase (MAGL) is more active in the degradation of 2-AG (Bisogno, Ligresti, & Di Marzo, 2005). As a result of the enzymatic degradation of these endocannabinoids, AEA is metabolized to arachidonic acid and ethanolamine, whereas 2-AG is metabolized to arachidonic acid and glycerol (Wang & Ueda, 2009). However, due to their lipid structure, other enzymes, such as the cyclooxygenase family, contribute to the metabolism process of endocannabinoids (Bozkurt, 2019).

The biological effects of cannabinoids are primarily mediated by the seven-transmembrane (7-TM) cannabinoid receptors CB1 and CB2 (Devane, Dysarz, Johnson, Melvin, & Howlett, 1988). However, they may also interact with other binding sites such as, transient receptor potential vanilloid 1 (TRPV1) (De Petrocellis, Nabissi, Santoni, & Ligresti, 2017; Howlett et al., 2002), GPR55 (Pulgar, Howlett, & Eldeeb, 2022; Ryberg et al., 2007), GPR18 (McHugh, Page, Dunn, & Bradshaw, 2012), GPR110 (Lee et al., 2016), GPR119 (Brown, 2007) and peroxisome proliferator-activated receptors (PPARs), principally PPARα (Brown, 2007).

Cannabinoid receptors are coupled to Gi/o proteins (Devane et al., 1988; Munro, Thomas, & Abu-Shaar, 1993). CB1R is densely expressed in a wide population of central nervous system cells (Hillard, 2014), adipose tissue (Borowska et al., 2018), type II alveolar cells (Cinar et al., 2017), and alveolar macrophages (Staiano et al., 2016). By regulating neurotransmitter release and bronchomotor tone, CB1R activation generally promotes bronchodilation and limits excessive bronchoconstriction (Grassin-Delyle et al., 2014). In contrast, CB2R is expressed significantly higher levels in immune cells (Jung, Lin, & Piomelli, 2022) and is widely distributed among immune cell populations in the lung, including lymphocytes, neutrophils, natural killer (NK) cells, and alveolar macrophages (Alexander, 2016; Bie, Wu, Foss, & Naguib, 2018; Qin et al., 2026). In the lung, CB2R activation primarily suppresses inflammation by immunomodulatory effects through inhibition of pro-inflammatory cytokines and immune-cell migration (Alshaarawy, Kurjan, Truong, & Olson, 2019; Borowska et al., 2018; Rakotoarivelo, Mayer, Simard, Flamand, & Di Marzo, 2024; Wen, Ribeiro, Tanaka, & Zhang, 2015).

Components of the ECS are synthesized and are functionally active in the respiratory system. These components modulate key processes in pulmonary physiology and disease pathogenesis, including inflammatory status, bronchial reactivity, and alveolar homeostasis (Bozkurt, 2019; Qin et al., 2026). The airways are sensitive to environmental irritants and stimuli that lead to inflammation, and increased inflammation is a critical pathophysiological process in most respiratory diseases. Therefore, the principal strategies for treating airway diseases are the inhibition of inflammation and maintaining bronchodilation. The ability of cannabinoids to regulate inflammation and induce bronchodilation has demonstrated the importance of these compounds in airway physiology and pathology (Bozkurt, 2019). CB1 gene expression has been reported to be increased in immune-system cells from individuals with allergic diseases (Martín-Fontecha et al., 2014). CB2 expression also increases under pathological conditions such as chronic inflammation in the immune system and brain injury (Maresz, Carrier, Ponomarev, Hillard, & Dittel, 2005; Patel, Davison, Pittman, & Sharkey, 2010). Studies investigating the effects of the endocannabinoid system in the airways indicate the importance of cannabinoid receptors. Because stimulation of CB1 receptors can suppress airway smooth-muscle contraction, this receptor is considered to make a more substantial contribution to the functional reactivity of the airways. This effect is thought to result from the inhibition of acetylcholine release from cholinergic nerves, and not from a direct smooth muscle effect (Bozkurt, 2019; Bozkurt, Kaya, Durlu-Kandilci, Onder, & Sahin-Erdemli, 2016; Bozkurt, Larsson, & Adner, 2016; Grassin-Delyle et al., 2014).

ALLERGIC AIRWAY DISEASES

Allergy is a global health issue affecting approximately one billion patients worldwide and has an increasing prevalence. The principal manifestations include allergic asthma, allergic rhinitis, atopic dermatitis (AD), food allergy, etc. Allergic diseases are generally regarded as type 2-mediated diseases, which are characterized by high levels of Immunoglobulin E (IgE) production against allergens (Akdis et al., 2020; Palomares, Akdis, Martín-Fontecha, & Akdis, 2017).

The immunological mechanisms of allergic diseases are considered in two phases: (i) sensitization and memory and (ii) the effector phase. The sensitization phase starts with an allergen exposure and leads to the production of allergen-specific CD4+ T-helper cell-2 (Th2) cells along with allergen-specific IgE antibodies. The resulting IgE antibodies infiltrate the tissues and bind to the high-affinity IgE receptor (FcεRI) on the mast cell surfaces and basophils, thereby inducing the sensitizing process to the allergen. Upon re-exposure, cross-linking of IgE-FcεRI on sensitized mast cells and basophils induces the release of numerous mediators involved in the immediate response. Initiation of late-phase reactions occurs through the accumulation of mediators and activation of aller-

gen-specific memory Th2 cells through pathways involving IgE-mediated antigen presentation by B cells and dendritic cells (DCs). In addition, epithelial cells release alarmins (TSLP, IL-33, or IL-25), which then, activate ILC2s, together with Th2 cells, produce IL-4, IL-5, IL-9, and IL-13 cytokines. IgE levels and eosinophilia are regulated by these cytokines, which also mediate inflammatory-cell recruitment, mucus production, and tissue inflammation, thereby leading to chronic disease and the emergence of more severe manifestations of allergy (Akdis et al., 2020; Palomares et al., 2017; Simon et al., 2020).

Allergic Asthma

The allergic form is the most common type of asthma, with an early-onset phenotype and accompanied by reversible limitation of expiratory airflow, bronchial hyperresponsiveness, and allergen-specific IgE production. It is driven by a Th2 immunoinflammatory cascade through IL-4, IL-5, IL-13 and triggers eosinophilic airway inflammation, mast cell activation, and subepithelial basement membrane thickening (Wenzel, 2012). On re-exposure to allergen, sensitized mast cells degranulate through the high-affinity IgE receptor (FcεRI). They release histamine, leukotrienes, and prostaglandins that trigger acute bronchoconstriction. Furthermore, eosinophil recruitment and activation sustain chronic airway inflammation, mucus hypersecretion, and airway hyperresponsiveness (Simon et al., 2020). Over time, this repeated inflammatory cycle contributes to airway remodelling, which underlies the progressive, sometimes irreversible airflow limitation seen in more severe diseases (Global Initiative for Asthma, 2026).

In asthma treatment, beta-2 agonists, short-acting (SABAs) in particular, and inhaled corticosteroids (ICSs) constitute the first-line treatment (Adams, Bestall, Malouf, Lasserson, & Jones, 2005; Kips & Pauwels, 2001; O'Byrne et al., 2001; Pauwels et al., 2003). Leukotriene receptor antagonists may be used when patients experience intolerable adverse effects associated with ICS use, have aspirin sensitivity, or have concomitant allergic rhinitis (Dahlén et al., 2002; Ducharme & Hicks, 2002; Philip et al., 2004). As disease severity increases, higher doses of ICSs or combination therapies including an ICS together with a long-acting beta-2 agonist (LABA) are preferred. Finally, add-on treatments are considered for patients who have persistent symptoms or exacerbations despite their current therapies. These treatments may include long-acting muscarinic antagonists, low-dose oral corticosteroids, bronchial thermoplasty, or biological therapies (Global Initiative for Asthma, 2018). Biological therapies are generally preferred in treatment-resistant patients with a type 2-high (T2-high) inflammatory pattern (Bjermer et al., 2016; Bleecker et al., 2016; Busse et al., 2001; Castro et al., 2015; Hanania et al., 2011; Soler et al., 2001; Wenzel et al., 2013; 2016). In such patients, anti-IgE (omalizumab) therapy (Hanania et al., 2011), anti-IL-5 agents (mepolizumab, benralizumab) or an anti-IL-4 agent (dupilumab) may be used (Wang, Liu, Lan, Li, & Mao, 2016; Wenzel et al., 2016).

Allergic Rhinitis

Allergic rhinitis (AR) is an inflammatory disorder of the nasal mucosa mediated by IgE. Following crosslinking of inhaled aeroallergens with IgE binds to mast cells in the nasal epithelium and submucosa and the cascade starts (Hellings et al., 2017). Mast cell degranulation releases histamine and other mediators that produce the symptoms of sneezing, rhinorrhoea, nasal itching, and congestion within minutes of exposure, followed by a later-phase infiltration of eosinophils, basophils, and Th2 lymphocytes that sustains mucosal inflammation for hours to days (Hellings et al., 2017). AR is mainly understood within a "unified airway" structure, indicating an overlapping inflammatory mechanism of the upper and lower airways in asthma and chronic rhinosinusitis (CRS). Accordingly, mucosal remodelling and immune signalling pathways identified in one compartment are frequently observed in others (Samitas, Carter, Kariyawasam, & Xanthou, 2018).

The evidence-based Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend the use of intranasal corticosteroids (INCSs) in AR patients (Brożek et al., 2017), which may be further supported by systemic glucocorticoids, saline irrigation, antibiotics, and anti-leukotriene agents (Dixon et al., 2015).

Challenges and Disadvantages of Current Therapies

Biological agents have gained significant success in allergic diseases. These agents can reduce allergic reactions and stand as a strong therapeutic option for unresponsive patients to standard medications. Therapies targeting cytokines that regulate the Th2 response are the most successful biological treatments. In contrast, targeting chemokines has not demonstrated sufficient efficacy (Ramírez-Jiménez et al., 2023). The failure of anti-chemokine therapies may be attributable to functional redundancy within the chemokine system and poor inhibition of receptors. In addition, chemokines have been shown to be released for shorter periods than Th2 cytokines, thereby limiting their effects on the allergic response. Studies aimed at developing novel biological agents are ongoing (Ramírez-Jiménez et al., 2023).

Although corticosteroids, bronchodilators, antihistamines, leukotriene receptor antagonists, and biologic therapies provide effective disease control for many patients, their benefits vary depending on the inflammatory phenotype, treatment adherence, and disease severity. Some patients remain symptomatic despite optimized therapy, while systemic adverse effects, long-term treatment burden, route of administration, and restricted eligibility for biologic agents may limit current approaches. These limitations support the investigation of additional pharmacological targets for allergic airway diseases (Global Initiative for Asthma, 2026; Brożek et al., 2017; Ramírez-Jiménez et al., 2023).

THE CONTRIBUTION OF THE ECS IN THE PATHOPHYSIOLOGY OF ALLERGIC AIRWAY DISEASES

The endocannabinoid system (ECS) has gained more importance in the past two decades, although it is still not completely identified as a modulator of airway immune function (Angelina, Perez-Diego, Lopez-Abente, & Palomares, 2020). Both cannabinoid receptors are expressed on structural airway cells (epithelium, smooth muscle, sensory nerve endings) as well as on the key effector cells of allergic diseases (mast cells, eosinophils, dendritic cells, natural killer cells, and innate lymphoid cells). The ECS lies at the crossroads between neuronal and immune control of the airway (Angelina et al., 2020; Larose et al., 2014). This section mainly examines how ECS signalling contributes to the pathophysiology of two of the most common allergic airway diseases: allergic asthma and allergic rhinitis. The endocannabinoid system exerts complex, bidirectional control over airway inflammation and mechanics. This regulation also involves cyclooxygenase-2 (COX-2) expression, directing eicosanoid metabolism toward either protective prostaglandins like PGE_2 or proinflammatory mediators, and acting through cannabinoid and non-cannabinoid receptors across respiratory tissues (Kolousek et al., 2023).

ECS in Allergic Asthma

The ECS appears to act on allergic asthma at three levels simultaneously: neuronal control of bronchomotor tone, direct regulation of effector immune cells, and broader modulation of the Th2 inflammatory environment. The net effect is genuinely bidirectional rather than uniformly protective or harmful (Craib, Ellington, Pertwee, & Ross, 2001; Kolousek et al., 2023).

Activation of CB1 receptors located on airway nerve endings produces bronchodilation and reduces cholinergic-driven bronchoconstriction, an effect demonstrated both in early human pharmacology

studies with inhaled THC and, more mechanistically, in isolated human airway preparations where cannabinoids inhibit prejunctional cholinergic contraction through CB1 (Angelina et al., 2020; Grassin-Delyle et al., 2014). This bronchoprotective, smooth-muscle-relaxant role is also supported by the finding that endogenous cannabinoids exert bidirectional control over airway responsiveness in animal models (Calignano et al., 2000). Recent work shows that inhaled anandamide acts as an airway relaxant and that reduced pulmonary levels of endocannabinoid-like lipids accompany airway hyperreactivity in ovalbumin-sensitized mice (Simon et al., 2022). In humans, allergen challenge of allergic asthma patients significantly raises anandamide concentrations in bronchoalveolar lavage (BAL) fluid, a finding that both supports a possible contribution of AEA in acute allergic response and raises the possibility that elevated AEA increases airway epithelial permeability, potentially worsening rather than limiting disease severity (Zoerner et al., 2011).

Unlike the CB1-related neuronal effect, CB2 signalling on eosinophils appears to aggravate allergic airway inflammation (Frei et al., 2016; Hurrell et al., 2022). A study showed that CB2 activation augments human and mouse eosinophil adhesion, migration, degranulation, and respiratory burst, along with upregulated CB2 expression on the eosinophils of symptomatic allergic donors (Hurrell et al., 2022). Genetic or pharmacological CB2 blockage reduced eosinophil-driven inflammation in an ovalbumin-induced asthma model, suggesting CB2 antagonism as a potential therapeutic strategy in eosinophilic asthma (Frei et al., 2016). A more recent study identified the endocannabinoid-like-lipid oleoylethanolamide as a driver of CB2-dependent eosinophil activation and lung recruitment in asthmatic patients' peripheral blood eosinophils, reinforcing this pro-inflammatory role (Kwon et al., 2024).

In apparent contrast to its role on eosinophils, CB2 signalling on natural killer (NK) cells appears to restrain allergic airway inflammation. A study showed a CB2 receptor-mediated regulation of NK cells that limits allergic airway inflammation in a murine model (Ferrini et al., 2017). However, another study in 2022 reported that CB2 engagement promotes group 2 innate lymphoid cells (ILC2s) expansion and enhances airway hyperreactivity, a Th2-amplifying effect (Hurrell et al., 2022). Taken together with the eosinophil and NK cell data, the literature indicates that CB2's net effect on allergic airway inflammation is highly cell-type dependent, which is why several reviews describe cannabinoid receptor pharmacology in asthma as complex and not yet ready for straightforward therapeutic translation (Angelina et al., 2020; Bozkurt, 2019).

ECS in Allergic Rhinitis

Disease-specific human data on the ECS in classic seasonal allergic rhinitis are more limited than in asthma (Lee & Im, 2025). Most of what we know comes from related conditions like chronic rhinosinusitis and nasal polyposis, which share underlying mechanisms with AR under the unified airway model, complemented by only a few AR-specific studies (Corrado et al., 2018; Kanda et al., 2019).

Using a serum-free organ culture model of human nasal polyp tissue, a study showed that CB1 stimulation and blockade directly affect the expression, degranulation, and maturation properties of human mucosal-type mast cells (hMMCs), the mast cell subtype most implicated in IgE-driven upper-airway allergic disease (Sugawara et al., 2013). Given that mast cell number and activity are substantially increased in allergic, IgE-associated nasal polyp disease relative to non-eosinophilic disease or healthy mucosa, this places CB1 signalling directly within the core effector pathway of allergic upper-airway inflammation (Lee et al., 2025; Sugawara et al., 2013). CB1 receptor expression significantly increases in atopic patients compared to non-atopic controls, providing broader systemic evidence that the ECS contributes to allergic disease states (Martín-Fontecha et al., 2014). Beyond

classical CB1/CB2 receptors, the endocannabinoid system contains non-cannabinoid receptors such as TRPV1 (De Petrocellis et al., 2004). TRPV1 can be activated by certain endocannabinoid-related lipids (De Petrocellis et al., 2004; Li et al., 2021). TRPV1 signalling is directly implicated in the itch sensation of seasonal allergic rhinitis, linking the broader endocannabinoid network to a hallmark symptom of AR and revealing a target for symptom management (Alenmyr, Högestätt, Zygmunt, & Greiff, 2009).

A study in 2018 was one of the first to demonstrate the expression of CB1 and CB2 receptors in human sinonasal mucosa, using quantitative RT-PCR and immunohistochemistry on nasal polyp tissues and non-inflamed control mucosa (Corrado et al., 2018).

THE POTENTIAL OF ECS AS A THERAPEUTIC TARGET

The involvement of the ECS in airway physiology and pathophysiology, together with its regulatory role in allergic inflammation, has highlighted its potential as a therapeutic target for allergic airway diseases. Therapeutic strategies targeting the ECS include the pharmacological modulation of cannabinoid receptors as well as modulation of endocannabinoid levels and metabolism (Angelina et al., 2020; Bozkurt, 2019; Nayak, Loblundo, & Bielory, 2023).

ECS's Therapeutic Potential for Allergic Asthma

Early experimental studies investigating the therapeutic effects of cannabinoids in allergic asthma demonstrated that phytocannabinoids could suppress allergen-induced inflammatory responses (Braun et al., 2011; Jan, Farraj, Harkema, & Kaminski, 2003; Vuolo et al., 2019). In OVA-sensitized A/J mice, administration of cannabinol (CBN) and THC was reported to suppress the increased mRNA expression of IL-2, IL-4, IL-5, and IL-13 in lung tissue and to reduce total and OVA-specific serum IgE levels and airway mucus production (Jan et al., 2003). In the same model, THC administration markedly reduced total cell and eosinophil counts in BALF, mediated by CB1/CB2-independent mechanisms (Braun et al., 2011). CBD can also reduce airway hyperreactivity and inflammatory responses (Vuolo et al., 2019). As these data suggest the potential of cannabinoids as therapeutic targets in allergic airway inflammation, studies with receptor modulators were performed.

The non-selective CB1 and CB2 agonist CP55,940 attenuated lung histopathological alterations, leukocyte and eosinophil infiltration, and mast cell activation in OVA-sensitized guinea pigs. In this study, CB1 or CB2 antagonist pre-treatments reversed the protective effects of CP55,940, supporting the contribution of both receptors in allergic airway responses (Giannini et al., 2008). The specific role of the CB2 receptor in airway inflammation was evaluated in OVA-sensitized guinea pigs and found to be effective in reducing antigen-induced tracheal plasma extravasation, which was attributed to the suppression of C-fiber activation and the consequent reduction in neuropeptide release (Fukuda, Abe, & Yoshihara, 2010).

In terms of airway reactivity, functional studies have demonstrated that CB1 receptors may regulate airway contractility through neuronal mechanisms. In isolated human bronchi, Δ9-THC, WIN55,212-2, and CP55,940 ligands have inhibited the nerve-mediated cholinergic contractions through prejunctional CB1 receptors (Grassin-Delyle et al., 2014). The selective CB1 agonists ACEA and ACPA also inhibited cholinergic contractions in NGF-exposed mouse tracheas, while ACEA also prevented NGF-induced increases in neuronal activity and airway nerve density (Bozkurt et al., 2016b). In an experimental model of non-atopic asthma, ACEA prevented the enhanced tracheal contractile response to 5-HT but did not reduce macrophage accumulation in BALF, indicating a predominantly functional rather than anti-inflammatory effect (Bozkurt et al., 2016a). In contrast, CB1 agonist ACEA showed no significant protective effects on methacholine-induced Penh values, inflammatory cell counts in BALF, or lung tissue inflammation in a murine OVA model, except for a reduction in serum

IL-4 levels. Conversely, the CB1 antagonist AM251 significantly reduced Penh values, inflammatory cell counts in BALF, and lung inflammation (Uysal et al., 2025). The role of the CB1 receptor was also investigated using a peripherally acting CB1 inverse agonist INV-202, which reduced airway hyperreactivity and improved lung compliance. However, it had no marked effect on inflammatory cell counts in BALF, airway mucus production, or subepithelial fibrosis (Morris et al., 2025). These findings suggest that the effects of CB1 modulation depend on the experimental model and the outcome evaluated. CB1 activation may inhibit neuronal mechanisms contributing to airway hyperreactivity, whereas CB1 antagonism or inverse agonism appears to exert protective effects in some models of allergic asthma.

The effects of selective CB2 receptor activation in allergic asthma appear to be heterogeneous. In an HDM-induced model, intranasal administration of selective CB2 agonists reduced the accumulation of CD4+ T-cells and eosinophils in the airways, and inhibited pulmonary Th2 cytokine production along with airway hyperreactivity (Ferrini, Hong, Roberts, & Jaffar, 2013). Similarly, the selective CB2 agonist AM1241 improved pulmonary function, attenuated airway inflammation, and oxidative stress in an OVA-induced rat model (Parlar & Arslan, 2020). In a murine OVA model, CB2 agonist JWH133 also dose-dependently reduced airway hyperreactivity, eosinophilic inflammation, Th2 cytokine levels, and lung histopathological alterations (Uysal et al., 2026). However, some studies indicate that the inhibition of the CB2 receptor may also exert protective effects in allergic airway inflammation. The selective CB2 inverse agonist Sch.336 suppressed pulmonary eosinophilia in an OVA-induced murine model of allergic asthma (Lunn et al., 2006). Moreover, CB2 receptor expression was increased in peripheral blood eosinophils from symptomatic allergic individuals, and JWH-133 enhanced eosinophil migration, adhesion, and CD11b expression. Consistent with these findings, the CB2 agonist JWH-133 increased airway hyperreactivity and eosinophil accumulation in OVA-challenged mice, whereas these effects were prevented by CB2 antagonism (Frei et al., 2016). The pro-inflammatory contribution of CB2 signalling has also been associated with innate lymphoid cell regulation. In an HDM-induced model, CB2 receptor deficiency of pharmacological antagonism reduced eosinophilic inflammation, type 2 cytokine production, and mucus secretion, whereas CB2 agonism increased eosinophilic inflammation. The accompanying increase in pulmonary NK cells and reduction in ILC2s in CB2-deficient mice suggested that CB2 signalling may regulate allergic inflammation through the NK cell-ILC2 axis (Ferrini et al., 2017). Accordingly, CB2 activation enhanced the proliferation and effector functions of pulmonary ILC2s and exacerbated ILC2-mediated airway hyperreactivity and inflammation, whereas genetic deletion or pharmacological antagonism of CB2 reduced responses induced by IL-33 and IL-25. Similar findings obtained in human ILC2s and humanized mouse model further supported this mechanism (Hurrell et al., 2022). More recently, treatment with a CB2 inverse agonist improved the Th1/Th2 balance and reduced airway wall and smooth muscle thickness in a chronic OVA-induced rat model. These effects were accompanied by suppression of TLR4/MyD88/NF-κB signalling, suggesting that CB2 inverse agonism may modulate immune imbalance and airway remodelling in chronic asthma (Zhou & Gao, 2026). Overall, the available evidence indicates that CB2 signalling in allergic asthma cannot be explained by a uniformly anti-inflammatory effect, rather its outcome appears to depend on the experimental model and the immune cell populations involved (Simard, Rakotoarivelo, Di Marzo, & Flamand, 2022).

In addition to the direct targeting of cannabinoid receptors, modulation of endocannabinoid concentrations and metabolism has emerged as another potential therapeutic strategy in asthma (Palomares, 2023). Evidence of the ECS in human allergic asthma was provided by a segmental allergen-challenge study, in which AEA concentrations in BALF increased and

positively correlated with eosinophil counts, IL-5, and eotaxin concentrations. However, whether this increase in AEA represents a pathogenic response or a compensatory mechanism remains unclear (Zoerner et al., 2011). The functional significance of AEA in the airways was subsequently demonstrated by its ability to induce airway relaxation and protect against airway hyperreactivity in OVA-sensitized mice. This effect was not associated with CB1 and CB2 receptors and instead includes the FAAH-mediated conversion of AEA to arachidonic acid, followed by activation of PGE_2/cAMP signalling. Accordingly, pharmacological inhibition or genetic manipulation of FAAH largely prevented AEA-induced airway relaxation. The identification of the same signalling components in airway epithelium and smooth muscle cells of humans further supports the potential relevance of this mechanism to human airways (Simon et al., 2022).

The therapeutic approach of targeting endocannabinoid metabolism was evaluated using the FAAH inhibitor URB597, the MAGL inhibitor JZL184, and the dual FAAH/MAGL inhibitor JZL195 in an OVA-induced guinea-pig model. URB597 reduced inflammatory-cell infiltration and pro-inflammatory cytokine production but did not significantly affect airway hyperreactivity. In contrast, JZL184 and JZL195 attenuated both airway inflammation and hyperreactivity. These findings suggest that inhibition of FAAH and MAGL enzymes may represent a potential pharmacological approach for airway inflammation and hyperreactivity in allergic asthma (Abohalaka et al., 2022). The effects of 2-AG on allergic inflammation also appear to depend on the target cell type. In mast cells isolated from OVA-sensitized guinea pigs, 2-AG concentration-dependently reduced antigen-induced histamine release when its hydrolysis was limited. This response was inhibited only by CB2 receptor antagonism, indicating a predominantly CB2-mediated mechanism (Vannacci et al., 2004). In contrast, 2-AG induced CB2-mediated migration of human peripheral blood eosinophils, whereas AEA did not elicit the same response. Thus, 2-AG may suppress mast-cell activation while promoting eosinophil recruitment, indicating that its effects in allergic inflammation vary depending on the responding cell population and the cellular outcome evaluated (Oka et al., 2004).

Pharmacological inhibition of endocannabinoid-metabolizing enzymes may also affect various bioactive lipids other than AEA and 2-AG, which share related metabolic pathways. FAAH inhibition can increase OEA and PEA concentrations in addition to AEA, whereas MAGL inhibition may alter the concentrations of several monoacylglycerols. Therefore, the effects of these inhibitors cannot be attributed exclusively to increased AEA or 2-AG levels and subsequent CB1/CB2 receptor activation (Di Marzo, 2018). Among these endocannabinoid-related mediators, PEA has demonstrated protective effects in allergic airway inflammation. Bronchial PEA levels were reduced in OVA-sensitized mice, whereas PEA administration prevented bronchial hyperreactivity and attenuated inflammatory-cell accumulation, pulmonary inflammation, and mast-cell activation without affecting plasma IgE levels (Roviezzo et al., 2017). In contrast, OEA has produced divergent effects depending on the signalling pathway involved. OEA increased the production of IL-6, IL-8, and IL-33 cytokines in airway epithelial cells and exacerbated eosinophilic inflammation, type 2 cytokine production, airway hyperreactivity, and pulmonary ILC2 responses in mice. It also increased CD69 expression in eosinophils obtained from asthma patients, suggesting that OEA may promote eosinophilic airway inflammation through the activation of ILC2s and eosinophils (Kwon et al., 2021). Consistently, the CB2 antagonist SR144528 reduced airway hyperreactivity, eosinophil accumulation, and inflammation in an OVA-induced asthma model (Kwon et al., 2024). However, OEA can exert protective effects through GPR119. In an OVA-induced model, OEA and the selective GPR119 agonist AR231453 reduced airway hyperreactivity, eosinophil accumulation, pulmonary inflammation, mucin secretion, pro-inflammatory cytokine expression, and ILC2 responses. The absence

of these effects in GPR119-deficient mice supported the involvement of GPR119 signalling (Lee & Im, 2025). Thus, the apparently opposing effect of OEA may reflect the engagement of different signalling pathways, with CB2-associated responses promoting and GPR119 activation suppressing allergic airway inflammation.

Overall, preclinical evidence supports the therapeutic potential of targeting ECS in allergic asthma. Nevertheless, the effects of cannabinoid modulation and alterations in endocannabinoid-related lipid metabolism vary according to the ligand, molecular target, responding cell population, and experimental model. This context-dependent activity highlights the complexity of the ECS and related lipid-signalling networks, while the clinical relevance of these approaches in human asthma remains to be further elucidated (Lewandowska, Rybacki, Graczyk, Wasniowska, & Kolodziej, 2025).

ECS's Therapeutic Potential for Allergic Rhinitis

Compared with allergic asthma, direct evidence supporting the therapeutic targeting of the ECS in allergic rhinitis remains limited. A scoping review of studies published up to February 2025 identified only five relevant studies, four of which were preclinical or *in vitro*, and found no clinical study directly evaluating cannabinoids as treatments for sinonasal inflammatory diseases (Lee et al., 2025). Available human-tissue studies provide primarily mechanistic evidence. In cultured human nasal polyp tissue, functional CB1 receptors were identified in mucosal-type mast cells. CB1 blockade or gene silencing increased mast-cell degranulation and numbers, whereas AEA and the selective CB1 agonist ACEA suppressed excessive degranulation, suggesting that endogenous CB1 signalling may restrain mast-cell activation and maturation in the airway mucosa (Sugawara et al., 2013). More direct pharmacological evidence was provided by a murine model of allergic rhinitis. The 1,2,4-triazole-enamide derivative 11g, identified as a potential CB1 antagonist, reduced pro-inflammatory cytokine expression and MAPK/NF-κB phosphorylation in LPS-stimulated macrophages. *In vivo*, it attenuated allergic symptoms, inflammatory-cell accumulation in nasal lavage fluid, and cellular infiltration of the nasal mucosa. However, because the CB1 dependence of these effects was not confirmed through genetic or pharmacological validation, its activity cannot yet be attributed exclusively to CB1 antagonism (Wang et al., 2025).

ECS-related lipid mediators have also been investigated in allergic rhinitis. PEA suppressed the differentiation of Th1, Th2, and Th17 cells and reduced sneezing, nasal rubbing, and peripheral Th2 cell frequency in OVA-sensitized mice. However, it did not alter eosinophil frequency or total IgE, and the reduction in OVA-specific IgE was not statistically significant, suggesting that its symptomatic effects may be associated primarily with modulation of T-cell responses (Soga et al., 2025). Clinical evidence remains less conclusive. In a randomized, double-blind study, PEA did not improve the primary 14-day reflective Total Nasal Symptom Score compared with placebo in the overall population. A benefit was observed during the second week only in participants with a baseline score greater than 4, while biomarker analyses were limited to a small subgroup. Therefore, the findings provide preliminary clinical support but require confirmation in larger studies (Briskey, Ebelt, & Rao, 2023).

Overall, human-tissue studies confirm the existence of ECS components in the upper airways and associated lymphoid tissues, while recent preclinical findings indicate potential benefits of CB1-related pharmacological modulation and PEA. Nevertheless, therapeutic evidence remains insufficient because of the small number and heterogeneity of available studies, limited receptor-specific validation, and inconclusive clinical findings.

CONCLUSION

Available evidence indicates that the ECS participates in the modulation of airway tone, immune-cell

activity, type 2 inflammation, and tissue remodelling across allergic airway diseases. However, its effects are not unidirectional. CB1- and CB2-dependent responses vary depending on the ligand, target cell, tissue compartment, experimental model, and outcome evaluated. This context dependence is particularly evident for CB2 signalling and for endocannabinoid-related mediators such as OEA and 2-AG.

Preclinical studies support the therapeutic potential of cannabinoid receptor ligands and inhibitors of endocannabinoid metabolism in allergic asthma, whereas direct evidence in allergic rhinitis remains limited. Future studies should distinguish receptor-dependent from receptor-independent effects, account for changes in related lipid mediators, and evaluate efficacy and safety in well-characterized human disease phenotypes before ECS-targeted strategies can be translated into routine clinical practice.

AUTHOR CONTRIBUTION STATEMENT

G.O.: Preparing the study text, reviewing the text, literature research. T.O.A.: Preparing the study text, literature research. K.E.: Preparing the study text, literature research. T.E.B.: Preparing the study text, reviewing the text, analysis and interpretation of the data, literature research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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