



Endocannabinoid modulation of allergic responses: Focus on the control of FcεRI-mediated mast cell activation

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ABSTRACT

Allergic reactions are highly prevalent pathologies initiated by the production of IgE antibodies against harmless antigens (allergens) and the activation of the high-affinity IgE receptor (FcεRI) expressed in the surface of basophils and mast cells (MCs). Research on the mechanisms of negative control of those exacerbated inflammatory reactions has been intense in recent years. Endocannabinoids (eCBs) show important regulatory effects on MC-mediated immune responses, mainly inhibiting the production of pro-inflammatory mediators. However, the description of the molecular mechanisms involved in eCB control of MC activation is far from complete. In this review, we aim to summarize the available information regarding the role of eCBs in the modulation of FcεRI-dependent activation of that cell type, emphasizing the description of the eCB system and the existence of some of its elements in MCs. Unique characteristics of the eCB system and cannabinoid receptors (CBRs) localization and signaling in MCs are mentioned. The described and putative points of cross-talk between CBRs and FcεRI signaling cascades are also presented. Finally, we discuss some important considerations in the study of the effects of eCBs in MCs and the perspectives in the field.

1. Introduction

Allergic diseases are highly prevalent and represent a significant

economic burden worldwide (Loh and Tang, 2018). Several allergy types are common in developing countries, where scarce resources limit their early diagnosis and treatment (Hossny et al., 2019). Examples of

Abbreviations: 2-AG, 2-arachidonoylglycerol; 5-LOX, Arachidonate 5-lipoxygenase; A-AcGs, 2-acylglycerols; AA, Arachidonic acid; ABDHD6, α,β-hydrolase domain-containing 6 protein; ABDHD12, α, β-hydrolase domain-containing 12 protein; AD, Atopic Dermatitis; AEA, anandamide; AIT, Allergen-specific immunotherapy; Ag, Antigen/Allergen; AKT, Protein kinase B (PKB); ALIA, Autocoid local injury antagonism; AP-1, Activator protein 1; BMMCs, Bone marrow-derived mast cells; BTK, Bruton's tyrosine kinase; cAMP, cyclic AMP; CBR, Cannabinoid receptors; CB1R, Cannabinoid receptor 1; CB2R, Cannabinoid receptor 2; COX, Cyclooxygenase; DAG, Diacylglycerol; DAGLαβ, diacylglycerol lipase alpha/beta; DNFB, Dinitrofluorobenzene; DNP, Dinitrophenyl; DUSP, Dual specificity phosphatases; eCBs, Endocannabinoids; ELK1, Ets-like 1 protein; ERK, Extracellular signal-regulated kinase; FAAH, Fatty acid amide hydrolase; FABPs, fatty acid binding proteins; FcεRI, High affinity IgE receptor; HSP, Heat shock protein; FLAT-1, FAAH-1-like anandamide transporter; Gab2, Grb2-associated binding protein 2; Grb2, Growth factor receptor-bound protein 2; HSL, Hormone sensitive lipase; IgE, Immunoglobulin E; ITAM, immunotyrosine-based activation motif; IF, immunofluorescence; IHC, immunohistochemistry; IKK, IκappaB kinase; IP3, Inositol 3-phosphate; JNK, Jun-N-terminal kinase; LAT, Linker for activation of T cells; LPS, Lipopolysaccharide; MAGL, Monoacylglycerol lipase; MAPK, Mitogen-activated protein kinase; MCs, Mast cell(s); MKP-1/3, MAPK phosphatases 1–3; NAAA, N-acylethanolamine-hydrolyzing acid amidase; NAES, n-acylethanolamines; NAPE-PLD, N-acyl phosphatidyl-ethanolamine specific phospholipase D; NAT, N-acyltransferase; NFAT, Nuclear factor of activated T cells; NFκB, Nuclear factor kappa light chain enhancer of activated B cells; NB, northern blot; NTAL, Non-T cell activation linker; Orai1, Calcium release-activated calcium modulator 1; pAEA, phosphoanandamide; PEA, palmitoylethanolamine; PDK1, Pyruvate dehydrogenase kinase 1; PI3K, Phosphatidylinositol-3 kinase; PI(3, 4, 5)P₃, Phosphatidylinositol (3,4,5)-trisphosphate; PI(4, 5)P₂, Phosphatidylinositol (4,5)-bisphosphate; PKA, Protein kinase A; PKCα/β, Protein kinase C α/β; PLA2, Phospholipase A2; PLCγ, Phospholipase Cγ; PP2A, Protein phosphatase 2A; PTPN22, Protein phosphatase 22; SHP1, SH2-containing inositol-5'-phosphatase 1; SHP1/2, Hematopoietic cell phosphatase 1/2; Sos, Son of sevenless; SCP, sterol carrier protein; SOCE, Store-operated Ca²⁺ entry; SNAP, Synaptosome associated protein 23; SNARE, Soluble NSF attachment protein receptor; STIM1, Stromal interaction molecule 1; SYK, Spleen-associated tyrosine kinase; RPMCs, Rat peritoneal mast cells; RBL-2H3, Basophilic leukemia cells of the secreting subline 2H3; TAG, Triacylglycerol; WB, Western Blot.

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allergic diseases are atopic eczema, allergic rhinitis, allergic asthma, food allergy, and, in the most extreme cases, anaphylaxis (Aldakheel, 2021). Most allergic pathologies lead to chronic inflammatory conditions that alter organ physiology, increasing tissue remodeling, aging, and destruction.

Allergies are considered type I (immediate) hypersensitivity reactions. They are also type 2 immune responses due to their pro-inflammatory nature and the cytokine profile that characterizes them. Although distinct cell types participate in those pathologies, they are characterized by an initial production of immunoglobulin E (IgE) antibodies, which bind to the high affinity IgE receptor (FcεRI) located mainly on the surface of mast cells (MCs) and basophils. In MCs, after recognizing specific antigens (Ag, allergens), IgE antibodies trigger the release of distinct inflammatory mediators (Aldakheel, 2021; Gause et al., 2020). Some allergens usually do not represent any danger, such as food components or pollens, but others, like toxins and venoms, can potentially induce damage. Rapid changes in tissue homeostasis, due to the alteration of vascular permeability and peripheral nerve terminal activation in response to pro-inflammatory mediators released by MCs, are characteristic of immediate hypersensitivity reactions (Galli and Tsai, 2012). The consequences of FcεRI-triggered activation of MCs depend on the extent of the stimulation and the tissue where those cells reside, since micro-ambient factors model MC phenotypes, and the released pro-inflammatory mediators differentially affect distinct tissue cells.

Allergies are complex diseases that can involve several organs, change over time due to distinct cell type activation, and often course with different comorbidities. As a result, fully efficient therapies against them are not available or are still under development. The central role of MC-derived mediators in initiating allergic reactions has led to the use of selective compounds which antagonize the actions of secreted pro-inflammatory substances (like antagonists of histamine H1 receptors or cysteinyl-leukotriene receptors) or block certain steps of the production of pro-inflammatory mediators. For example, steroids repress cytokine synthesis, chromones and antioxidants non-specifically inhibit degranulation of MCs (Zhang et al., 2016); and other drugs act on specific tissues to avoid deleterious effects of a particular allergic reaction (e.g., β-adrenergic receptor agonists for asthma treatment). Also, recombinant molecules that diminish circulating IgE (such as omalizumab) are utilized to treat severe cases of some allergic diseases. However, its route of administration and cost are important limitations for their extended use. To date, the most effective strategy to control allergic reactions in the long term is allergen-specific immunotherapy (AIT) to skew the immune response and induce tolerance. However, this procedure presents variable results depending on antigen preparation, allergy type, and administration route (subcutaneous, sublingual, or oral) (Bonertz et al., 2018; Passalacqua and Canonica, 2016).

Because of distinct secondary effects or non-effective control of allergic inflammation with current therapies, new research avenues have been opened to identify physiological negative control points of MC activation (Borriello et al., 2014; Siebenhaar et al., 2018). As cannabinoids (CBs) have anti-inflammatory actions in distinct murine models of allergy (Braun et al., 2011; Gaffal et al., 2013), activation of the endocannabinoid (eCB) system has emerged as a physiological mechanism that could limit the extent of allergic inflammatory reactions. However, pro-inflammatory effects of cannabinoids on allergic reactions have also been described (Frei et al., 2016; Mimura et al., 2012), suggesting that the eCB system exerts complex regulatory functions in allergy, probably depending on general immune status, tissue-specific micro-environment where MCs reside, particular phenotype of MC, the intensity of antigen stimuli, or other conditions.

This review aims to summarize relevant information on the effects of cannabinoids in the activation of MCs by IgE/Ag complexes, starting with the general characteristics of MCs and the FcεRI signaling system. Then, a detailed description of the eCB system and its composition in MCs is presented. Relevant studies regarding the effects of eCBs on

FcεRI-dependent activation of MCs are mentioned to show confirmed and putative molecular points of cross-talk between eCBs and IgE/Ag-activated signaling systems. Also, some considerations about the study of eCB effects on MCs and perspectives of the field are included. Finally, specific studies on the effects of CBs on human allergic reactions are mentioned.

2. Mast cells and their activation through the high-affinity IgE receptor

MCs are immune cells present in all the vascularized tissues of the body. Studies in mice indicate that MCs arise from erythroid-myeloid progenitors in the yolk sac during the early steps of hematopoiesis. Later, MCs are produced by the aorta-gonad-mesonephros from hematopoietic stem cells. In posterior developmental stages, those progenitors travel to the fetal liver, where MCs are produced for a certain time. In adult mice, the bone marrow is the central organ to produce MC progenitors; there, MCs differentiate from a common myeloid progenitor that evolves into the granulocyte-monocyte progenitor and then to the basophil-MC common progenitor. Although studies on MC origin in humans are scarce, some cell progenitors have been isolated and proposed to generate eosinophils (Eos), basophils (Bas) and MC precursors (MCp) from bone marrow (Velten et al., 2017) and cord blood (Zheng et al., 2018). Also, a population giving rise to MCp alone has been purified from human peripheral blood (Dahlin et al., 2016). Some of the difficulties related to identifying human MC precursors are being resolved with innovative technologies, such as single-cell transcriptomic analysis (Derakhshan et al., 2022). In general, it is accepted that immature bone marrow-derived precursors in adult mice and humans are recruited to the tissues, where they complete their differentiation under the influence of locally produced mediators and micro-environmental conditions (reviewed by St. John et al., 2022). Once mature, MCs are located close to endothelial cells of capillaries and surrounding peripheral nerve terminals in a way that their secreted mediators affect local and systemic vascular permeability and neural transmission. MCs are particularly abundant in tissues that are in contact with environmental stimuli, such as the skin and the intestinal and lung mucosas. However, they are also found in distinct central nervous system structures, such as the meninges, where they modulate blood-brain barrier permeability, microglia, and neuron activation (reviewed in Forsythe, 2019).

With numerous membrane receptors and sensing molecules, mature MCs initiate diverse tissue responses triggered by venoms, bacterial and viral products, neurotransmitters, and antigens, among other molecules. In addition, these cells detect discrete microenvironment changes and orchestrate immune responses ranging from low-level surveillance to high-intensity deleterious inflammatory reactions (Frossi et al., 2017). MCs can selectively release numerous pre-formed pro-inflammatory mediators, such as histamine, serotonin, heparan sulfate, proteases (chymase, tryptase), and some cytokines. Also, they rapidly synthesize and release lipid mediators (such as leukotrienes, prostaglandins, and thromboxanes) and cytokines that require gene transcription and protein modification reactions. In addition, MCs produce anti-inflammatory molecules, such as IL-10 and TGF-β (see Mukai et al., 2018 and references therein).

The initiation of allergic reactions relies on the presence of FcεRI receptors on the MC plasma membrane that, after the engagement of a complex signaling cascade (Fig. 1), allow them to rapidly respond to the presence of IgE/Ag complexes and initiate the intense inflammatory response observed in allergic reactions (Galli et al., 2020; Galli and Tsai, 2012). The FcεRI is a multimeric cell surface receptor formed by an α, a β, and two γ subunits (the latter ones bound by a disulfide bridge). The α chain binds IgE, whereas the β and γ chains participate in signal transduction. The formation of aggregates initiated by IgE/Ag complexes bound to the α chain, capable of recruiting β and γ subunits, is a key event for signaling to start.

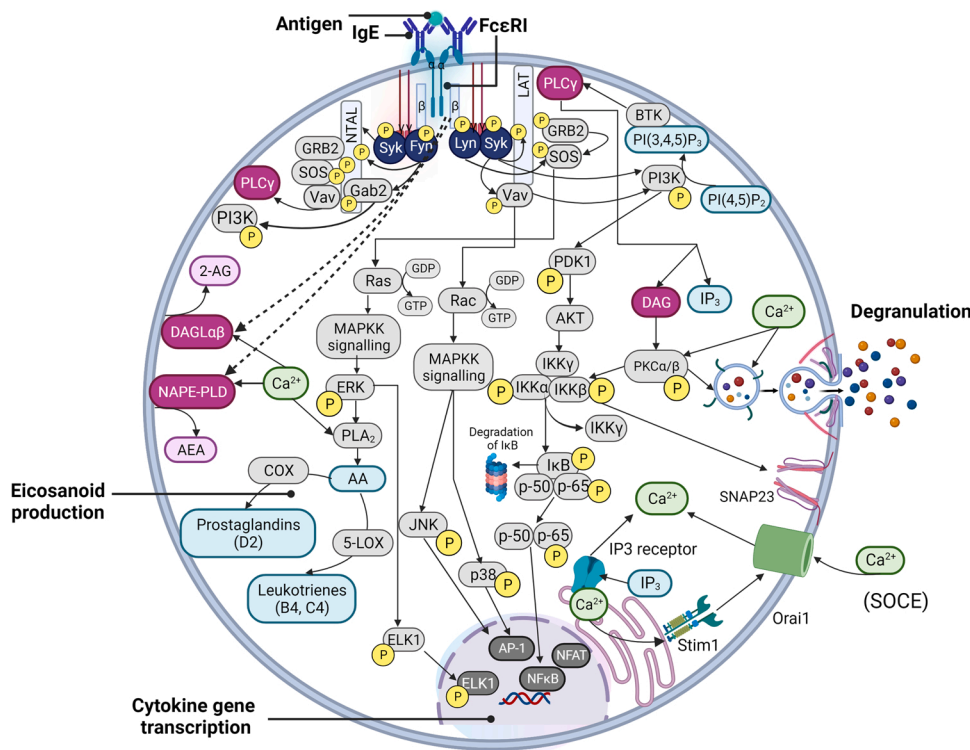


Fig. 1. Main signaling events triggered after activation of the FcεRI receptor in MCs. IgE/Ag-mediated cross-linking of FcεRI receptors leads to the activation of two Src family kinases (Fyn and Lyn). Those kinases phosphorylate the ITAMs of the β and γ receptor subunits. Then, Syk kinase is recruited and activated, causing the phosphorylation of LAT and NTAL adapters. This bifurcates the signaling cascade into two main arms, named the Fyn/NTAL and the Lyn/LAT ones. The branch commanded by Fyn kinase leads to the activation of PI3K and contributes to the nuclear translocation of NFκB by regulating IKK. This pathway also plays a role in the opening of receptor-activated calcium channels that contribute to degranulation (not shown). On the other hand, the Lyn kinase-dependent signaling branch controls PLCγ activation, which produces IP3 and DAG. IP3 causes calcium exit from intracellular stores and the opening of store-operated calcium channels (such as Orai1) through a STIM1-dependent mechanism. On the other hand, DAG activates classical isoforms of PKC, which also participate on NFκB nuclear translocation through phosphorylation of IKK. Both arms of the signal transduction system contribute to MAPK activation by a pathway requiring Grb2, Sos and Ras, leading to the nuclear translocation of other transcription factors such as AP-1, NFAT and ELK-1 to promote cytokine gene expression. FcεRI signaling system also leads to the production of pro-inflammatory lipid mediators, such as prostaglandins and

leukotrienes, through the activation of COX and 5-LOX. The synthesis of endocannabinoids can occur via DAGLα/β and NAPE-PLD activation, although details on the mechanisms are not well described. See text for details. Created with BioRender.com.

One of the earliest steps after FcεRI cross-linking is the tyrosine phosphorylation of the immunoreceptor tyrosine-based activation motifs (ITAMs) in the FcεRI β and γ chains. That early event allows the recruitment and activation of at least the two Src family kinases (Lyn and Fyn), which control two main recognized branches of the signaling system. After Lyn and Fyn activation, another tyrosine kinase (spleen tyrosine kinase, Syk) is activated and, together with Lyn or Fyn, phosphorylate transmembrane adapters such as LAT (linker for the activation of T cells). The Lyn/Syk/LAT signaling pathway leads to forming a LAT-scaffolded complex that contains distinct proteins, such as the guanine nucleotide exchange factor Vav1 and Btk (Bruton's tyrosine kinase), among others. Inside the complex, Vav1 is necessary for the activation of the γ1 and γ2 isoforms of phospholipase C (PLCγ1 and PLCγ2) and calcium mobilization (Manetz et al., 2001). PLC produces IP3 (inositol-1,4,5-trisphosphate) and DAG (diacylglycerol) from their precursor phosphatidylinositol-4,5-bisphosphate (PIP2), leading to an increase in intracellular Ca²⁺ concentrations due to the depletion of endoplasmic reticulum (ER) stores and the opening of membrane calcium channels (Li et al., 2022; Saitoh et al., 2000). DAG is a co-factor for activating classical PKC isoforms that participate in the phosphorylation of proteins necessary for the degranulation process (Hepp et al., 2005). Upon Vav phosphorylation, the small GTPase protein Rac exchanges GDP for GTP. In turn, Rac/GTP stimulates mitogen-activated protein kinases (MAPKs)-dependent signaling cascades, culminating in the activation of the c-Jun N-terminal kinase (JNK) and p38 MAP-kinase (p38 mitogen-activated protein kinase) (Crespo et al., 1996; Crespo et al., 1997; Salojin et al., 1999).

The LAT-dependent complex also activates extracellular signal-regulated kinase (ERK) MAPK through the well-known Grb/Sos/Ras axis. MAPK activation and [Ca²⁺]_i increase contribute to the nuclear translocation of transcription factors such as NFAT (nuclear factor for

activated T cells), AP-1 (activator protein 1), and Elk1 (ETS transcription factor), among others. Endoplasmic reticulum Ca²⁺ stores depletion activates the stromal interaction molecule (STIM)1, which interacts with the calcium release-activated calcium (CRAC) channels, such as Orai-1, Orai-2, and others (Clemens and Lowell, 2019).

The early-activated Fyn kinase induces the phosphorylation of the scaffolding protein NTAL (non-T cell activation linker), which forms a complex with the adapter Grb2, Vav1, and Grb2-associated binder 2 (Gab2). Phosphorylated Gab2 is the principal recruiter of the enzyme phosphatidylinositol-3-kinase (PI3K) (Parravicini et al., 2002). This branch of the signaling system leads to the membrane translocation of the 3-phosphoinositide-dependent protein kinase 1 (PDK1) and the serine-threonine kinase AKT (Gomez et al., 2005; Parravicini et al., 2002), events necessary for the degranulation process and cytokine production. PI3K also participates in the activation of p38 MAPK to produce IL-4 in MCs (Hirasawa et al., 2000). In addition, the Fyn-controlled pathway contributes to the activation of NFκB (nuclear factor kappa-light chain enhancer of activated B cells) transcription factor. Once the IKKγ regulator subunit is ubiquitinated, the kinase complex composed by IKKα/IKKβ phosphorylates the inhibitor IκB subunit at serines 32 and 36, changing its conformation and creating a destruction motif that is polyubiquitinated, leading IκB to proteasomal degradation. These processes allow the translocation of p50/p65 NFκB subunits to the nucleus and the synthesis of TNF mRNA (Lallena et al., 1999; Peng et al., 2005; reviewed in Perkins, 2007). It is worth mentioning that PKC is involved in the phosphorylation of IKKβ to activate NFκB pathway (Lallena et al., 1999). The Fyn-dependent signaling cascade also controls cytoplasmic phospholipase A2 (cPLA2) activation and connects the FcεRI triggering event to the synthesis of arachidonic acid (AA) derivatives, such as leukotrienes, prostaglandins, and lysophospholipid-derivatives. IgE/Ag-dependent stimulation of

MCs also activates the synthesis of the endocannabinoid 2-araquidonoylethanolglycerol (2-AG), mediated by the diacylglycerol lipase (DAGL) enzyme (Kennerly, 1987).

The secretion of pre-formed mediators depends on the rise of $[Ca^{2+}]_i$. Exocytosis events rely on the activity of the N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) and accessory proteins. The most important members of the syntaxin (STX) family of proteins involved in FcεRI-receptor-induced secretion are the plasma membrane-attached STX-4 (Paumet et al., 2000) and STX-3 (Sanchez et al., 2019), whereas the vesicle associated membrane proteins (VAMPs) 3 and 8 also participate in the secretory process in some MC subtypes (Tiwari et al., 2009; Tiwari et al., 2008). In its final steps, degranulation requires the participation of the membrane protein SNAP23 (Agarwal et al., 2019), which is phosphorylated by IKK and leads to the fusion of secretory granules to the plasma membrane (Suzuki and Verma, 2008). The molecules coupling calcium mobilization to granule movement and fusion in MCs are members of the synaptotagmin (Syt) family of proteins (reviewed by Lorentz et al., 2012). In particular, Syt2 has been involved in the secretion of pre-formed mediators such as β-hexosaminidase and histamine (Melicoff et al., 2009) and is thought to be also involved in the granule-plasma membrane fusion (reviewed in Blank et al., 2014; Maximov et al., 2009). As other immune cell receptors, the FcεRI triggers mechanisms that limit excessive MC stimulation, including the activation of protein and lipid phosphatases, antioxidant pathways, and the protein tomosyn-1 that is activated by the δ isoform of protein kinase C (PKCδ) and interacts with syntaxins to prevent degranulation (Madera-Salcedo et al., 2018).

FcεRI receptor signaling leads to epigenetic changes in MCs. For example, the histone deacetylase 3 (HDAC3) controls the chemokine CCL-2 synthesis in response to IgE/Ag complexes due to increased interaction with the β chain of the receptor and the small GTPase Rac-1 (Kim et al., 2019; Kim et al., 2012). However, the specific consequences of HDAC3 activation and other enzymes leading to long-lasting phenotypic changes in MCs are still under investigation (Monticelli and Leoni, 2017).

Recent evidence has shown that the signal transduction cascade activated by FcεRI receptor leads to the release of a truncated version of the α subunit of the receptor (known as the soluble isoform of FcεRI, sFcεRI) to the extracellular space, which is detected in human serum (Dehlink et al., 2011; Platzer et al., 2011). That event requires the activation of Src-family protein kinases and endo/lysosomal acidification (Moñino-Romero et al., 2018). sFcεRI has been shown to bind free IgE and prevent FcεRI crosslinking, exerting inhibitory actions on IgE/Ag-mediated activation of MCs in a systemic sensitization murine model (Moñino-Romero et al., 2018). Future research will give light on the signaling pathways leading to the production of sFcεRI and this putative pathway of negative control activated by IgE/Ag complexes in MCs.

3. Bioactive lipids and the control of inflammation

Lipids are not only an energy source, they are also modulators of inflammatory reactions, which can lead to chronic diseases, such as cancer, cardiovascular, neurodegenerative, or autoimmune diseases, mainly acting in an autocrine or paracrine manner (Leuti et al., 2020). These lipids bind to specific receptors and transporters, modulating the activity of distinct receptors and enzymes (Bulfone-Paus et al., 2017). Activation of enzymes that catabolize membrane phospholipids to produce signaling lipids occurs after FcεRI receptor cross-linking by IgE/Ag complexes. The best-known signaling pathway to bioactive lipid production involves PLA2, which produces pro-inflammatory molecules, such as prostaglandins and leukotrienes (Fig. 1). By acting in neighboring cells, those mediators amplify initial activation signals and generate clinical symptoms in allergic diseases (Castellani et al., 2009; Funk, 2001). Bioactive lipids can be eicosanoids (e.g., prostaglandins and leukotrienes), phospholipids/sphingolipids (e.g.,

sphingosine-1-phosphate), specialized pro-resolving lipid mediators (e.g., resolvins), and endocannabinoids (e.g., N-palmitoylethanolamine, PEA; anandamide, AEA, and 2-arachidonoylethanolglycerol, 2-AG). All these molecules have different and non-redundant functions in the inflammatory process, acting in an autocrine/paracrine fashion to orchestrate multiple cell responses (Chiurchiù et al., 2018; Chiurchiù and Maccarrone, 2016). The following sections provide information on the autacoid actions of eCBs.

3.1. eCBs, Autacoid Local Inflammation Antagonism (ALIA), and limitation of tissue damage

We refer to “autacoid” as the organic substance locally synthesized on demand by cells. These molecules act as feedback modifiers that participate as resolvers in physiological processes (Keppel Hesselink, 2015). Furthermore, they might act as bridges connecting arms of early and late immunity, modulating cytokine production to favor a specific type of immune reaction (Chiurchiù et al., 2018; Keppel Hesselink, 2015; Zhang et al., 2019). The first evidence of the local anti-inflammatory properties of eCBs described a functional interaction between PEA (an N-acyl-ethanolamide) and MCs to regulate exacerbated responses. This mechanism was called autacoid local inflammation antagonism (ALIA) (Aloe et al., 1993). Later evidence exhibited that PEA had different protective effects on neural excitotoxicity (Skaper et al., 1996). The mechanism of action of N-acyl-ethanolamides was later related to resolution at sites of damage in addition to inflammation, so the meaning of the term ALIA was modified to autacoid local injury antagonism (ALIA) (Levi-Montalcini et al., 1996). The long-chain fatty acids ethanolamines involved in the ALIA process are called ALIAMides. They include PEA, N-stearoyl ethanolamine (NSE), AEA, oleoyl ethanolamide (OEA), and stearoyl ethanolamide (SEA) (Chiurchiù et al., 2018; Dalle Carbonare et al., 2008; Facci et al., 1995; Feigin et al., 2017; Levi-Montalcini et al., 1996).

Although initially described in MCs, most of the evidence on the role of eCBs in the ALIA-like mechanism comes from their reported function in neurons and glia in the central nervous system. Even though MCs are not excitable cells, they have certain similarities to neurons (Babina et al., 2022). For example, both cell types require a calcium threshold to release mediators contained within the cell; the activation of signaling cascades downstream of their receptors triggers changes in some common molecules, and the translocation of transcription factors for gene synthesis shares some characteristics. Those similarities have permitted the extrapolation of several eCB actions and mechanisms described in neurons to MCs. Experimental results indicate that eCBs are produced and act similarly in neuronal damage and allergic reactions. For example: A) *eCBs are produced on demand at the injury site*. Several studies have pointed to the increased eCB concentrations at damage sites as a protective mechanism. Evidence shows that AEA levels increase twenty minutes after kainic acid (KA) administration in a model to evoke neuronal excitotoxicity, and an AEA uptake inhibitor diminishes KA-induced seizures (Marsicano et al., 2003). Also, in a model of allergic contact dermatitis, AEA and 2-AG concentrations increase (Haruna et al., 2017; Karsak et al., 2007). Petrosino et al. observed the production of several eCBs, induced by an initial stimulus of a pseudoallergic reaction (Petrosino et al., 2019). The increase in AEA content resulting from inhibiting the fatty acid amide hydrolase (FAAH), the enzyme responsible for its degradation, also decreases the allergic response (Karsak et al., 2007). Controversially, some studies have reported a differential production of neuronal 2-AG and AEA levels; for example, microglial cells produce twenty and nine times more AEA and 2-AG, respectively, than neurons at basal levels. Also, increased eCB levels have been detected in neuroinflammation (Walter et al., 2002, 2003). B) *eCBs contribute to the resolution of the inflammatory process*. In a KA excitotoxicity model, the stimulation of cannabinoid receptor 1 (CB1R) at the injury site induces gene expression related to reducing excessive neuronal activity (Marsicano et al., 2003). Cannabinoid receptor 2

(CB2R) activation diminishes the release of cytochrome c from mitochondria and increases levels of p-ERK1/2 at injury sites to improve the physiological resolution (Li et al., 2014). In addition, CBR can contribute to diminishing pro-inflammatory factors in an allergy model, by reducing cytokine synthesis (Cruz et al., 2018), immune cell infiltration (Braun et al., 2011; Haruna et al., 2017), tissue swelling (Gaffal et al., 2013; Haruna et al., 2017), and macrophage migration (Gaffal et al., 2013). C) *The eCB system is involved in the effector mechanisms of ALIAs.* The very first study in which the pro-homeostatic function of PEA was observed, suggested the participation of CB2R (Levi-Montalcini et al., 1996). Above all, a correlation exists between several proteins that synthesize, metabolize, transport or recognize the CB implicated in the inflammation process. Nonetheless, the specific element of the eCB system involved in controlling allergic reactions that could help maintain the adequate balance between inflammation and resolution has yet to be found.

In the next section, a detailed description of the eCB system is provided, emphasizing the parallelisms found in its components and functions between neural and immune responses.

4. The endocannabinoid system

4.1. eCBs, CBRs and enzymes

As previously mentioned, the endocannabinoid system comprises the cannabinoid receptors (CBRs), their endogenous ligands (eCBs), and the enzymes participating in their synthesis and degradation. eCBs are lipid-derived signaling molecules synthesized and released on demand, in response to specific physiological stimuli that increase intracellular Ca^{2+} concentrations. There are two families of eCBs, the N-acyl ethanolamines (NAEs) and the 2-Acylglycerols (2-AGs). Each group's most studied and characterized members are AEA and 2-AG, respectively (Di Marzo, 2018; Maccarrone et al., 2015) (see Table 1). However, there are other biochemically and structurally related eCBs. These include PEA, 2-arachidonylethanolamine (anandamide), 2-AGE, o-arachidonylethanolamine (virodhamine), and N-arachidonylethanolamine (NADA) (Fig. 2) (Angelina et al., 2020).

In immune cells, eCBs regulate cell migration and inflammatory mediators production (Almogi-Hazan and Reuven, 2020; Cabral et al., 2015). CB1R and CB2R primarily mediate these effects (Howlett et al., 2002; Kaplan, 2013; Turcotte et al., 2016). 2-AG is a full agonist with

moderate affinity for CB1R and CB2R, while AEA is a partial agonist with a high affinity for CB1R and a low affinity for CB2R (Pertwee, 2015).

CB1R and CB2R are coupled to inhibitory $G_{i/o}$ proteins, whose stimulation inhibits adenylyl cyclase, reducing cAMP levels and protein kinase A (PKA) activity, and activates mitogen-activated protein kinase (MAPK) pathways to regulate nuclear transcription factors (Howlett, 2005). Nevertheless, it has been reported that in MCs CB1R agonists increase cAMP response in a dose-dependent manner at levels similar to those of forskolin, and this effect is abolished by pertussis toxin, indicating that the effect is dependent on $G_{i/o}$ proteins (Rhee et al., 2000; Small-Howard et al., 2005, see following sections). CB1R can also couple to G_{s} proteins, stimulating adenylyl cyclase and increasing cAMP (Bonhaus et al., 1998; Chen et al., 2010), although this has not yet been demonstrated in cells of the immune system (Kaplan, 2013), neither has the coupling of the CB2R to G_{s} proteins in MCs. Finally, CB1R and CB2R inhibit voltage-dependent calcium channels and CB1R, but not CB2R, activate G protein-gated inwardly rectifying potassium channels (GIRK) (Turcotte et al., 2016).

AEA and 2-AG can also act on GPR55 receptors (Pertwee et al., 2010; Sharir and Abood, 2010) and the nuclear Peroxisome Proliferator-Activated Receptors (PPARs) PPAR α and PPAR γ (Bouaboula et al., 2005; O'Sullivan, 2016). Both GPR55 and PPAR γ receptors participate in cannabinoid-mediated effects on immune function (Li et al., 2013; O'Sullivan and Kendall, 2010). AEA also acts on Transient Receptor Potential (TRP) channels, particularly the vanilloid receptor TRPV1 (Di Marzo and De Petrocellis, 2010; Tóth et al., 2009; Zygmunt et al., 1999) and 2-AG can bind to a functional binding site in the GABA $_A$ receptor, modulating its function when GABA levels are low (Sigel et al., 2011) (Fig. 3B).

CB1R and CB2R share 44% sequence identity (Munro et al., 1993); CB1Rs are highly expressed in the central nervous system (CNS) but are also present in peripheral tissues, including immune cells. CB2R was considered for a long time to be expressed only in peripheral immune cells, but its expression in other tissues (Liu et al., 2009), including brain microglia (Maresz et al., 2005; Tanasescu and Constantinescu, 2010; Van Sickle et al., 2005; Walter et al., 2003), astrocytes (Tanasescu and Constantinescu, 2010), and neurons (Jordan and Xi, 2019; Liu, T., et al., 2017; Liu, Q.R. et al., 2017; Zhang et al., 2017) has been confirmed, which may indicate an important role of the eCB system in neuroprotection and neuroinflammation. In the immune system, the CB2R order of expression is B cells > NK cells > monocytes/macrophages > neutrophils > CD8 T-cells > CD4-T cells. CB2R expression is usually higher than CB1R (Galiègue et al., 1995; Parolaro, 1999; Tanasescu and Constantinescu, 2010), and depends on the cell activation state (Braile et al., 2021). In addition, CBRs are expressed in MCs (Espinosa-Riquer et al., 2019), dendritic cells, basophils, and eosinophils (Braile et al., 2021).

AEA and 2-AG membrane precursors are localized in the lipid membranes of neurons and immune cells. These eCBs are synthesized upon demand by cleavage of their precursors and released to the extracellular space. Recent evidence suggests that eCBs are also stored in cell organelles (Maccarrone, 2017). AEA synthesis occurs mainly through two biosynthetic pathways; the first one involves the sequential action of N-acyltransferase (NAT) on phosphatidylethanolamine, generating N-acyl-phosphatidylethanolamine (NAPE), followed by the action of N-acyl-phosphatidylethanolamine-phospholipase D (NAPE-PLD), producing AEA (Schmid et al., 1983). The second route involves the cleavage of NAPE phosphodiester bond by a NAPE-phospholipase C (NAPE-PLC), generating phosphoanandamide (pAEA), which is dephosphorylated by phosphatases, including the protein tyrosine phosphatase PTPN22, to render AEA. This last pathway has been studied in immune cells and is involved in the AEA synthesis stimulated by LPS in macrophages (Liu et al., 2006; Rahaman and Ganguly, 2021). In contrast, NAPE-PLD, the classic AEA biosynthetic pathway, only occurs as a rescue pathway when PLC action is

Table 1
Most studied eCBs and their main characteristics.

	2-AG	AEA
Synthesis	On demand, in response to an increase in intracellular Ca^{2+} levels	On demand, in response to an increase in intracellular Ca^{2+} levels
Precursors	Phosphatidylinositol-4,5-bisphosphate [PI(4,5)P ₂] or triacylglycerol (TAG)	Arachidonic acid and phosphatidylethanolamine or phosphoanandamide (pAEA)
Synthesis enzymes	PI(4,5)P ₂ phosphatase – PLA – PLC γ – DAGL	NAT –NAPE –NAPE-PLD NAPE –PLC –protein phosphatase (PTPN22)
Metabolism enzymes	HSL – DAGL	FAAH, NAAA
Main metabolites	MAGL, ABHD6, ABHD12	Arachidonic acid and ethanolamine
Transporters	FABP5	FABP 5, FABP 7. Also FLAT, heat shock protein 70 (Hsp 70) and albumin, SCP-2
Affinity for CB1R	K _i = 472 nM (full agonist)	K _i = 89 nM (partial agonist)
Affinity for CB2R	K _i = 1400 nM	K _i = 321 nM
Agonist actions at receptors other than CB1R/CB2R	TRPV1, GABA _A , PPAR γ , and GPR55,	TRPV1, GPR55 and PPARs

Endocannabinoids

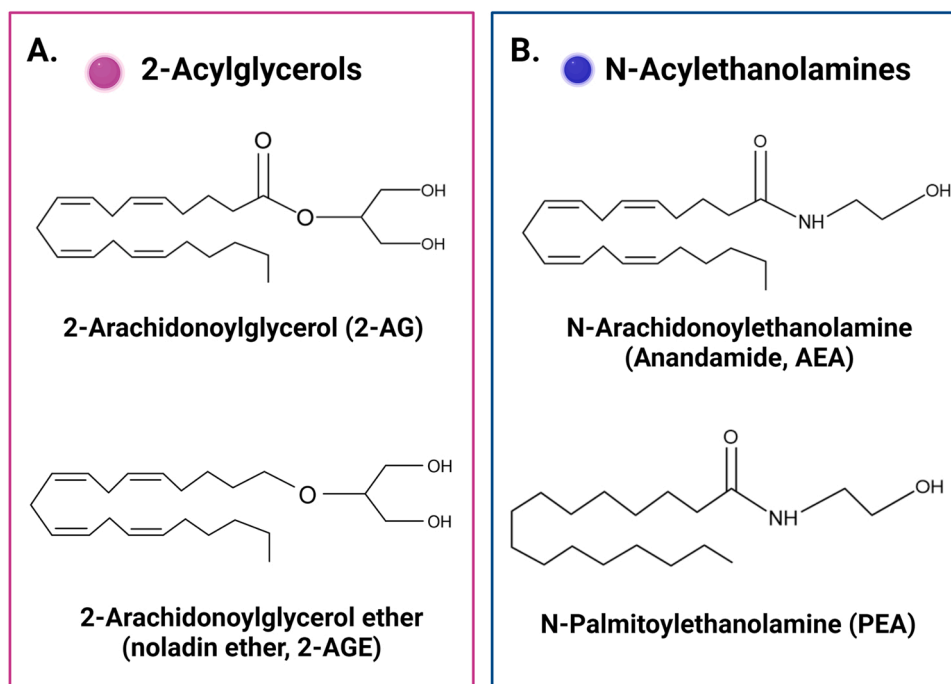


Fig. 2. Chemical structure of main endocannabinoids. Endocannabinoids are a family of bioactive lipids constituted by two groups: the N-acylethanolamines (NAEs) and the 2-Acylglycerols (2-AcGs), which differ in their chemical structure. A. 2-Arachidonoylglycerol and noladin ether belong to the 2-AcGs group B. Anandamide and N-palmitoyl ethanolamine are members of the NAEs group. Created with BioRender.com.

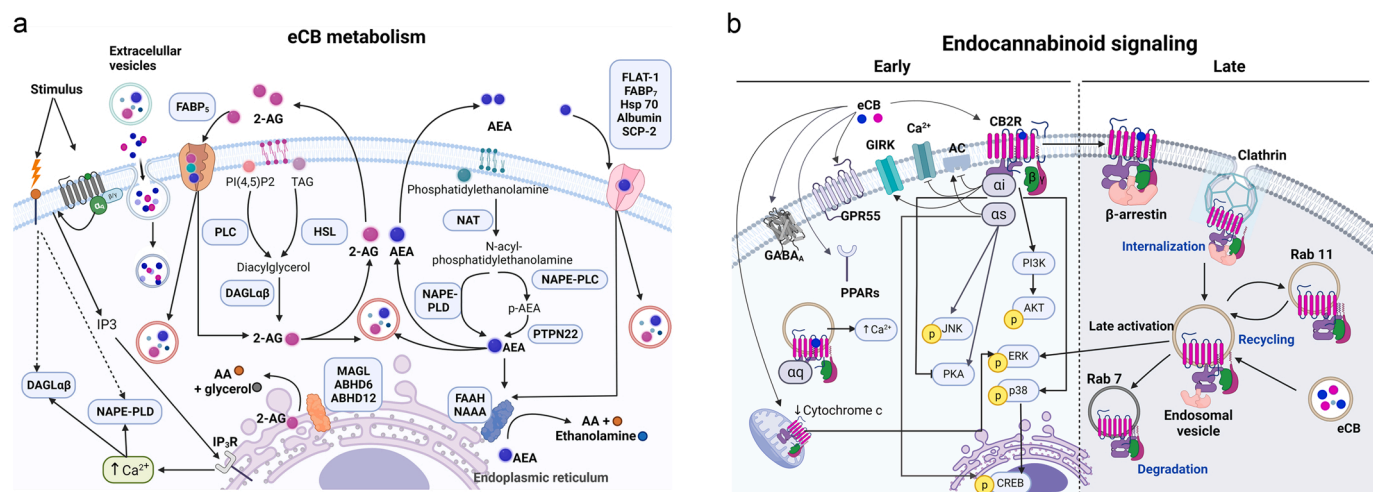


Fig. 3. Endocannabinoid metabolism, recognition and activation of signaling pathways. A. eCB Metabolism. In the case of on-demand eCB synthesis, triggering stimuli lead to intracellular calcium rise and activation of the diacylglycerol lipase (DAGL) and the N-acyl-phosphatidylethanolamine specific phospholipase D (NAPE-PLD). Those enzymes synthesize 2-AG and AEA, respectively. DAGL metabolizes the DAG produced by PLC from PI4,5P2 or by hormone sensitive lipase (HSL) from triacylglycerol (TAG) to form 2-AG. On the other hand, NAPE-PLD metabolizes N-acyl-phosphatidylethanolamine produced by N-acyl-transferase (NAT) from membrane phosphatidylethanolamine. Also, AEA is synthesized by NAPE-PLC, which generates p-AEA from N-acyl-phosphatidylethanolamine. This compound is then dephosphorylated by the PTPN22 phosphatase. eCBs can be stored in vesicles, secreted to activate their receptors or degraded by enzymes such as the monoacylglycerol lipase (MAGL), α , β -hydrolase domain-containing 6 protein (ABHD6), α , β -hydrolase domain-containing 12 protein (ABHD12), fatty acid amide hydrolase (FAAH), and N-acylethanolamine-hydrolyzing acid amidase (NAAA). Exogenous eCBs are transported to the interior of cells through the fatty acid binding proteins (FABPs) 5 and 7, and the FAAH-1-like anandamide transporter (FLAT)– 1. AEA is also transported bound to albumin, the heat shock protein (HSP)– 70 and the sterol carrier protein (SCP)– 2. eCBs can also enter the cells through extracellular vesicles that are internalized to the cytosol. See text for details. B. Endocannabinoid signaling. eCBs bind to distinct receptors, such as GABA_A, PPARs, GIRK channels and GPCRs, such as GPR55, CB1R and CB2R. The best characterized one in the immune system is the CB2R that is expressed also in mitochondria and intracellular vesicles. Generally, eCBs elicit a rapid response mediated by GPCRs located at the plasma membrane and coupled to heterotrimeric G proteins. GPCR signaling continues after membrane receptors bind β -arrestin and are internalized in clathrin-coated vesicles. Intracellular signaling is mediated by β -arrestin. CB2 receptors traffic to Rab7 or Rab11-decorated vesicles, to be degraded or recycled, respectively. Intracellular eCBs can activate internalized receptors. See text for details. Created with BioRender.com.

compromised in these cells (Liu et al., 2006) (Fig. 3A).

2-AG is synthesized by the sequential hydrolysis of an arachidonoyl containing phosphatidylinositol 4,5-bisphosphate [PI(4,5)P₂], first by phospholipase C (PLC), yielding DAG, followed by diacylglycerol lipase (DAGL) (Lu and MacKie, 2016). There are two isoforms of DAGL α and β ; DAGL α appears to be the main isoform responsible for 2-AG production in the brain, while DAGL β seems important for 2-AG production during immune responses as demonstrated in macrophages (Hsu et al., 2012; Rahaman and Ganguly, 2021) and in PEA-induced 2-AG production from the RBL-2H3 cell line (Petrosino et al., 2019). 2-AG can also be produced from triacylglycerol (TAG), which is hydrolyzed by hormone-sensitive lipase (HSL) producing DAG, which is further processed by DAGL generating 2-AG (Baggelaar et al., 2018). In some immune cells, the 2-AG biosynthetic pathway seems to have specific characteristics; for example, in rat microglial cells, the blockade of PLC did not affect the levels of 2-AG. At the same time, inhibition of phosphatidic acid phosphohydrolase reduced the production of this eCB, demonstrating that in those cells, the main biosynthetic pathway to produce 2-AG requires the hydrolysis of phosphatidic acid but not that of PI(4,5)P₂ (Carrier et al., 2004; De Filippis et al., 2008). In contrast, other evidence demonstrates that in macrophages and microglia, the immune cell-restricted PLC γ 2 seems responsible for producing DAG, which differs from the classic biosynthetic pathway in neurons that requires PLC β (Jing et al., 2021).

The release of eCBs in the brain is induced by increased postsynaptic Ca²⁺ levels after depolarization-induced Ca²⁺ influx, mediated by voltage-gated Ca²⁺ channels or postsynaptic Gq/11- coupled GPCRs activation, like the group I metabotropic glutamate receptors (mGluR1 & mGluR5). These two stimuli enhance eCB release (Ohno-Shosaku et al., 2002) and enable eCB release in response to small Ca²⁺ increases simultaneously to weak receptor activation, a phenomenon termed Ca²⁺-assisted receptor-driven eCB release (Ca-RER) (Hashimoto et al., 2007). In the immune system, the production of eCBs can happen in response to immunoglobulins (Lau and Chow, 2003; Nam et al., 2016), LPS (Espinosa-Riquer et al., 2019), platelet-activating factor (PAF) (Berdyshev et al., 2001), PEA (Petrosino et al., 2019), capsaicin (a TRPV1 agonist), THC, and AEA, among others.

Inactivation of eCBs occurs by cellular uptake, mediated by putative eCB transporters localized in the cellular membrane (Chicca et al., 2012), followed by intracellular degradation. The FAAH, localized on the endoplasmic reticulum, mediates AEA hydrolysis, generating AA and ethanolamine; however, a second pathway for its degradation is AEA oxidation by cyclooxygenase-2 (COX-2) producing prostamides (Woodward et al., 2008), and by the 12- and 15- lipooxygenases (LOX), which derivatives have biological activity mediated by CBR, PPAR- α and TRPV1 (Yates and Barker, 2009). FAAH has been identified in human mast cells (HMC-1). However, its activity was measurable only in the presence of 5-lipoxygenase inhibitors and a low pH. This suggests that FAAH is located in lysosomes and mitochondria in MCs, in contrast to other cell types, in which FAAH is a plasma membrane-bound protein and works at a pH of around 9 (Maccarrone et al., 2000; Ueda et al., 1999).

Three enzymes mainly mediate 2-AG hydrolysis: monoacylglycerol lipase (MAGL), alpha/beta domain containing hydrolase 6 (ABHD6), and alpha/beta domain containing hydrolase 12 (ABHD12), all of which produce AA and glycerol (Blankman et al., 2007). In addition, 2-AG can also be oxidized by COX-2 and 12- and 15-LOXs (Yates and Barker, 2009) and, under some conditions, hydrolyzed by FAAH (Lu and MacKie, 2016). ABHD6 plays an important role in the regulation of the 2-AG production and levels in response to estradiol and progesterone, reducing the activation of the endocannabinoid system in leukocytes of females (Drehmer et al., 2019; Vannacci et al., 2002), a process that has not been described in other cells.

4.2. eCB transport system

An AEA transport system across the plasma membrane (AMT) was proposed in the late nineties (Hillard et al., 1997), a notion later supported by data from several research groups (Beltramo and Piomelli, 2000; Rakhshan et al., 2000). Notwithstanding, the existence of an eCB membrane transporter (EMT) is still under debate, awaiting its molecular characterization (Deutsch, 2016). Being lipids, eCBs are diffusible to some extent in cellular membranes. In line with this feature, several studies have concluded that eCB uptake occurs by passive diffusion, in which FAAH enzymatic activity generates an inward concentration gradient that serves as the driving force for AEA diffusion (Glaser et al., 2003). In addition, the idea that eCBs are sequestered into an intracellular compartment after diffusion, or bind to an intracellular binding protein before metabolizing, complements this mechanism (Hillard and Jarrahian, 2003). eCB uptake has also been proposed to occur by endocytosis, a process in which AEA or 2-AG bind to a membrane carrier protein located within caveolae lipid rafts, which form vesicles by endocytosis, sequestering the eCB (Yates and Barker, 2009). Moreover, a bidirectional movement of AEA and 2-AG across cell membranes has been documented, with both eCBs competing for a common putative cell membrane transporter (Chicca et al., 2012).

Hydrolysis is an intracellular event, and since eCBs lipid nature hinders their movement across aqueous media (cytosol), intracellular carriers (fatty acid binding proteins FABPs) have been proposed to be responsible for eCB cytosolic trafficking towards the hydrolysis site (Kaczocha et al., 2009) and transport to effector and sequestration sites (Fowler, 2013). AEA intracellular transporters (AIT) have been found in different cell types. They include FABP-5 and -7, driving AEA to the endoplasmic reticulum for catabolism (Kaczocha et al., 2009) or to nuclear PPARs (Kaczocha et al., 2012), albumin and the heat shock protein 70 (HSP70) (Oddi et al., 2009), the FAAH-1-like AEA transporter (FLAT-1) (Fu et al., 2012) and the sterol carrier protein 2 (SCP-2) (Liedhegner et al., 2014). In contrast to AEA, little is known about the intracellular transport of 2-AG; however, evidence for intracellular 2-AG transport by FABP5 has been provided (Nicolussi et al., 2014).

Like the cytosol, the extracellular space/synaptic cleft is hydrophilic; a property hindering eCB diffusion and suggesting that cell-to-cell movement would require extracellular transporters. There is in vitro evidence that astrocytes release FABP5 and synapses, suggesting that, in addition to its intracellular eCB transporter role, FABP may serve as an extracellular transporter (Haj-Dahmane et al., 2018). Recently, it was suggested that extracellular membrane microvesicles, produced by microglia, serve as AEA extracellular transporters (AET) in the brain (Gabielli et al., 2015). It remains to be determined if this putative transport mechanism is common to 2-AG.

Challenging the classical idea that AEA is produced on demand, storage of this eCB has been reported in adiposomes (lipid droplets), sharing this compartment with their catabolic enzyme FAAH (Oddi et al., 2008), a finding suggesting that AEA may be stored. Similarly, a preexisting 2-AG pool is present in sperms (Miller et al., 2016), suggesting that this eCB can also be stored. However, more studies are needed to support the hypothesis that eCBs are intracellularly stored and this possibility must also be tested in immune cells. Also, besides the “on-demand” synthesis of eCBs, AEA and 2-AG are tonically produced in the brain because the inhibition of MAGL or FAAH activity in the absence of neuronal activation increases 2-AG and AEA levels and potentiates synaptic transmission through CB1R-dependent mechanisms (Kaczocha and Haj-Dahmane, 2022; Oubrain et al., 2021).

4.3. Evidence for the existence of an eCB system in MCs

The interest in the eCB system in MCs has led to identifying the distinct components (including receptors, enzymes involved in their synthesis and degradation, and the eCBs themselves) in distinct MCs preparations. It is important to emphasize the different MC subsets

where the eCB system has been described, as MCs change their characteristics and protein expression according to their origin and environment. In this regard, it is expected that not all MC subsets will behave equally or express the same elements of the eCB system. For example, the rat basophilic cell line RBL-2H3 and the human mast cell line HMC-1 cell are malignantly transformed; therefore, they may not reflect tissue or primary cultured MCs (Babina et al., 2005; Falcone et al., 2018; Feoktistov and Biaggioni, 1996; Guhl et al., 2003, 2010; Le et al., 2011; Moiseeva et al., 2012). The same happens with murine BMMCs that mature with factors added to the culture medium and with tissue MCs that mature in situ according to their environment presenting significant differences in their transcripts (Akula et al., 2020; Malbec et al., 2007). In humans, even cells from a same tissue may change their eCB expression profile according to the donor, which varies if the donor was stimulated or not. An example of this situation in humans is illustrated in the database Fantom5 human promoterome view and listed in the table below, where MCs obtained from the skin of the same donor change CB1R expression in response to FcεRI stimulation. Table 2 enlists the different studies demonstrating the existence of an eCB system in MC models, the methods used by each group to support that evidence, and the main effects of eCBs on MC responses.

4.4. Intracellular localization of CBRs in MCs

Classically, CBRs are observed at the plasma membrane of neurons and other cell types, where they signal through the Gα_i protein in a short time-lapse. After that, GPCRs are phosphorylated and bind to β-arrestin. This leads to their internalization, removing receptors from the plasma membrane and activating intracellular effectors later, such as the mitogen-activated kinases (MAPK) (Calebiro and Godbole, 2018). For example, CB1R undergoes rapid clathrin-mediated internalization after agonist stimulation, and it can be recycled to the plasma membrane or enter the degradative pathways (Hsieh et al., 2002; Stadel et al., 2011). CB2R phosphorylation and agonist-mediated internalization have been demonstrated (Bouaboula et al., 1999). Once internalized, CB2Rs follow the recycling pathway with the participation of the small GTPase Rab11 (Grimsey et al., 2011). It is worth mentioning that CBR trafficking studies have been complicated by the presence of a large intracellular pool of CB1R and CB2R, detected both in transfected cell lines and native CBR-expressing tissues (Castaneda et al., 2013; Grimsey et al., 2010).

Internalization was initially associated with receptor signaling desensitization, but evidence indicates that this process can induce prolonged receptor signaling from intracellular compartments (Calebiro and Godbole, 2018). This is the case of internalized CB1R (Brailoiu et al., 2011) and CB2R (Brailoiu et al., 2014), which have been found to be functional. Intracellular CB1R has been identified in mitochondria of both neurons and astrocytes and suggested to signal to inhibit mitochondrial respiration (Mendizabal-Zubiaga et al., 2016). They have also been localized on lysosomes, which activation mobilizes Ca²⁺ from the endoplasmic reticulum and lysosomal calcium stores (Brailoiu et al., 2011), and on endolysosomal vesicles (Brailoiu et al., 2011; Grimsey et al., 2010), as well as intracellularly in axons of the basal ganglia (Pickel et al., 2004). CB2R has been localized on endolysosomes, where its activation releases Ca²⁺ from intracellular stores (Brailoiu et al., 2014).

In some MC preparations, specifically in bone marrow-derived mast cells (BMMCs) generated in the presence of interleukin IL-3, CBRs are only detected inside the cells, in vesicles that include recycling endosomes, late endosomes and lysosomes (Espinosa-Riquer et al., 2019). Moreover, recent observations from our laboratory utilizing confocal microscopy show that CBRs are located intracellularly in BMMCs, where low co-localization of both receptors is detected. Remarkably, CBRs change their localization after cell sensitization with monomeric IgE and are then detected in clearly distinct intracellular compartments (Fig. 4). This phenomenon is not observed in other MC types, where CBRs localize at the plasma membrane, such as the rat basophilic cell line

RBL-2H3 (Small-Howard et al., 2005), suggesting that intracellular localization of these receptors may depend on the MC type and the conditions of the culture.

It remains unknown if the intracellular localization of CBRs in some cell preparations is part of a desensitization process or reflects an intracellular signal transduction mechanism that occurs in addition to the classical autacoid signaling cascade. Desensitization and internalization of CBRs could be related to the culture media used. For example, it is known that commercial fetal bovine serum (FBS) contains variable amounts (250–700 nM) of bioactive lipids, including 2-AG, which might affect CBR recycling processes and significantly influence the outcome of experiments using isolated cells (Marazzi et al., 2011).

5. Effects of eCBs on IgE/Ag-dependent MC activation

Cannabinoids exert mainly inhibitory actions in experimental allergy models and MC activation, both in vivo and in vitro. Those results lead to the proposal of the eCB system as a suitable target for the control of MC-initiated inflammatory reactions in the skin and other organs (Harvima et al., 2014; Sugawara et al., 2012). One of the first observations on the inhibitory actions of eCBs on MC activation was made using PEA in a section of ear pinna of rats (Aloe et al., 1993). Although the triggering agent in that study was substance P, and the intensity of that stimulus is considered lower than the one induced by the IgE receptor (Frossi et al., 2017), those initial investigations generated a starting point for other studies that led to propose the eCB system as a modulator of allergic responses. Since then, several studies have been performed to characterize the effects of distinct eCBs in different types of MCs stimulated with IgE/Ag complexes (Table 3).

In RBL-2H3 cells, PEA binds to CB2R, downregulating MC activation triggered by IgE/Ag, and, interestingly, those effects were not observed with AEA, that antagonized the actions of PEA (even when the last one was used at higher concentrations) (Facci et al., 1995). In another study, using the same cell line, 2-AG (100 μM) and methanandamide (10 μM) increased the release of β-hexosaminidase and serotonin after the stimulation with IgE/Ag complexes, while AEA had a null effect on the same response (Granberg et al., 2001). Notably, preincubation with CBR antagonists and subsequent treatment with PEA (100 μM) decreased FcεRI-induced MC secretory response (Granberg et al., 2001).

In other MC types, such as BMMCs, AEA inhibits, in a concentration-dependent manner, degranulation triggered by FcεRI receptors (Cruz et al., 2018). The same effect is observed utilizing the selective CB2R agonist HU308 (1 μM) and the GPR55 agonist LPI (10 μM). Interestingly, the inhibitory effect of those agonists is not prevented by the cell pre-treatment with pertussis toxin (PTX). Since CB2R is preferentially coupled to Gα_i and GPR55 to Gα_{11/13}, this result suggests that effects of eCB on degranulation occurs with the participation of CB2R-GPR55 heteromers rather than the Gα_i protein (Cruz et al., 2018). On the other hand, participation of the CB1R in the modulation of MCs' responses stimulated with IgE/Ag complexes has also been proposed. The selective CB1R agonist methanandamide (0.1–10 μM) decreased the antigen-stimulated serotonin release in RBL-2H3, and a CB1R antagonist reversed this effect (Samson et al., 2003; Small-Howard et al., 2005). Besides, the knockdown of the CB1R and the CB1R antagonist AM251 (1 μM) enhanced the degranulation of human mucosal-type MCs from a nasal polyp associated with allergic rhinitis (Sugawara et al., 2013).

In vivo, utilizing a model of atopic dermatitis induced by oxazolone, AEA and α-oleoyl oleoylamine serinol (α-OOS, a CB1R selective agonist) improved the recovery of the epithelial barrier diminishing the inflammatory process (Kim et al., 2015). Those compounds also inhibited the production of cAMP stimulated with forskolin in a concentration-dependent manner in RBL-2H3 cells (Nam et al., 2016). Therefore, the participation of Gα_i proteins in the inhibitory effects of cannabinoids (particularly of CB1R agonists) on FcεRI-dependent activation of MCs can be suggested.

When signal transduction of CBRs is analyzed in MCs, data indicate

Table 2

Components of the eCB system reported in mast cells.

Mast cell subset	Culture conditions or methods for sample collection	Method of detection	Reference
Enzymes for AEA and PEA synthesis (Enzyme type not specified)			
RBL-2H3	Cells were cultured in MEM, 10% bovine serum, 1% penicillin: streptomycin Stimulation with <i>S. chromofuscus</i> PLD, ionomycin, or HSA-DNP	Radioactive detection Gas chromatographic-electron impact mass spectrometric identification.	(Bisogno et al., 1997)
N-acyl phosphatidyl-ethanolamine specific phospholipase D (NAPE-PLD)			
RBL-2H3	Cells were cultured in EMEM supplemented with glutamine, penicillin, streptomycin and 15% FBS	q-PCR Increase of AEA production (in response to substance P (SP) and PEA stimulation). Transcriptomic analysis of ex vivo, cultured MCs from one donor stimulated through the FcεRI (Heliscope CAGE, Delve 0.95)	(Petrosino et al., 2019)
Human skin mast cells	Cells were isolated from tissue. Total RNA extraction with miRNeasy Mini-v1.0	Transcriptomic analysis of ex vivo, cultured MCs from four unstimulated donors. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser
Human skin mast cells	Cells were isolated from tissue. OP-RNA total RNA extraction with Trizol-ethanol	Transcriptomic analysis of ex vivo, cultured MCs from four unstimulated donors. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser
Diacylglycerol lipase-α (DAGL-α)			
RBL-2H3	Cells were cultured in EMEM supplemented with glutamine, penicillin, streptomycin and 15% FBS	q-PCR Enzyme activity assay Increase of 2-AG production (in response to SP and PEA stimulation).	(Petrosino et al., 2019)
Human skin mast cells	Cells were isolated from tissue. OP-RNA total RNA extraction with Trizol-ethanol	Transcriptomic analysis of ex vivo, cultured MCs from two unstimulated donors. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser
Diacylglycerol lipase-β (DAGL-β)			
RBL-2H3	Cells were cultured in EMEM supplemented with glutamine, penicillin, streptomycin and 15% FBS	q-PCR Enzyme activity assay Increase of 2-AG production (in response to SP and PEA stimulation).	(Petrosino et al., 2019)
Purified MCs from the peritoneal cavity of C57BL/6 mice	Cells were obtained with pre-warmed PBS flushed in the peritoneal cavity and enriched with magnetic bead-separation and frozen in liquid nitrogen	Proteomic analysis (MS/MS spectra searched against FASTA database, MaxQuant platform)	(Plum et al., 2020) Supplementary table 6
Human skin mast cells	Cells were isolated from tissue. Total RNA extraction with miRNeasy Mini-v1.0	Transcriptomic analysis of ex vivo, cultured MCs from one donor stimulated through the FcεRI (Heliscope CAGE, Delve 0.95).	Fantom5 Zenbu genome browser
Human skin mast cells	Cells were isolated from tissue. OP-RNA total RNA extraction with Trizol-ethanol	Transcriptomic analysis of ex vivo, cultured MCs from four unstimulated donors. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser
Cannabinoid receptor 1 (CB1R)			
RBL-2H3	Cells were cultured in MEM supplemented with 15% FBS, L-glutamine and penicillin+streptomycin	Use of specific antagonist on mast cell secretion induced by DNP-HAS.	(Granberg et al., 2001)
RBL-2H3 and P815 (mastocytoma cell line)	Cells were cultured in DMEM supplemented with 10% FBS and glutamine	NB WB	(Samson et al., 2003)
Rat peritoneal mast cells	Cells were obtained from peritoneal lavages and maintained in HEPES buffer, supplemented with BSA, then, purified with Percoll gradient	Specific agonists and antagonists on FcεRI induced histamine secretion.	(Lau and Chow, 2003)
RBL-2H3 And BMMCs	Cells were cultured in DMEM supplemented with FBS and glutamine IL-3	WB Flow cytometry	(Small-Howard et al., 2005)
Human skin mast cells	Cells were obtained from human skin from different parts of the body and then frozen in liquid nitrogen	Immunostaining with specific antibodies	(Ständer et al., 2005)
RBL-2H3	Cells were cultured in DMEM supplemented with FBS, L-glutamine penicillin, and streptomycin	RT-PCR	(Giudice et al., 2007)
Rat mast cells from granulomatous tissue	Granulomatous tissue fixed in 10% formalin and stained with toluidine blue	Use of specific agonists	(De Filippis et al., 2008)
Dog skin mast cells	Tissue from skin biopsies, placed in neutral-buffered 4% formalin and embedded in paraffin, then, stained with H&E	IHC	(Campora et al., 2012)
hMNCs (Human mucosal-type mast cells) in nasal polyps (NP)	NPs were maintained in supplemented serum-free William E medium	IF Binding assays with specific fluorescent ligand	(Sugawara et al., 2013)
Sickle (<i>HbSS-BERK</i>) mice skin mast cells	Skin biopsies were incubated in DMEM supplemented with antibiotics, l-glutamine, and HEPES	Agonists and degranulation analysis	(Vincent et al., 2016)
RBL-2H3 and BMMCs	Cells were cultured in DMEM supplemented with 10% FBS and penicillin/streptomycin Cultured with IL-3 in DMEM with 10% heat inactivated FBS, 2-mercaptoethanol, glutamine and 20% WEHI-3-conditioned medium containing IL-3	Agonist on ionomycin- and IgE/antigen- dependent degranulation and proliferation assays	(Nam et al., 2016)
Mice ear skin mast cells	Dorsal and ventral halves were incubated in HBSS and treated to separate the epidermis and to work with the remaining tissue.	Transcriptomic analysis (Affymetrix Mouse Gene 1.0 ST, ImmGen, Multiplot Studio module of GenePattern software)	(Dwyer et al., 2016)

(continued on next page)

Table 2 (continued)

Mast cell subset	Culture conditions or methods for sample collection	Method of detection	Reference
BMMCs	Cells were cultured in RPMI media supplemented with mercaptoethanol, HEPES, pyruvate, IL-3, SCF, antibiotic, antimycotic, non-essential aminoacids and 10% FBS	RT-PCR (RNA extracted by Trizol treatment cDNA kit from Thermo Fisher Scientific)	(Cruz et al., 2018)
BMMCs from C57BL6/J mice	Cells were cultured in media supplemented with FBS, IL-3, and SCF	RT-PCR	(Espinosa-Riquer et al., 2019)
RBL-2H3	Cells were cultured in EMEM supplemented with glutamine, penicillin, streptomycin and 15% FBS	WB q-PCR	(Petrosino et al., 2019)
Human skin mast cells	Cells were isolated from tissue. Total RNA extraction with miRNeasy Mini-v1.0	Transcriptomic analysis of ex vivo, cultured MCs from one donor stimulated through the FcεRI. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser
Human skin mast cells	Cells were isolated from tissue. OP-RNA total RNA extraction with Trizol-ethanol	Transcriptomic analysis of ex vivo, cultured MCs from unstimulated donor. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser
Cannabinoid receptor 2 (CB2R)			
RBL-2H3 and RPMCs (Rat peritoneal mast cells)	Cells were cultured in EMEM supplemented with glutamine, penicillin and 20% FBS	mRNA (hybridization; no detection of CB ₁) Radioligand binding	(Facci et al., 1995)
RBL-2H3	Cells were cultured in MEM supplemented with 15% FBS, L-glutamine and penicillin+streptomycin	Use of specific antagonist on mast cell secretion induced by DNP-HSA.	(Granberg et al., 2001)
Guinea pig mast cells from peritoneal and pleural cavities	Pleural and peritoneal washings and isolated by density gradient with Ficoll. Then, resuspended in Sorensen buffer	Use of specific agonists and antagonists on histamine release induced with ovalbumin.	(Vannacci et al., 2002)
Rat peritoneal mast cells	Cells were obtained from peritoneal lavages and maintained in HEPES buffer supplemented with BSA, then, purified with Percoll gradient	Specific agonists and antagonists on FcεRI induced histamine secretion.	(Lau and Chow, 2003)
RBL-2H3 and BMMCs	Cells were cultured in DMEM supplemented with FBS and glutamine	WB Flow cytometry	(Small-Howard et al., 2005)
Human skin mast cells	Cells were obtained from human skin from different parts of the body and then frozen in liquid nitrogen	Immunostaining with specific antibodies.	(Ständer et al., 2005)
Mice ear pinna skin mast cells	Homogenates of the ear in formamide following by incubation at 50° C	Ear oedema induced by compound 48/80 with specific agonist and PEA.	(Jonsson et al., 2006)
RBL-2H3	Cultured in DMEM supplemented with 10% FBS, L-glutamine, penicillin, streptomycin	RT-PCR	(Giudice et al., 2007)
Human endometrial mast cells	Cells were cultured in RPMI medium supplemented with 10% foetal calf serum, glutamine, and antibiotics	Use of specific agonist on A23187-induced mast cell degranulation.	(Iuvone et al., 2008)
Rat mast cells from granulomatous tissue	Granulomatous tissue fixed in 10% formalin and stained with toluidine blue	Use of specific agonists	(De Filippis et al., 2008)
Dog skin mast cells	Tissue from skin biopsies placed in neutral-buffered 4% formalin and embedded in paraffin, then, stained with H&E	IHC	(Campora et al., 2012)
Human skin mast cells (ex-vivo, expanded and stimulated)	Digestion of skin and purification of mast cells with anti-human c-Kit microbeads. For expansion, cells were cultured with IL-4 +SCF. Stimulation was achieved with FcεRI crosslinking	Transcriptomic analysis (Heliscope CAGE, Delve 0.95 data submitted to fantom5)	(Motakis et al., 2014)
Sickle (<i>HbSS-BERK</i>) mice skin mast cells	Cells were obtained from skin punch biopsies and stained with toluidine blue or immunostained	Agonists and degranulation analysis	(Vincent et al., 2016)
BMMCs	Cells were cultured in RPMI media supplemented with mercaptoethanol, HEPES, pyruvate, IL-3, SCF, antibiotic, antimycotic, non-essential aminoacids and 10% FBS	RT-PCR (RNA extracted by trizol treatment cDNA kit from Thermo Fisher Scientific)	(Cruz et al., 2018)
Mast cells of the lamina propria of dogs' colon	Tissues were collected and washed in PBS, fixed and processed to obtain cryosections	IF	(Galiazzo et al., 2018)
BMMCs from C57BL6/J mice	Cells were cultured in ulture media supplemented with FBS, IL-3, and SCF	RT-PCR WB IF	(Espinosa-Riquer et al., 2019)
RBL-2H3	Cells were cultured in EMEM supplemented with glutamine, penicillin, streptomycin and 15% FBS	q-PCR	(Petrosino et al., 2019)
Human skin mast cells	Cells were isolated from tissue. Total RNA extraction with miRNeasy Mini-v1.0	Use of specific agonist and antagonist. Transcriptomic analysis of ex vivo, cultured MCs from one donor, unstimulated and stimulated through the FcεRI. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser
Human skin mast cells	Cells were isolated from tissue. OP-RNA total RNA extraction with Trizol-ethanol	Transcriptomic analysis of ex vivo, cultured MCs from unstimulated 4 different donors. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser
G protein-coupled receptor 55 (GPR55)			
HMC-1	BMMCs	RT-PCR WB	(Cantarella et al., 2011)
BMMCs	Cells were cultured in RPMI media supplemented with mercaptoethanol, HEPES, pyruvate, IL-3, SCF, antibiotic, antimycotic, non-essential aminoacids and 10% FBS	RT-PCR (RNA extracted by trizol treatment cDNA kit from Thermo Fisher Scientific)	(Cruz et al., 2018)
Mast cells of the lamina propria from dogs' colon	Tissues were collected and washed in PBS, fixed, and processed to obtain cryosections	IF	(Galiazzo et al., 2018)
Human skin mast cells	Cells were isolated from tissue. OP-RNA total RNA extraction with Trizol-ethanol	Transcriptomic analysis of ex vivo, cultured MCs from unstimulated donor. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser

(continued on next page)

Table 2 (continued)

Mast cell subset	Culture conditions or methods for sample collection	Method of detection	Reference
Anandamide (AEA) transporter (Type not specified)			
RBL-2H3	Cells were cultured in MEM, 10% bovine serum, 1% penicillin: streptomycin Stimulation with <i>S. chromofuscus</i> PLD, ionomycin, or HSA-DNP	¹⁴ C-AEA and ¹⁴ C-PEA uptake	(Bisogno et al., 1997)
HMC-1	Cells were cultured in Iscove's medium with 10% calf serum, α-thioglycerol at 5%	³ H-AEA uptake	(Maccarrone et al., 2000)
RBL-2H3	Cells were cultured in DMEM with 10% FBS supplemented with glutamine, penicillin/streptomycin	AEA uptake analysis and inhibition by other compounds.	(Rakhshan et al., 2000)
RBL-2H3	Cells were cultured in MEM supplemented with 10% FBS, non-essential aminoacids and PEST	³ H-AEA and ³ H-PEA uptake and effect of transport inhibitor (AM404)	(Jacobsson and Fowler, 2001)
Fatty acid amide hydrolase (FAAH)			
RBL-2H3 RBL-1	Cells were cultured in MEM, 10% bovine serum, 1% penicillin: streptomycin Stimulation with <i>S. chromofuscus</i> PLD, ionomycin, or HSA-DNP	Production of ¹⁴ C-ethanolamine	(Bisogno et al., 1997)
RBL-2H3	Cells were cultured in MEM, 10% bovine serum, 1% penicillin: streptomycin	¹⁴ C-AEA hydrolysis inhibition by other eCB	(Di Marzo and Deutsch, 1998)
HMC-1	Cells were cultured in Iscove's medium with 10% calf serum, α-thioglycerol at 5%	AEA hydrolysis assay and use of specific inhibitors	(Maccarrone et al., 2000)
RBL-3H3	Cells were cultured in DMEM with 10% FBS supplemented with glutamine, penicillin/streptomycin	Enzymatic activity assay in the absence and presence of inhibitors.	(Rakhshan et al., 2000)
RBL-2H3	Cells were cultured in MEM supplemented with 10% FBS, non-essential aminoacids and PEST	Effect of FAAH inhibitors	(Jacobsson and Fowler, 2001)
RBL-2H3	Cells were cultured in EMEM supplemented with glutamine, penicillin, streptomycin and 15% FBS	q-PCR	(Petrosino et al., 2019)
N-acethylethanolamine hydrolizing acid amidase (NAAA)			
RBL-2H3	Cells were cultured in EMEM supplemented with glutamine, penicillin, streptomycin and 15% FBS	q-PCR	(Petrosino et al., 2019)
Mice peritoneal exudate cells and Mouse MCs	Cells were obtained with pre-warmed PBS flushed in the peritoneal cavity and enriched with magnetic bead-separation and frozen in liquid nitrogen	Proteomic analysis (MS/MS spectra searched against FASTA database, MaxQuant platform)	(Plum et al., 2020) Supplementary tables 4 and 6
Human skin mast cells	Cells were isolated from tissue. Total RNA extraction with miRNeasy Mini-v1.0	Transcriptomic analysis of ex vivo, cultured MCs from one donor, unstimulated and stimulated by triggering the FcεRI with a monoclonal antibody. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser
Human skin mast cells	Cells were isolated from tissue. OP-RNA total RNA extraction with Trizol-ethanol	Transcriptomic analysis of ex vivo, cultured MCs from unstimulated 4 different donors. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser
Monoacylglycerol lipase (MAGL)			
RBL-2H3	Cells were cultured in EMEM supplemented with glutamine, penicillin, streptomycin and 15% FBS	q-PCR	(Petrosino et al., 2019)
Human skin mast cells	Cells were isolated from tissue. Total RNA extraction with miRNeasy Mini-v1.0	Transcriptomic analysis of ex vivo, cultured MCs from one donor, unstimulated and stimulated through the FcεRI. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser
Human skin mast cells	Cells were isolated from tissue. OP-RNA total RNA extraction with Trizol-ethanol	Transcriptomic analysis of ex vivo, cultured MCs from unstimulated 4 different donors. (Heliscope CAGE, Delve 0.95)	Fantom5 Zenbu genome browser

that CBR1 and CBR2 activate non-redundant pathways. In RBL-2H3 cells, the use of an equipotent CB1R and CB2R agonist increased AKT and ERK phosphorylation, but this effect was not replicated with a CB1R specific agonist (Samson et al., 2003). Discerning the role of individual components of the eCB system in MCs is challenging because numerous factors need to be considered (see the following sections).

5.1. Possible molecular mechanisms of CB-mediated inhibition of FcεRI-dependent reactions in MCs

Derived from the investigation of the signaling pathways activated by CBs and the mechanisms of FcεRI negative control, some mechanisms of CB-mediated inhibition of the FcεRI signaling system have been described or can be postulated. Evidence shows that CBs inhibit molecules activated by the IgE receptor or activate pathways involved in known inhibitory loops of the FcεRI receptor signaling system (Siebenhaar et al., 2018). Distinct points of potential or probed negative crosstalk between CBRs and FcεRI signaling system are presented in Table 4 and discussed in this section.

Studies analyzing gene transcription after stimulation of RBL-2H3

cells in the presence of the synthetic cannabinoid CP55940 revealed that CB2R triggering activates the PI3K-AKT signaling pathway (Samson et al., 2003). Those studies also showed that CP55940 prevented FcεRI-induced serotonin release (Samson et al., 2003). Normally, PI3K plays a positive role in the FcεRI-dependent signaling system (Kim et al., 2008 and references therein), participating in degranulation and cytokine synthesis. However, as a negative regulatory loop, PI3K activation leads to the Lyn-dependent recruitment and activation of the SH2-containing inositol-5'-phosphatase 1 (SHIP1), which dephosphorylates PI(3,4,5)P3 and importantly limits IgE/Ag-induced degranulation and cytokine synthesis (Dobranowski and Sly, 2018; Hernandez-Hansen et al., 2004; Xiao et al., 2005). Since CBRs activate PI3K and promote the synthesis of PI(3,4,5)P3 (Gu et al., 2019) and 2-AG induces SHIP accumulation in BMMCs (Espinosa-Riquer et al., 2019), it is possible to speculate that cannabinoids lead to increased SHIP activity in MCs, diminishing the FcεRI-dependent activation.

Another plausible mechanism of inhibitory crosstalk between CBRs and FcεRI receptors is the activation of protein phosphatases. Protein Tyrosine Phosphatases (PTPs), such as SHP-1, downregulate important events in FcεRI and other immune receptors signaling cascades

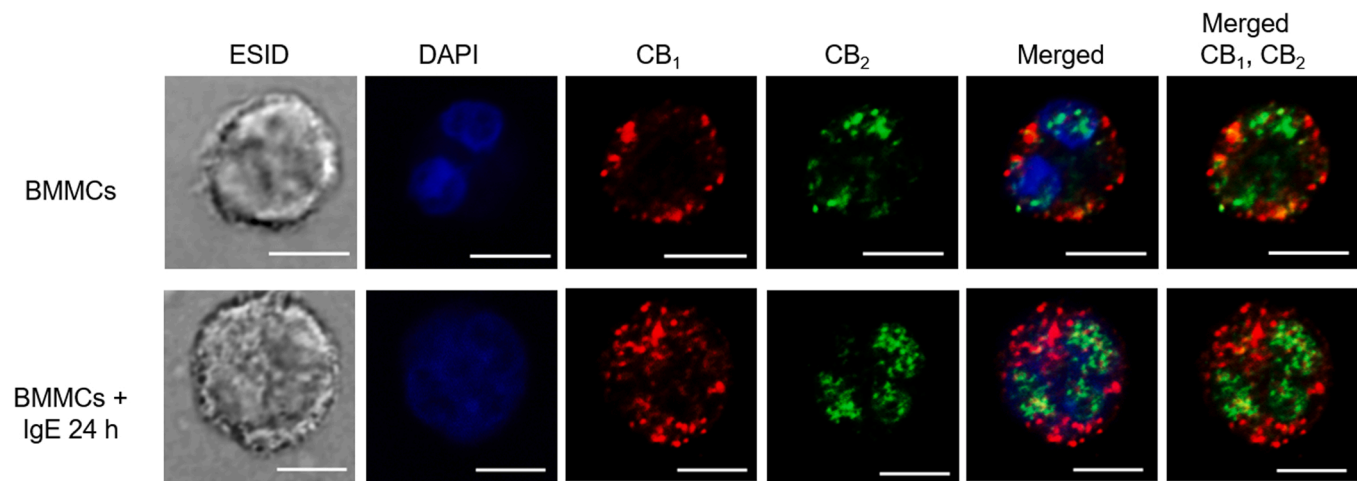


Fig. 4. Intracellular localization CB1R and CB2R in BMMCs. Cells were sensitized or not for 24 h with a monoclonal anti-dinitrophenyl IgE (SPE-7 clone, 100 ng/ml) and then fixed and treated for confocal microscopy. CB1R and CB2R were detected using commercial specific primary antibodies followed by secondary antibodies coupled to Alexa Fluor 568 for CB1 (red) or Alexa Fluor 488 for CB2 (green). Nuclei were detected using DAPI (blue). Calibration bar = 5 μ m.

(Samayawardhena and Pallen, 2010; Tonks, 2006; Zhu et al., 2010). In BMMCs, SHP-1 negatively regulates IgE/Ag-induced IL-13 and IL-6 production (Kamata et al., 2003) and LAT phosphorylation (Kamata et al., 2003; Nakata et al., 2008). CB1R activates those phosphatases in N18TG2 neuroblastoma cells (Dalton and Howlett, 2012), and it is possible to hypothesize that this could also happen in MCs. On the other hand, MAPK phosphatases (also known as DUSPs, such as MKP-1) downregulate Fc ϵ R1 signaling (Maier et al., 2007). Cannabinoids seem to induce the synthesis of MAPK phosphatases to avoid inflammation. For example, JWH015 enhanced spinal MKP1–3 expression and activity in an L5 nerve injury-induced model of allodynia to exert antinociceptive effects (Landry et al., 2012). Also, AEA induces MKP-1 expression in microglial cells, diminishing inflammation and protecting neurons from death due to excitotoxicity (Eljaschewitsch et al., 2006). Those results allow to hypothesize that induction of DUSPs by CBR triggering could occur in MCs and interfere with the activation of MAPK by IgE/Ag complexes. Interestingly, glucocorticoids, a group of potent anti-inflammatory compounds, induce the expression of DUSPs in BMMCs (Maier et al., 2007), suggesting that cannabinoids and glucocorticoids could share some common mechanisms to limit inflammation triggered by the Fc ϵ R1 receptor. Although the expression of MAPK phosphatases by cannabinoids has not been shown in MCs, this is an attractive possibility.

Other phosphatases, such as the Serine-Threonine Protein Phosphatase 2 A (PP2A), mediate Fc ϵ R1-triggered events in MCs. Inhibition of this molecule enhances IL-6 production in response to IgE/Ag complexes in the HMC-1 human MC line and BMMCs (Boudreau et al., 2004). Interestingly, CB1R activates PP2A to limit the cannabinoid-induced ERK 1/2 activation in N18TG2 neuroblastoma cells (Dalton and Howlett, 2012), and a derivative of cannabidiol activates a pathway formed by PP2A, B55a, and the hypoxia-inducible factor (HIF) to diminish inflammation in a model of brain injury in mice (Navarrete et al., 2022). If similar events of PP2A activation participate in the negative effects of cannabinoids on MC-mediated allergic reactions is not known.

Classical studies demonstrated that cAMP elevation inhibits IgE/Ag-induced MC activation (Weston and Peachell, 1998), leading to hypothesize that the trigger of receptors coupled to G α_i proteins (which inhibit adenylyl cyclase, AC, activity) could cause the opposite effect. Since, paradoxically, CBRs are coupled to G α_i and inhibit IgE/Ag-triggered activation of MCs, a careful analysis of the kinetics of cAMP production in MCs after CBR stimulation has been performed. Studies on RBL-2H3 cells suggest that the negative effect of cannabinoids on IgE/Ag-dependent MC activation could be related to a late cAMP increase induced by CB1R triggering. In those studies, the CB1R

agonist methanandamide induced an expected early decrease in cAMP levels but also caused a late increase of this second messenger in RBL-2H3 cells due to a super activation of AC that, in turn, blocked Fc ϵ R1-dependent MC secretion of pro-inflammatory mediators (Small-Howard et al., 2005). The late production of cAMP was related to the CB1R-induced transcriptional expression of types V and VI adenylyl cyclase isoforms that produced a cAMP retarded wave. Authors suggested that some anti-inflammatory effects of CB1 ligands could be derived from the sustained cAMP accumulation (Small-Howard et al., 2005). This G $\alpha_{i/o}$ -coupled receptor-dependent increase in cAMP has been well described in distinct cell systems and with different ligands and receptors (reviewed in Brust et al., 2015). It is known as heterologous sensitization of AC and is best observed following the removal of the agonist, after addition of a receptor antagonist, or a ligand that activates AC. In this regard, since activation of Fc ϵ R1 induces the release of pro-inflammatory mediators capable of activating AC in an autocrine fashion (such as PGE2), it is possible to speculate that continuous Gi-coupled CBR activation could sensitize the cAMP response to PGE2 produced after IgE/Ag stimulation and lead to the inhibition of Fc ϵ R1 signaling system. Accordingly, some studies have shown that the PGE2 receptors (EPG2) increase cAMP, activate PKA, block Fc ϵ R1-dependent calcium flux, and inhibit the Fyn kinase-dependent signaling cascade in MCs (Serra-Pages et al., 2012). The specific mechanism of cAMP/PKA-dependent inhibition of the Fyn kinase branch of Fc ϵ R1 has not been described.

Evidence shows that CBs also modify calcium mobilization after Fc ϵ R1 triggering. Utilizing BMMCs and the cell line RBL-2H3, it was reported that CBR agonists decrease the intracellular calcium rise activated by the IgE receptor or by a calcium ionophore in a dose-dependent manner (Cruz et al., 2018; Gullledge et al., 2018). The inhibitory effects of cannabinoids on calcium mobilization seem to be related to the impairment of key events of the process, such as the replenishment of intracellular calcium stores. For example, in human endothelial, rat pancreatic, and RBL-2H3 cell lines loaded with Fura-2AM and stimulated with thapsigargin, the N-arachidonoyl glycine (NAGly) inhibits SOCE by interfering with STIM1 and Orail1 coupling, in a time and concentration dependent-fashion (Deak et al., 2013). On the other hand, in HEK293 and NG108–15 cell lines, the direct stimulation of CB1R located in endosomal compartments with CB1R agonist microinjections increases intracellular calcium concentration (Brailoiu et al., 2011). Since it is known that CBRs located in lysosomes can be coupled to G α_q proteins, further investigations are required to clarify if the increase of Ca²⁺ triggered from these compartments does modify the Ca²⁺ influx triggered by stimulation of the Fc ϵ R1 receptor. In some cases, such as in

Table 3Immunomodulatory effects of CBRs on FcεRI and mast cell stimulation *in vitro* and in allergy models.

Cannabinoid ligand	Experimental model	MC subtype/culture conditions or experimental conditions	Proposed mechanism of inhibition	References
CBR agonist PEA	IgE/DNP-HSA (<i>In vitro</i>)	RBL-2H3 cultured in Eagle's minimum essential medium supplemented with L-glutamine, penicillin, and FBS. Peritoneal MCs collected by peritoneal lavage of male Wistar rats.	CB2R agonist inhibited MC activation. AEA antagonizes PEA inhibition.	(Facci et al., 1995)
CB1R, CB2R agonists PEA, AEA, 2-AG CB1R agonist Methanandamide	IgE/DNP-HSA (<i>In vitro</i>)	RBL-2H3 cultured in Eagle's minimum essential medium (MEM) supplemented with FBS, L-glutamine, penicillin, and streptomycin.	PEA decreased MC degranulation. AEA had no effect. 2-AG and methanandamide increased MC activation.	(Granberg et al., 2001)
CB1R, CB2R agonists CP55940 CB1R agonist Methanandamide	IgE/DNP-HSA (<i>In vitro</i>)	RBL-2H3M1 cultured in DMEM with FBS and glutamine.	CB1R agonist suppresses the secretory response. CB2R stimulation modulates certain kinases.	(Samson et al., 2003)
CB1R agonist Methanandamide	IgE/DNP-HSA (<i>In vitro</i>)	RBL-2H3 cultured in DMEM (Dulbecco's modified Eagle's medium) supplemented with FBS and L-glutamine. BMMCs (Bone marrow-derived mast cells) expanded in media supplemented with IL-3.	CB1R agonist inhibited MC serotonin release.	(Small-Howard et al., 2005)
CB1R agonists α-oleoyl oleoylamine ethanolamine (α-OOE) and α-oleoyl oleoylamine serinol (α-OOS)	IgE/DNP-HSA (<i>In vitro</i>)	RBL-2H3 culture in Dulbecco's modified Eagle's medium supplemented with FBS, penicillin/streptomycin. Bone marrow derived-cultured mast cells derived from femoral bone marrow cells of BALB/c mice maintained in DMEM with FBS, 2-mercaptoethanol, glutamine, and WEHI-3-conditioned medium with IL-3.	CB1R agonist inhibited RBL-2H3 histamine and β-hexosaminidase release.	(Nam et al., 2016)
CB1R agonists α-oleoyl oleoylamine ethanolamine (α-OOE) and α-oleoyl oleoylamine serinol (α-OOS) CB1R, CB2R agonist AEA	Oxazolone-Induced Atopic Dermatitis Model (<i>In situ</i>)	Mice were sensitized topically with oxazolone solution (1%) and exposed to oxazolone (0.1%) at 10-day intervals.	CB1R agonists and AEA diminished histamine serum concentrations.	(Nam et al., 2016)
CB1R, CB2R agonist AEA CB2R agonist HU308 CB1 antagonist AM251	IgE/DNP-HSA (<i>In vitro</i>)	BMMCs cultured in RPMI supplemented with β-mercaptoethanol, HEPES, pyruvate, IL-3, SCF, antibiotic/antimycotic, non-essential aminoacids, and FBS.	AEA inhibited β-hexosaminidase release and TNF, IL-6, IL-3, IL-10, IL-2 and IL-4 mRNA synthesis. CB2R inhibited β-hexosaminidase release.	(Cruz et al., 2018)
CB1R, CB2R agonists Alkylamides A15	IgE/DNP-HSA Calcium ionophore A23187 (<i>In vivo, in vitro</i>)	Bone marrow cells isolated from C57BL/6 cultured in RPMI-1640 with FBS, aminoacids, HEPES, sodium pyruvate, penicillin, streptomycin, IL-3, and SCF. RBL-2H3 cells were cultured in MEM supplemented with FBS.	CB1R antagonist had no effect. A15 decreased histamine and β-hexosaminidase release. A15 inhibited TNF and PGE release, and prevent the increase of intracellular calcium.	(Gulledge et al., 2018)
CB1R, CB2R allosteric modulator CBD CB1R, CB2R agonist CP55940, WIN 55212-2 CB2R agonist JWH-133	IgE/DNP-HSA (<i>In vitro</i>)	RBL-2H3 cultured in DMEM supplemented with FBS, L-glutamine, penicillin, and streptomycin.	CBD and JWH-133 increased β-hexosaminidase release. CP 55,940 and WIN 55212-2 decreased β-hexosaminidase release.	(Giudice et al., 2007)
CB1R and CB2R agonist AEA CB1R agonist ACEA CB1R antagonist AM251	Human Mucosal-type Mast Cells (hMMCs) Nasal polyp (NP) associated with allergic rhinitis. (<i>In situ</i>)	Human NP samples were obtained from male and female patients, who had a polypectomy. Isolated NPs were cut into small pieces and maintained in supplemented serum-free William's E medium.	ACEA and AEA decreased MC degranulation. CB1 antagonist increased degranulation and hMMC total number.	(Sugawara et al., 2013)
CB1R, CB2R agonist THC CB2R agonist HU308 CB1R antagonist SR141716A CB2R antagonist SR144528	Dinitrofluorobenzene (DNFB)-induced ear allergic dermatitis in C57BL6/J mice. (<i>In vivo</i>)	Mice were sensitized with 0.2% DNFB in the abdomen, and then challenged with 0.3% DNFB in the ears.	THC decreased ear swelling. HU308 had no effect and even increased ear swelling. SR141716A and SR144528 increased ear swelling.	(Karsak et al., 2007)
No Pharmacological treatment was used	Ovalbumin and 2,4-DNFB-induced ear allergic dermatitis. model in CB2-KO C57BL6/J mice. (<i>In vivo</i>)	Mice were sensitized with 1% DNFB five times at 7-days and challenged with DNFB.	Ear swelling and edema were suppressed in CB2-KO mice in comparison with WT mice.	(Mimura et al., 2012)

Table 4

Probed or putative points of negative crosstalk between CBRs and FcεRI signaling cascades.

Molecule/Process involved in FcεRI signaling	Role on FcεRI signaling cascade	Effect of CBs	Experimental model or cell type	Reference
SH2-containing inositol-5'-phosphatase 1 (SHIP1)	Dephosphorylates PI(3,4,5)P3 to limit FcεRI stimulation	2-AG induces SHIP accumulation	BMMCs (Culture media supplemented with FBS, IL-3, and SCF)	(Espinosa-Riquer et al., 2019)
Protein Tyrosine Phosphatase SHP 1 (SHP-1)	Decreases Src kinase and LAT phosphorylation. SHP-1 negatively regulates IL-13 and IL-6 production stimulated by FcεRI in mast cells.	WIN55212-2 (CB1R agonist) activates SHP-1	Murine N18TG2 neuronal cells	(Dalton and Howlett, 2012)
Mitogen-activated phosphatase 1 (MKP-1, also known as DUSP1)	Down-regulates MAPKs activated by FcεRI. MKP-1 dephosphorylates p38, ERK1/2 and JNK.	JWH015 (CB2R agonist) induces activation of MKP1 AM630 (CB2R antagonist) decreases MKP1 expression AEA increases MKP-1 expression	Rat model of neuropathic pain (L5 nerve transection) BV-2 microglial cells activated by LPS	(Landry et al., 2012) (Eljaschewitsch et al., 2006)
Protein Phosphatase 2A (PP2A)	Dephosphorylates distinct proteins of FcεRI signaling system	WIN55212-2 (CB1R agonist) activates PP2A VCE-004.8 (cannabidiol aminoquinone derivative, PPARγ/CB2R agonist) activates PP2A and decreases neuroinflammation	Murine N18TG2 neuronal cells Murine model of traumatic brain injury	(Dalton and Howlett, 2012) (Navarrete et al., 2022)
Cyclic adenosine 3',5'-monophosphate (cAMP)	High concentrations of cAMP inhibit mast cell degranulation	CB1 stimulation causes activation of the superactivable isoform of AC and a late increase of cAMP	RBL-2H3 (DMEM supplemented with FBS and glutamine)	(Small-Howard et al., 2005)
Calcium mobilization	Depletion of Ca ²⁺ stores of the endoplasmic reticulum is sensed by STIM1, which interacts with Orai to activate the principal calcium influx called SOCE.	NAGly inhibits SOCE by interfering with STIM1 and Orai1 coupling in a time and concentration dependent-manner	Human endothelial cell line EA.hy926, rat pancreatic b-cell line INS-1 832/13, and cell line RBL-2H3. Culture conditions not specified.	(Deak et al., 2013)
Nuclear factor-κB (NF-κB)	IKK phosphorylates IκB, leading to its degradation. The complex p50/p65 is translocated to cell nucleus to promote gene transcription.	2-AG inhibits IKK phosphorylation stimulated by LPS WIN55,212-2 (cannabinoid receptor agonist) inhibits IκB phosphorylation and NFκB nuclear translocation β-caryophyllene (CBR agonist) reduces NF-κB phosphorylation induced by LPS. These effects are reversed by AM630 (CB2R antagonist)	BMMCs (Culture media supplemented with FBS, IL-3, and SCF) Chronic cerebral hypoperfusion model in rats Collagen antibody-induced arthritis (CAIA) experimental model in mice	(Espinosa-Riquer et al., 2019) (Su et al., 2017) (Irrera et al., 2019)
5-Lipoxygenase (5-LOX, codified by the Alox5 gene)	Biosynthesis of leukotrienes that amplify the allergic inflammation	JWH015 (CB2R agonist) decreases JNK phosphorylation and Alox5 gene transcription.	Model of leukocyte migration. Tail transfection of zebrafish larvae	(Liu et al., 2013)

neurons and endothelial cells, inhibiting the increase in intracellular calcium generates an unresponsive state that prevents the release of distinct mediators (Fleming et al., 1999; Kovacs et al., 2012; Stempel et al., 2016). In the case of the FcεRI receptor, impaired calcium signal affects PKC phosphorylation, degranulation, and NFAT-dependent cytokine transcription (Baba et al., 2008; Wang et al., 2021).

Certain CBs exert inhibitory functions in MC-induced allergic reactions decreasing the synthesis of pro-inflammatory cytokines. For example, AEA decreased some of the IgE/Ag-induced mRNA synthesis, including TNF-α in BMMCs (Cruz et al., 2018). This cytokine is transcribed in MCs by the activation of the NFκB transcription factor (Liu et al., 2017), which is one of the targets of the FcεRI receptor signaling cascade, via the activation of IKK (Kalesnikoff et al., 2002). Interestingly, stimulation of CB2R inhibits IKK phosphorylation caused by bacterial lipopolysaccharide (LPS) in BMMCs, preventing the nuclear translocation of the p-65 NFκB subunit and causing a decrease in the accumulation of TNF mRNA (Espinosa-Riquer et al., 2019). If eCBs block IKK phosphorylation after IgE receptor triggering is currently investigated. In other models of inflammation, such as chronic cerebral hypoperfusion, the inhibitory actions of CBs on IKK phosphorylation and the blocking of NFκB nuclear translocation have also been reported (Irrera et al., 2019; Jüttler et al., 2004; Su et al., 2017). Also, in a murine model of arthritis, β-caryophyllene, a CB2R agonist, decreased the mRNA of NFκB and increased the PPAR-γ receptor expression to ameliorate the inflammation (Irrera et al., 2019). The cannabinoid dexamabinol decreased NFκB activation and exerted neuroprotective actions in neurons independently of the classical CBRs (Jüttler et al., 2004). In accordance with an inhibitory effect of CBs on NFκB

activation, a FAAH inhibitor avoids the nuclear translocation of that transcription factor and the synthesis of cytokines (Su et al., 2017). Future research will describe the effect of eCBs on NFκB-dependent synthesis of pro-inflammatory cytokines in MCs and its consequences in allergic reactions.

Finally, there are suggestive data on the inhibitory effect of cannabinoids on the synthesis of pro-inflammatory lipid-derived mediators. For example, in a model of inflammation of a tail transection of zebrafish larvae, CB2R activation decreased JNK phosphorylation and, with this, the transcription of the *Alox5* gene (Liu et al., 2013). *Alox5* gene encodes the 5-LOX lipooxygenase, important for the synthesis of leukotrienes that amplify the allergic inflammation. If those effects of eCBs occur in MCs is still under investigation.

In conclusion, it has been shown that CBRs can activate inhibitory control loops of the FcεRI signaling pathway or inhibit proteins that positively connect the IgE receptor with degranulation or cytokine synthesis. Most of the potential points of negative crosstalk between CBRs and FcεRI remains to be fully described in MCs. Fig. 5 schematizes main potential and tested inhibition points of FcεRI signaling cascade triggered by CBs.

6. Considerations in the study of MC modulation by eCB

Although our comprehension of the eCB system in the immune system has grown in the last decades, there still needs to be more information about its specific regulation and participation in pathological conditions initiated by MCs. There are multiple *in vivo* and *in vitro* studies assessing the ability of cannabinoids to reduce inflammatory

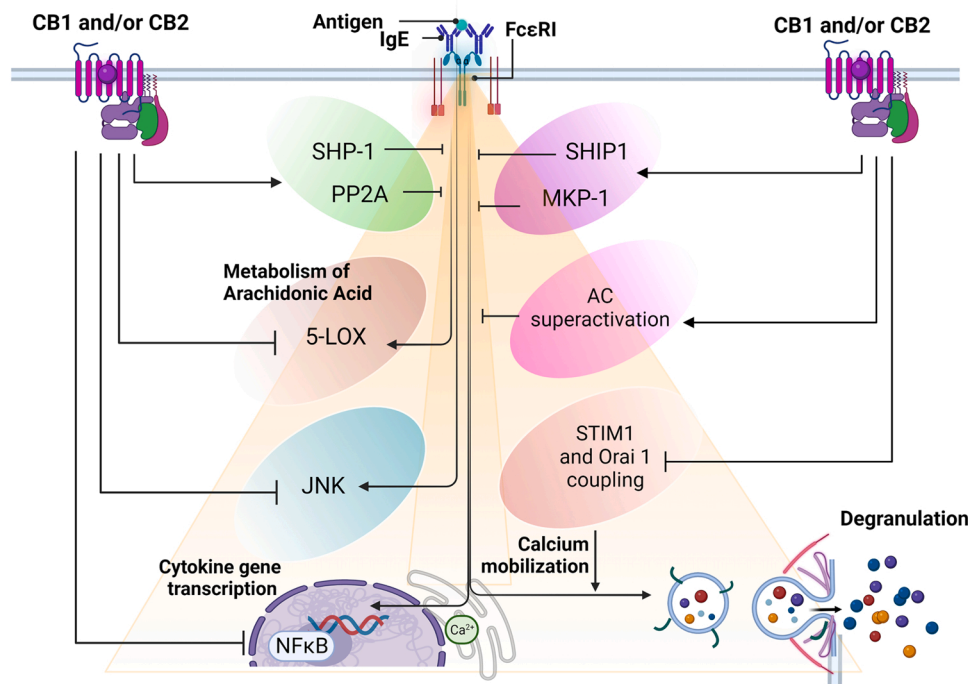


Fig. 5. Potential points of CBRs and FcεRI receptor negative crosstalk. The scheme summarizes demonstrated or suggested points of negative control of CBRs on the FcεRI signaling system in MCs. Main proteins participating in the inhibition of FcεRI receptor signaling and activated by CB receptors (such as SHP-1, PP2A, SHIP1, and MKP-1) are shown. Also, FcεRI-triggered processes that are inhibited by CBRs are included (i.e., AA metabolism, cytokine gene transcription, calcium mobilization and degranulation). See text and Table 4 for details. Created with BioRender.com.

processes related to allergies (Table 3). Nevertheless, it is not possible to obtain general conclusions because some results have been difficult to reproduce, and some studies show paradoxical responses. Since the eCB system is composed of numerous elements finely regulated, minor alterations in the amounts of certain enzymes or receptors, together with the production of other chemical mediators, can alter the final outcomes of a given experiment. On the other hand, MCs constitute a cell lineage with a remarkable capacity for adaptation to the environment. Since immature precursors from the blood enter resident tissues to finish their differentiation, the phenotype of this cell type is distinct from other immune cells but highly variable among particular populations (Dwyer et al., 2016). Studies analyzing the effects of eCBs, or the presence of components of the eCB system in MCs should restrict their observations to the specific type of MC utilized. A careful consideration of the possible variables that participate in the effects of eCBs in MCs (such as IgE sensitization of cultured cells) is necessary for proper data interpretation.

One of the reasons that could explain the variability of the effects reported for cannabinoids in distinct studies in MCs is the use of different solvents to dilute them. Organic solvents, such as dimethyl-sulfoxide (DMSO), ethanol and acetonitrile, significantly affect MC responses, causing mainly their inhibition (Granberg et al., 2001). For example, it is known that DMSO inhibits tyrosine phosphorylation, which is needed to trigger degranulation in RBL-2H3 cells (Koo and Kim, 2009). In addition, low ethanol concentrations inhibit antigen-mediated histamine release, but induce its secretion at high concentrations (Ruiz and Gomes, 2000). Since these solvents are widely used in both in vitro and in vivo studies of MCs, it is crucial to rule their effect when evaluating activation parameters of MCs.

On the other hand, it is important to consider the limits of pharmacological approaches utilized to analyze the effects of eCBs in FcεRI-triggered responses, since intracellular localization of CBRs occurs in distinct MC subtypes (such as BMHCs). Thus, particular agonists and antagonists could differentially reach the intracellular receptors. Also, components of an intracellular CBR signaling cascade could be different from those described for membrane receptors. For example, β-arrestins could play an essential role in intracellular signaling (Nogueras-Ortiz and Yudowski, 2016; Soethoudt et al., 2017), and some ligands could

induce the interaction between CBRs and β-arrestins with more efficacy than others, causing differential signaling and receptor recycling (Ibsen et al., 2019).

Another factor to consider is that effects of eCBs are dependent on their concentration. For example, elevated concentrations of CB1R agonists produce the super-activation of AC via $G\alpha_{i/o}$, contrary to the expected inhibitory effect (Small-Howard et al., 2005). Hence, measuring only cellular responses that reflect classical activation of the inhibitory G protein signaling pathway may not fully allow the analysis of the complete pathway activated by eCBs. Also, growing evidence on the desensitized or constitutively active state of CBRs in other systems has gained relevance. For example, in Chinese hamster ovary (CHO) cells expressing the human and mouse CB2R, preincubation with an inverse agonist improves the efficacy of synthetic cannabinoids (Mancini et al., 2009), suggesting a pre-activated state of CBRs. It remains to be investigated if this phenomenon occurs in MCs.

Finally, when the effects of cannabinoids are evaluated in MC-dependent allergic reactions in vivo, it should be taken into account that other immune cells produce eCBs and express CBRs. The existence of a functional eCB system has been observed in other immune cells and tissues, such as endothelium (Opitz et al., 2007), B cells (Lee et al., 2001; Sido et al., 2016), macrophages (Dotsey et al., 2017), and dendritic cells (Dotsey et al., 2017; Gaffal et al., 2020). Then, the effects of eCBs in a single cell type should be carefully considered when extrapolating results to an inflammatory condition observed in vivo.

7. Perspectives on the research of cannabinoid control of inflammatory reactions mediated by MCs

Research on the effects of cannabinoids on physiology of MCs and MC-mediated allergic inflammatory reactions is far from being complete. Despite the numerous studies describing the anti-inflammatory actions of cannabinoid compounds and the characterization of the eCB system in this particular cell type, important questions remain unanswered. With every new advance in the understanding of physiology of MCs and its control by CBs, novel consequences of the use of these compounds on allergic reactions are inferred, but only sometimes are those observations directly corroborated by in vivo studies. In this

section, we present aspects that are rising as relevant for the future study of cannabinoid actions and inflammatory reactions promoted by MCs (Fig. 6).

7.1. Effects of chronic cannabinoid consumption on MC-mediated inflammatory reactions

Due to the increase in the chronic recreational use of marijuana and the reported inhibitory effects of cannabinoids on the immune system, it is essential to analyze the effects of its consumption on inflammatory processes that depend on the activation of MCs (Khoury et al., 2022; Maggirwar and Khalsa, 2021). Unfortunately, studies analyzing the effect of long-term cannabinoid consumption on FcεRI-triggered responses are scarce. However, an anti-inflammatory effect has been observed in some studies. For example, in a model of arthritis induced in Balb/c mice, the chronic supplementation of β-caryophyllene, a CB2R agonist, reduces the levels of MC-derived mediators, such as IL-6, TNF-α, matrix metalloproteinases 3 and 9, increasing the amount of the anti-inflammatory cytokine IL-13 (Irrera et al., 2019).

On the other hand, chronic consumption of cannabinoids frequently occurs in the senior adult. Old age is a physiological state in which the immune system loses the ability to mount adequate inflammatory responses to resolve potentially harmful stimuli (Chatterjee and Gashev, 2012). Since MCs are known to undergo senescence and present changes in their ability to respond and in their microenvironment (Chatterjee and Gashev, 2012; Kundu et al., 2020), it is expected that future research will be conducted to provide information on the eCB system and activation of MCs in the context of aging (Fig. 6A).

7.2. Effects of cannabinoids on IgE/Ag and MC-dependent protective responses

In parallel with the discovery of inhibitory actions of eCBs on activation MCs, the role of this cell type and its activation through the FcεRI receptor in protective immune reactions against parasites and bacteria has emerged. For example, almost all parasitic infections can cause an increment in non-specific IgE in the host (Pritchard, 1993), patients with atopy (increased IgE levels in serum) mount a better protective immune

response against these infections and IgE levels positively correlate with a better outcome (Faulkner et al., 2002; Lynch et al., 1998). On the other hand, it is known that the Th2 type of immune response is triggered for the clearance of parasites and that specific cytokines such as IL-4, IL-13 and metalloproteases such as mMCP1, mMCP6 that are needed to IgE production and are released by MCs, contribute to the recruitment of eosinophils and basophils to fight the infection (Mukai et al., 2016; Voehringer et al., 2004).

Recently, it was found that activation of MCs through the IgE/FcεRI receptor axis also participates in the defense against *Staphylococcus aureus* (SA) infection (Starkl et al., 2020). In that study, it was shown that the epicutaneous infection of SA induces Th2-type immunity, with an increase in IgE plasma levels. Mice challenged with a second infection had a better prognosis than those who did not develop the allergic-like response or did not express the FcεRI receptor. Analyzing the secretome of MCs purified from infected animals and challenged with IgE/Ag complexes, an increase in enzymes with proteolytic and antibacterial activities was found. In light of these findings, MCs and their FcεRI receptor have been considered the “allergic arm of the innate immune system” (Starkl et al., 2020). Therefore, it is expected that future studies will evaluate the effects of cannabinoids on the physiological protective responses against bacteria and other micro-organisms elicited by MCs and the FcεRI (Fig. 6B).

7.3. The entourage effect

The term “entourage effect” refers to the synergistic effects of eCBs with other compounds that do not bind to CBRs but modulate the eCB system (Ho et al., 2008). Some examples of “entourage compounds” are PEA and oleoyletanolamide (OEA), of which PEA is the best studied in MCs. PEA is a cannabinoid-like fatty acid amide co-synthesized with AEA in response to actual or potential damage to counteract the inflammatory response. Other effects attributed to PEA are neuroprotection and antinociception (Valenza et al., 2022). PEA is a PPAR-agonist, a GPR55 agonist, and a positive TRPV1 allosteric modulator (Petrosino et al., 2016; Rankin and Fowler, 2020). Although PEA has minimal affinity for CB1R and CB2R, it indirectly activates these receptors by increasing eCB levels. There is evidence that PEA

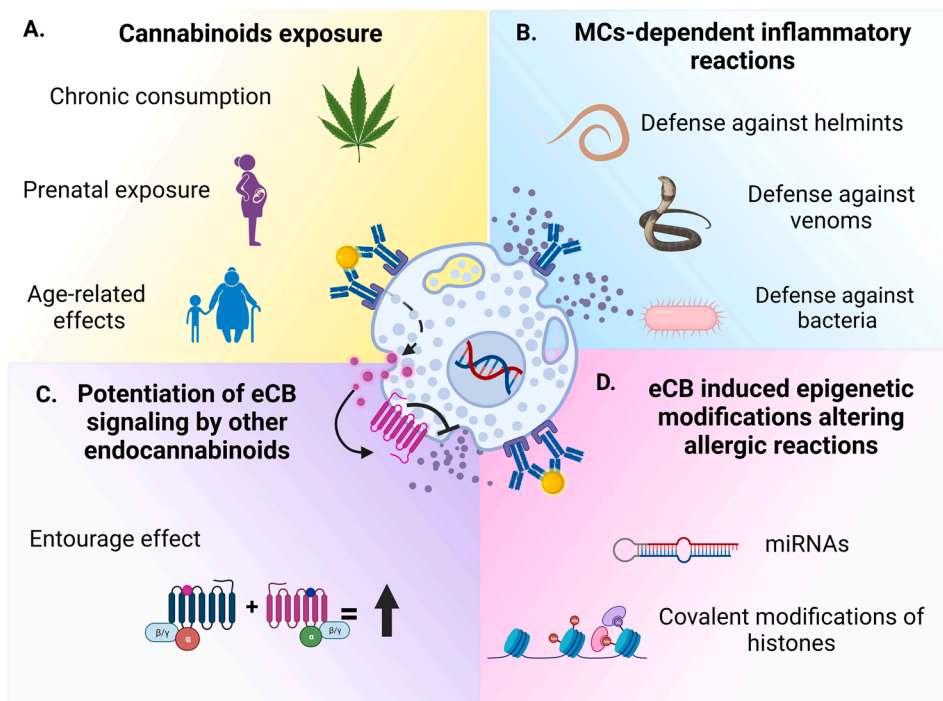


Fig. 6. Perspectives in the study of cannabinoids and MC-mediated immune responses. A. Research is needed to understand important aspects of cannabinoid effects on MC activation. For example, the effect of chronic cannabinoid exposure on MC functions, the effects of cannabinoids on MCs in the elderly and the consequences of prenatal exposure to CBs on MC-elicited inflammatory responses. B. Since MCs are involved in important innate immunity protective responses against toxins and venoms, future research should address the potentially deleterious effects of cannabinoids on those reactions. C. Studies regarding entourage effect of distinct cannabinoids on MC functions will give light on the complex effects exerted by those compounds in allergic reactions; D. Epigenetic modifications induced by eCBs in MCs could change the threshold and intensity of allergic reactions. Finally, future research will give light on the potential phenotypic changes induced by eCB-induced epigenetic modifications in MCs. Created with BioRender.com.

administration reduces the degranulation in the RBL-2H3 cell line, decreasing inflammation (Facci et al., 1995). Despite the lack of affinity for CB2R, specific antagonists of this receptor subtype effectively block PEA's actions. This occurs because PEA increases 2-AG synthesis by stimulating the activity of DAGL (Petrosino et al., 2019). In addition, PEA downregulates FAAH in human breast cancer cells (HBCC), which also results in enhanced AEA levels (Di Marzo et al., 2001). On the other hand, PEA reduces microglia and astrocyte activation via PPAR- α activation (Scuderi et al., 2011, 2012). Exogenous PEA administration in adequate formulations (micronized and co-micronized) ameliorates neurological and neurodegenerative diseases involving neuro-inflammatory processes, including Parkinson's and Alzheimer's diseases, multiple sclerosis, amyotrophic lateral sclerosis, and autism. In addition, PEA supplementation reduces inflammatory and neuropathic pain and increases the efficacy of opioid and non-opioid analgesics (Petrosino and Schiano Moriello, 2020).

OEA is another fatty acid compound with entourage effects. Like PEA, OEA does not bind to CB1R or CB2R but facilitates other cannabinoids' actions (Valastro et al., 2017). Cannabidiol has CB1R/CB2R-independent effects but can also act as an entourage compound because it indirectly prevents AEA degradation by competitively binding the FABPs that transport AEA to the endoplasmic reticulum. In addition, CBD acts as a PPAR γ agonist (Henson et al., 2021). Further studies are needed to discover which proteins within the antigen-activated MC signaling cascade communicate with the eCB system to generate the entourage effect.

Interestingly, the entourage effect is not observed with other active compounds in the marijuana plant, even though some anti-inflammatory effects have been reported when studied individually. For example, terpenoids such as limonene, beta caryophyllene, alpha and pinene, linalool, and beta-myrcene (at micromolar concentrations) did not change the membrane potential of CB1R and CB2R expressing AtT20 cells and did not change the maximal effect of the CP55940 compound. This absence of effect was also observed in the hyperpolarization and other responses triggered by delta9-THC (Santiago et al., 2019). Those results indicate that the entourage effect observed with some cannabinoids could share some molecular mechanisms that are unrelated to terpenoid-activated intracellular processes. Future research should be performed to describe molecular processes behind the immunomodulatory effects of compounds contained in marijuana plants (Fig. 6 C).

7.4. Epigenetic modifications induced by cannabinoids in MCs

Future research will also give light on the epigenetic changes that the use of cannabinoids can induce in MCs. The available information shows a correlation between the exposure of pregnant mothers to cannabinoids and the offspring's predisposition to present psychiatric diseases (Smith et al., 2020). Also, there are some reports about the influence of certain cannabinoids on the expression of microRNAs (miRNAs) related to inflammatory processes (Jackson et al., 2014; Sido et al., 2015). Specifically, there are reports on the influence of cannabinoids on the generation of type 2 immune responses associated with allergies. For example, in node cells of mice challenged with a superantigen, it was reported that the administration of THC modifies the acetylation and methylation of histones leading to the expression of Th2 cytokines (Yang et al., 2014). In addition, in a murine model of delayed hypersensitivity (DH) carried out by T cells, it was observed that the administration of THC increases microRNA miR-21-5p, and this contributes to the increase in the expression of PTEN and to the decrease in PI3K/AKT signaling (Sido et al., 2016), which ameliorates the inflammation. Since certain miRNAs have been related to the development of asthma, it is reasonable to hypothesize that cannabinoids could participate in the modulation of several miRNA related to MC activation in the lung. Finally, eCB-dependent epigenetic changes in MCs could alter the threshold and the intensity and composition of inflammatory reactions

orchestrated by this cell type (Fig. 5D).

8. Cannabinoids and the control of human allergic reactions

Although the inhibitory effects of the endocannabinoid system on high-intensity, deleterious inflammatory reactions have been widely studied in pre-clinical models and cell cultures, the participation of the eCB system and the inhibitory effect of cannabinoids in the complex pathology of human allergic diseases remains an open field of research. The involvement of the eCB system in allergic reactions in humans has been inferred from some experimental evidence. For example, CB1R expression is increased in tonsils from allergic rhinitis patients compared to non-atopic donors (Martín-Fontecha et al., 2014) and CB1R activation prevents mucosal MC (from nasal polyps) activation and maturation (Sugawara et al., 2013). In the case of allergic asthma (a complex pathology that courses with sensitization and effector phases, Palomares et al., 2017), increased levels of AEA have been observed in the bronchoalveolar lavage fluid of patients upon allergen challenge and CB1R mRNA levels are increased in asthmatics compared to non-asthmatic subjects (Martín-Fontecha et al., 2014; Zoerner et al., 2011).

As mentioned in previous sections, until now, AIT is the only therapeutic approach that shows long-term inhibitory effects on allergic reactions in humans. This strategy frequently promotes tolerance induction but has been questioned due to safety and efficacy issues (reviewed in Durham and Shamji, 2022). The lack of efficient therapies for allergic diseases has prompted the research on the mechanisms that naturally dampen MC activation to propose new strategies for allergy control. However, to date, information about clinical trials and randomized studies on the use of cannabinoids for the control of allergic reactions is limited to a few studies (as reported in PubMed) (Table 5).

9. Concluding remarks

In recent years, evidence has accumulated indicating that the eCB system is an essential negative regulator of IgE/Ag-dependent activation of MCs. Since the initial description of a lipid-mediated autocrine control loop for releasing proinflammatory mediators in MCs, enzymes, receptors, and ligands of the eCB system have been found in that cell type. eCBs activate inhibitory pathways that alter the Fc ϵ RI signal transduction system and inhibit several reactions needed for the synthesis and release of pro-inflammatory mediators after IgE/Ag stimulation of MCs. Experimental evidence suggests, however, that the effects of specific eCBs on MC activation depend on numerous variables, such as the concentration of bioactive lipids in the tissue microenvironment or cell culture media, the cellular localization of CBRs, and the MC phenotype. Since allergic reactions triggered by MCs constitute an important health problem worldwide, and the control of MC-dependent inflammatory reactions has been identified as a therapeutic target for distinct chronic diseases, it is expected that research on the mechanisms behind the inhibitory actions of eCBs in that cell type will continue growing. Research evaluating the effect of cannabinoid administration on allergic reactions in humans has shown possible benefits in AD; however, more studies are needed regarding other allergic conditions, such as asthma and food allergies. Finally, with the emerging participation of the IgE/Fc ϵ RI/axis in protective reactions against pathogens, the regulatory role of the eCB system on MC activity should be carefully evaluated in the design of therapeutic strategies against allergic reactions.

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Table 5
Clinical and Randomized Controlled Trials testing the Effects of Cannabinoids in Allergic Reactions in humans.

Study Type	Experimental design and main results	Reference
Randomized Controlled Trial	A group of ten inpatient asthmatics were subjected to a single inhalation of 200 µg of THC or placebo. Salbutamol (100 µg) was used for comparison. Blood pressure, forced expiratory volume in one second (FEV1), forced vital capacity (FVC), peak flow rate (PFR) and self-rating mood scales (SRMS) were recorded in a double-blind fashion. Salbutamol and THC treatments significantly improved ventilatory function. Maximal bronchodilation occurred faster with salbutamol but THC eventually produced the same effects (one hour later).	(Williams et al., 1976)
Randomized Controlled Trial	A group of eleven healthy men and five asthmatic subjects was treated with Δ-9 THC or placebo. Authors found that aerosolized Δ-9 THC induced significant bronchodilation but also caused irritation of the airways.	(Tashkin et al., 1976)
Randomized Controlled Trial	Five asthmatic patients were treated with low doses of Δ-9 THC and ventilatory function was evaluated. Small doses (100 µg) of Δ-9 THC given by aerosol caused significant improvement of peak expiratory flow rate (PEFR) and FEV1.	(Hartley et al., 1978)
Randomized Controlled Trial	An extract containing <i>Echinacea purpurea</i> -derived alkylamides, able to activate CB2 receptor, was applied to human skin following the Human Repeat Insult Patch Test for atopic dermatitis (AD). The extract-based cream reduced the score of AD (SCORAD) in a statistically significant manner. Also, the tested extract caused increased levels of epidermal lipids, ceramide and cholesterol in the skin at day 15 of treatment.	(Oláh et al., 2017)
Randomized Controlled Trial	A formulation of cannabidiol and aspartame (JW-100) was tested in a group of atopic dermatitis patients. Cannabidiol alone or placebo were administered to some individuals. Changes were documented using the Investigator's Static Global Assessment (ISGA) score for AD. After two weeks of treatment, the ISGA score was importantly reduced in the JW-100 group compared to placebo or CBD alone groups.	(Gao et al., 2022)
Clinical Trial	Authors tested the effect of the synthetic cannabinoid nabilone on the acute bronchoconstriction response in six asthmatic subjects. Bronchodilation following nabilone was intermediate between that of terbutaline and placebo in the healthy subjects but was equivalent to placebo in the asthmatics. The authors concluded that oral nabilone (2 mg) does not result in significant acute bronchodilation in patients with asthma.	(Gong et al., 1983)
Clinical Trial	Twenty mild AD patients were subjected to a twice daily application of a topical emulsion containing the aliamide adelmidrol (2%). Complete resolution with no detectable side effects was observed in 80% of patients after 4 weeks of treatment, with no relapses after an 8-week follow up.	(Pulvirenti et al., 2007)

CRedit authorship contribution statement

Rubí Monserrat Osorio Pérez: Investigation, Writing – original draft preparation, Figure design; **Zyanya Patricia Espinosa-Riquer:** Investigation, Writing – original draft preparation; **Gabriela Rodríguez-Manzo:** Investigation, Verification, Writing – original draft preparation; **Silvia L. Cruz:** Conceptualization, Investigation, Writing –

review & editing; **Claudia González-Espinosa:** Conceptualization, Writing – original draft preparation, presentation, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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References

Agarwal, V., Naskar, P., Agasti, S., Khurana, G.K., Vishwakarma, P., Lynn, A.M., Roche, P.A., Puri, N., 2019. The cysteine-rich domain of synaptosomal-associated protein of 23 kDa (SNAP-23) regulates its membrane association and regulated exocytosis from mast cells. *Biochim. Et. Biophys. Acta - Mol. Cell Res.* 1866 (10), 1618–1633. <https://doi.org/10.1016/j.bbamcr.2019.06.015>.

Akula, S., Paivandy, A., Fu, Z., Thorpe, M., Pejler, G., Hellman, L., 2020. How relevant are bone marrow-derived mast cells (BMMCs) as models for tissue mast cells? a comparative transcriptome analysis of BMMCS and peritoneal mast cells. *Cells Vol. 9* (9). <https://doi.org/10.3390/cells9092118>.

Aldakheel, F.M., 2021. Allergic diseases: A comprehensive review on risk factors, immunological mechanisms, link with COVID-19, potential treatments, and role of allergen bioinformatics. *Int. J. Environ. Res. Public Health* 18 (22). <https://doi.org/10.3390/ijerph182212105>.

Almogi-Hazan, O., Reuven, O., 2020. Cannabis, the endocannabinoid system and immunity—the journey from the bedside to the bench and back. *Int. J. Mol. Sci. Vol. 21* (Issue 12) <https://doi.org/10.3390/ijms21124448>.

Aloe, L., Leon, A., Levi-Montalcini, R., 1993. A proposed autacoid mechanism controlling mastocyte behaviour. *Agents Actions* 39 (1 Supplement), 145–147. <https://doi.org/10.1007/BF01972748>.

Angelina, A., Pérez-Diego, M., López-Abente, J., Palomares, O., 2020. The role of cannabinoids in allergic diseases: collegium internationale allergologicum (CIA) update 2020. *Int. Arch. Allergy Immunol.* 181 (8), 565–584. <https://doi.org/10.1159/000508989>.

Baba, Y., Nishida, K., Fujii, Y., Hirano, T., Hikida, M., Kurosaki, T., 2008. Essential function for the calcium sensor STIM1 in mast cell activation and anaphylactic responses. *Nat. Immunol.* 9 (1), 81–88. <https://doi.org/10.1038/ni1546>.

Babina, M., Schülke, Y., Kirchhof, L., Guhl, S., Franke, R., Böhm, S., Zuberbier, T., Henz, B.M., Gombart, A.F., 2005. The transcription factor profile of human mast cells in comparison with monocytes and granulocytes. *Cell. Mol. Life Sci. CMLS* 62 (2), 214–226. <https://doi.org/10.1007/s00018-004-4480-6>.

Babina, Magda, Franke, K., Bal, G., 2022. How “neuronal” are human skin mast cells. *Int. J. Mol. Sci.* 23 (18) <https://doi.org/10.3390/ijms231810871>.

Baggelaar, M.P., Maccarrone, M., van der Stelt, M., 2018. 2-Arachidonoylglycerol: A signaling lipid with manifold actions in the brain. *Prog. Lipid Res.* 71 (November 2017), 1–17. <https://doi.org/10.1016/j.plipres.2018.05.002>.

Beltramo, M., Piomelli, D., 2000. Carrier-mediated transport and enzymatic hydrolysis of the endogenous cannabinoid 2-arachidonoylglycerol. *NeuroReport* 11 (6), 1231–1235. <https://doi.org/10.1097/00001756-200004270-00018>.

Berdyshev, E.V., Schmid, P.C., Krebsbach, R.J., Schmid, H.H., 2001. Activation of PAF receptors results in enhanced synthesis of 2-arachidonoylglycerol (2-AG) in immune cells. *FASEB J.: Off. Publ. Fed. Am. Soc. Exp. Biol.* 15 (12), 2171–2178. <https://doi.org/10.1096/fj.01-0181com>.

Bisogno, T., Maurelli, S., Melch, D., De Petrocellis, L., Di Marzo, V., 1997. Biosynthesis, uptake, and degradation of anandamide and palmitoylethanolamide in leukocytes. *J. Biol. Chem.* 272 (6), 3315–3323. <https://doi.org/10.1074/jbc.272.6.3315>.

Blank, U., Madera-Salcedo, I.K., Danelli, L., Claver, J., Tiwari, N., Sánchez-Miranda, E., Vázquez-Victorio, G., Ramírez-Valadez, K.A., Macías-Silva, M., González-Espinosa, C., 2014. Vesicular trafficking and signaling for cytokine and chemokine secretion in mast cells. *Front. Immunol.* 5. <https://doi.org/10.3389/fimmu.2014.00453>.

Blankman, J.L., Simon, G.M., Cravatt, B.F., 2007. A comprehensive profile of brain enzymes that hydrolyze the endocannabinoid 2-arachidonoylglycerol. *Chem. Biol.* 14 (12), 1347–1356. <https://doi.org/10.1016/j.chembiol.2007.11.006>.

Bonertz, A., Roberts, G.C., Hoefnagel, M., Timon, M., Slater, J.E., Rabin, R.L., Bridgewater, J., Pini, C., Pfaar, O., Akdis, C., Goldstein, J., Poulsen, L.K., van Ree, R.,

- Rhyner, C., Barber, D., Palomares, O., Sheikh, A., Pawankar, R., Hamerlijnck, D., Vieths, S., 2018. Challenges in the implementation of EAACI guidelines on allergen immunotherapy: A global perspective on the regulation of allergen products. *Allergy: Eur. J. Allergy Clin. Immunol.* 73 (1), 64–76. <https://doi.org/10.1111/all.13266>.
- Bonhaus, D.W., Chang, L.K., Kwan, J., Martin, G.R., 1998. Dual activation and inhibition of adenylyl cyclase by cannabinoid receptor agonists: evidence for agonist-specific trafficking of intracellular responses. *J. Pharmacol. Exp. Ther.* 287 (3), 884–888.
- Borriello, F., Granata, F., Varricchi, G., Genovese, A., Triggiani, M., Marone, G., 2014. Immunopharmacological modulation of mast cells. *Curr. Opin. Pharmacol.* 17 (1), 45–57. <https://doi.org/10.1016/j.coph.2014.07.002>.
- Bouaboula, M., Dussosoy, D., Casellas, P., 1999. Regulation of peripheral cannabinoid receptor CB2 phosphorylation by the inverse agonist SR 144528. Implications for receptor biological responses. *J. Biol. Chem.* 274 (29), 20397–20405. <https://doi.org/10.1074/jbc.274.29.20397>.
- Bouaboula, M., Hilairat, S., Marchand, J., Fajas, L., Le Fur, G., Casellas, P., 2005. Anandamide induced PPAR γ transcriptional activation and 3T3-L1 preadipocyte differentiation. *Eur. J. Pharmacol.* 517 (3), 174–181. <https://doi.org/10.1016/j.ejphar.2005.05.032>.
- Boudreau, R.T.M., Hoskin, D.W., Lin, T.-J., 2004. Phosphatase inhibition potentiates IL-6 production by mast cells in response to Fc ϵ R1-mediated activation: involvement of p38 MAPK. *J. Leukoc. Biol.* 76 (5), 1075–1081. <https://doi.org/10.1189/jlb.1003498>.
- Braile, M., Marcella, S., Marone, G., Galdiero, M.R., Varricchi, G., Loffredo, S., 2021. The interplay between the immune and the endocannabinoid systems in cancer. *Cells* Vol. 10 (6), 1282. <https://doi.org/10.3390/cells10061282>.
- Brailoiu, G.C., Oprea, T.I., Zhao, P., Abood, M.E., Brailoiu, E., 2011. Intracellular cannabinoid type 1 (CB1) receptors are activated by anandamide. *J. Biol. Chem.* 286 (33), 29166–29174. <https://doi.org/10.1074/jbc.M110.217463>.
- Brailoiu, G.C., Deliu, E., Marcu, J., Hoffman, N.E., Console-Bram, L., Zhao, P., Madesh, M., Abood, M.E., Brailoiu, E., 2014. Differential activation of intracellular versus plasmalemmal CB2 Cannabinoid receptors. *Biochemistry* 53 (30), 4990–4999. <https://doi.org/10.1021/bi500632a>.
- Braun, A., Engel, T., Aguilar-Pimentel, J.A., Zimmer, A., Jakob, T., Behrendt, H., Mempel, M., 2011. Beneficial effects of cannabinoids (CB) in a murine model of allergen-induced airway inflammation: Role of CB1/CB2 receptors. *Immunobiology* 216 (4), 466–476. <https://doi.org/10.1016/j.imbio.2010.09.004>.
- Brust, T.F., Conley, J.M., Watts, V.J., 2015. G α /o-coupled receptor-mediated sensitization of adenylyl cyclase: 40 years later. *Eur. J. Pharmacol.* 763, 223–232. <https://doi.org/10.1016/j.ejphar.2015.05.014>.
- Bulfone-paus, S., Nilsson, G., Draber, P., Blank, U., Levi-schaffer, F., 2017. Positive and negative signals in mast cell activation. *Trends Immunol.* 1–11. <https://doi.org/10.1016/j.it.2017.01.008>.
- Cabral, G.A., Ferreira, G.A., Jamerson, M.J., 2015. In: Pertwee, Roger G. (Ed.), *Endocannabinoids and the Immune System in Health and Disease*. Springer International Publishing, pp. 185–211. https://doi.org/10.1007/978-3-319-20825-1_6.
- Calebiro, D., Godbole, A., 2018. Internalization of G-protein-coupled receptors: Implication in receptor function, physiology and diseases. *Best. Pract. Res. Clin. Endocrinol. Metab.* 32 (2), 83–91. <https://doi.org/10.1016/j.beem.2018.01.004>.
- Campora, L., Miragliotta, V., Ricci, E., Cristino, L., Di Marzo, V., Albanese, F., Federica della Valle, M., Abramo, F., 2012. Cannabinoid receptor type 1 and 2 expression in the skin of healthy dogs and dogs with atopic dermatitis. *Am. J. Vet. Res.* 73 (7), 988–995. <https://doi.org/10.2460/ajvr.73.7.988>.
- Cantarella, G., Scollo, M., Lempereur, L., Saccani-Jotti, G., Basile, F., Bernardini, R., 2011. Endocannabinoids inhibit release of nerve growth factor by inflammation-activated mast cells. *Biochem. Pharmacol.* 82 (4), 380–388. <https://doi.org/10.1016/j.bcp.2011.05.004>.
- Carrier, E.J., Kearn, C.S., Barkmeier, A.J., Breese, N.M., Yang, W., Nithipatikorn, K., Pfister, S.L., Campbell, W.B., Hillard, C.J., 2004. Cultured rat microglial cells synthesize the endocannabinoid 2-arachidonylglycerol, which increases proliferation via a CB2 receptor-dependent mechanism. *Mol. Pharmacol.* 65 (4), 999–1007. <https://doi.org/10.1124/mol.65.4.999>.
- Castaneda, J.T., Harui, A., Kiertcher, S.M., Roth, J.D., Roth, M.D., 2013. Differential expression of intracellular and extracellular CB2 cannabinoid receptor protein by human peripheral blood leukocytes. *J. Neuroimmune Pharmacol.* 8 (1), 323–332. <https://doi.org/10.1007/s11481-012-9430-8>.
- Castellani, M.L., Felaco, M., Pandolfi, F., Salini, V., De Amicis, D., Orso, C., Vecchiet, J., Tetè, S., Ciampoli, C., Conti, F., Cerulli, G., Caraffa, A., Antinolfi, P., Cuccurullo, C., Felaco, P., Kempuraj, D., Boscolo, P., Sabatino, G., Shaik, Y.B., 2009. Mast cells and arachidonic acid cascade in inflammation. *Eur. J. Inflamm.* 7 (3), 131–137. <https://doi.org/10.1177/1721727x0900700302>.
- Chatterjee, V., Gashev, A.A., 2012. Aging-associated shifts in functional status of mast cells located by adult and aged mesenteric lymphatic vessels. *Am. J. Physiol. Heart Circ. Physiol.* 303 (6), H693–H702. <https://doi.org/10.1152/ajpheart.00378.2012>.
- Chen, X., Yang, W., Fan, Y., Luo, J., Hong, K., Wang, Z., Yan, J., Chen, X., Lu, J., Benovic, J., Zhou, N., 2010. Structural determinants in the second intracellular loop of the human cannabinoid CB1 receptor mediate selective coupling to G α s and G α i. *Br. J. Pharmacol.* 161 (8), 1817–1834. <https://doi.org/10.1111/j.1476-5381.2010.01006.x>.
- Chicca, A., Marazzi, J., Nicolussi, S., Gertsch, J., 2012. Evidence for bidirectional endocannabinoid transport across cell membranes. *J. Biol. Chem.* 287 (41), 34660–34682. <https://doi.org/10.1074/jbc.M112.373241>.
- Chiurchiù, V., Maccarrone, M., 2016. Bioactive lipids as modulators of immunity, inflammation and emotions. *Curr. Opin. Pharmacol.* 29, 54–62. <https://doi.org/10.1016/j.coph.2016.06.005>.
- Chiurchiù, V., Leuti, A., Smoun, R., Mechoulam, R., Maccarrone, M., 2018. Bioactive lipids ALIAmides differentially modulate inflammatory responses of distinct subsets of primary human T lymphocytes. *FASEB J.* 32 (10), 5716–5723. <https://doi.org/10.1096/fj.20180107R>.
- Clemens, R.A., Lowell, C.A., 2019. CRAC channel regulation of innate immune cells in health and disease. *Cell Calcium* 78, 56–65. <https://doi.org/10.1016/j.ceca.2019.01.003>.
- Crespo, P., Bustelo, X.R., Aaronson, D.S., Coso, O.A., Lopez-Barahona, M., Barbacid, M., Gutkind, J.S., 1996. Rac-1 dependent stimulation of the JNK/SAPK signaling pathway by Vav. *Oncogene* 13 (3), 455–460.
- Crespo, P., Schuebel, K.E., Ostrom, A.A., Gutkind, J.S., Bustelo, X.R., 1997. Phosphotyrosine-dependent activation of Rac-1 GDP/GTP exchange by the vav proto-oncogene product. *Nature* 385 (6612), 169–172. <https://doi.org/10.1038/385169a0>.
- Cruz, S.L., Sánchez-Miranda, E., Castillo-Arellano, J.I., Cervantes-Villagrana, R.D., Illarra-Sánchez, A., González-Espinosa, C., 2018. Anandamide inhibits Fc ϵ R1-dependent degranulation and cytokine synthesis in mast cells through CB2 and GPR55 receptor activation. Possible involvement of CB2-GPR55 heteromers. *Int. Immunopharmacol.* 64, 298–307. <https://doi.org/10.1016/j.intimp.2018.09.006>.
- Dahlin, J.S., Malinovskii, A., Öhrvik, H., Sandelin, M., Janson, C., Alving, K., Hallgren, J., 2016. Lin- CD34hi CD117int/hi Fc ϵ R1+ cells in human blood constitute a rare population of mast cell progenitors. *Blood* 127 (4), 383–391. <https://doi.org/10.1182/blood-2015-06-650648>.
- Dalle Carbonare, M., Del Giudice, E., Stecca, A., Colavito, D., Fabris, M., D'Arrigo, A., Bernardini, D., Dam, M., Leon, A., 2008. A saturated N-acyl ethanolamine other than N-palmitoyl ethanolamine with anti-inflammatory properties: a neglected story. *J. Neuroendocrinol.* 20 (SUPPL. 1), 26–34. <https://doi.org/10.1111/j.1365-2826.2008.01689.x>.
- Dalton, G.D., Howlett, A.C., 2012. Cannabinoid CB1 receptors transactivate multiple receptor tyrosine kinases and regulate serine/ threonine kinases to activate ERK in neuronal cells. *Br. J. Pharmacol.* 165 (8), 2497–2511. <https://doi.org/10.1111/j.1476-5381.2011.01455.x>.
- De Filippis, D., Russo, A., D'Amico, A., Esposito, G., Concetta, P., Cinelli, M., Russo, G., Iuvone, T., 2008. Cannabinoids reduce granuloma-associated angiogenesis in rats by controlling transcription and expression of mast cell protease-5. *Br. J. Pharmacol.* 154 (8), 1672–1679. <https://doi.org/10.1038/bjp.2008.211>.
- Deak, A.T., Groschner, L.N., Alam, M.R., Seles, E., Bondarenko, A.I., Graier, W.F., Malli, R., 2013. The endocannabinoid N-arachidonoyl glycine (NAGly) inhibits store-operated Ca $^{2+}$ entry by preventing STIM1-orai1 interaction. *J. Cell Sci.* 126 (4), 879–888. <https://doi.org/10.1242/jcs.118075>.
- Dehlink, E., Platzer, B., Baker, A.H., LaRosa, J., Pardo, M., Dwyer, P., Yen, E.H., Szépfalusi, Z., Nurko, S., Fiebiger, E., 2011. A soluble form of the high affinity IgE receptor, Fc ϵ -Epsilon-RI, circulates in human serum. *PLoS ONE* 6 (4), e19098. <https://doi.org/10.1371/journal.pone.0019098>.
- Derakhshan, T., Boyce, J.A., Dwyer, D.F., 2022. Defining mast cell differentiation and heterogeneity through single-cell transcriptomics analysis. *J. Allergy Clin. Immunol.* 150 (4), 739–747. <https://doi.org/10.1016/j.jaci.2022.08.011>.
- Deutsch, D.G., 2016. A personal retrospective: Elevating anandamide (AEA) by targeting fatty acid amide hydrolase (FAAH) and the fatty acid binding proteins (FABPs). *Front. Pharmacol.* 7 (OCT), 1–7. <https://doi.org/10.3389/fphar.2016.00370>.
- Di Marzo, V., De Petrocellis, L., 2010. Endocannabinoids as regulators of transient receptor potential (TRP) channels: a further opportunity to develop new endocannabinoid-based therapeutic drugs. *Curr. Med. Chem.* 17, 1430–1449.
- Di Marzo, V., Melck, D., Orlando, P., Bisogno, T., Zagoory, O., Bifulco, M., Vogel, Z., De Petrocellis, L., 2001. Palmitoylethanolamide inhibits the expression of fatty acid amide hydrolase and enhances the anti-proliferative effect of anandamide in human breast cancer cells. *Biochem. J.* 358 (Pt 1), 249–255. <https://doi.org/10.1042/0264-6021:3580249>.
- Di Marzo, Vincenzo, 2018. New approaches and challenges to targeting the endocannabinoid system. *Nat. Rev. Drug Discov.* 17 (9), 623–639. <https://doi.org/10.1038/nrd.2018.115>.
- Di Marzo, Vincenzo, Deutsch, D.G., 1998. Biochemistry of the endogenous ligands of cannabinoid receptors. *Neurobiol. Dis.* 5 (6), 386–404. <https://doi.org/10.1006/nbdi.1998.0214>.
- Dobranowski, P., Sly, L.M., 2018. SHIP negatively regulates type II immune responses in mast cells and macrophages. *J. Leukoc. Biol.* 103 (6), 1053–1064. <https://doi.org/10.1002/JLB.3MIR0817-340R>.
- Dotsey, E., Ushach, I., Pone, E., Nakajima, R., Jasinskas, A., Argueta, D.A., Dillon, A., DiPatrizio, N., Davies, H., Zlotnik, A., Crompton, P.D., Felgner, P.L., 2017. Transient cannabinoid receptor 2 blockade during immunization heightens intensity and breadth of antigen-specific antibody responses in young and aged mice. *Sci. Rep.* 7 (1), 42584. <https://doi.org/10.1038/srep42584>.
- Drehmer, M.N., Muniz, Y.C.N., Marrero, A.R., Löfgren, S.E., 2019. Gene expression of ABHD6, a key factor in the endocannabinoid system, can be modulated by female hormones in human immune cells. *Biochem. Genet.* 57 (1), 35–45. <https://doi.org/10.1007/s10528-018-9871-8>.
- Durham, S.R., Shamji, M.H., 2022. Allergen immunotherapy: past, present and future. *Nat. Rev. Immunol.* <https://doi.org/10.1038/s41577-022-00786-1>.
- Dwyer, D.F., Barrett, N.A., Austen, K.F., Immunological Genome Project Consortium, 2016. Expression profiling of constitutive mast cells reveals a unique identity within the immune system. *Nat. Immunol.* 17 (7), 878–887. <https://doi.org/10.1038/ni.3445>.
- Eljaschewitsch, E., Witting, A., Mawrin, C., Lee, T., Schmidt, P.M., Wolf, S., Hoertnagl, H., Raine, C.S., Schneider-Stock, R., Nitsch, R., Ullrich, O., 2006. The endocannabinoid anandamide protects neurons during CNS inflammation by

- induction of MKP-1 in microglial cells. *Neuron* 49 (1), 67–79. <https://doi.org/10.1016/j.neuron.2005.11.027>.
- Espinosa-Riquer, Z.P., Ibarra-Sánchez, A., Vibhushan, S., Bratti, M., Charles, N., Blank, U., Rodríguez-Manzo, G., González-Espinoza, C., 2019. TLR4 receptor induces 2-AG-dependent tolerance to lipopolysaccharide and trafficking of CB2 receptor in mast cells. *J. Immunol.* j1800997. <https://doi.org/10.4049/jimmunol.1800997>.
- Facci, L., Dal Toso, R., Romanello, S., Buriani, A., Skaper, S.D., Leon, A., 1995. Mast cells express a peripheral cannabinoid receptor with differential sensitivity to anandamide and palmitoylethanolamide. *Proc. Natl. Acad. Sci. USA* 92 (8), 3376–3380. <https://doi.org/10.1073/pnas.92.8.3376>.
- Falcone, F.H., Wan, D., Barwary, N., Sagi-Eisenberg, R., 2018. RBL cells as models for in vitro studies of mast cells and basophils. *Immunol. Rev.* 282 (1), 47–57. <https://doi.org/10.1111/immr.12628>.
- Faulkner, H., Turner, J., Kamgno, J., Pion, S.D., Boussinesq, M., Bradley, J.E., 2002. Age- and infection intensity-dependent cytokine and antibody production in human trichuriasis: the importance of IgE. *J. Infect. Dis.* 185 (5), 665–672. <https://doi.org/10.1086/339005>.
- Feigin, V.L., Norrving, B., Mensah, G.A., 2017. Glob. Burd. Stroke 439–449. <https://doi.org/10.1161/CIRCRESAHA.116.308413>.
- Feoktistov, I., Biaggioni, I., 1996. Role of adenosine in asthma. *Drug Dev. Res.* 39 (3–4), 333–336. [https://doi.org/10.1002/\(SICI\)1098-2299\(199611/12\)39:3/4<333::AID-DDR14>3.0.CO;2-2](https://doi.org/10.1002/(SICI)1098-2299(199611/12)39:3/4<333::AID-DDR14>3.0.CO;2-2).
- Fleming, I., Schermer, B., Popp, R., Busse, R., 1999. Inhibition of the production of endothelium-derived hyperpolarizing factor by cannabinoid receptor agonists. *Br. J. Pharmacol.* 126 (4), 949–960. <https://doi.org/10.1038/sj.bjp.0702381>.
- Forsythe, P., 2019. Mast cells in neuroimmune interactions. *Trends Neurosci.* 42 (1), 43–55. <https://doi.org/10.1016/j.tins.2018.09.006>.
- Fowler, C.J., 2013. Transport of endocannabinoids across the plasma membrane and within the cell. *FEBS J.* 280 (9), 1895–1904. <https://doi.org/10.1111/febs.12212>.
- Frei, R.B., Luschni, P., Parzmair, G.P., Peinhaupt, M., Schranz, S., Fauland, A., Wheelock, C.E., Heinemann, A., Sturm, E.M., 2016. Cannabinoid receptor 2 augments eosinophil responsiveness and aggravates allergen-induced pulmonary inflammation in mice. *Allergy* 71 (7), 944–956. <https://doi.org/10.1111/all.12858>.
- Frossi, B., Mion, F., Tripodo, C., Colombo, M.P., Pucillo, C.E., 2017. Rheostatic functions of mast cells in the control of innate and adaptive immune responses. *Trends Immunol.* 38 (9), 648–656. <https://doi.org/10.1016/j.it.2017.04.001>.
- Fu, J., Bottegoni, G., Sasso, O., Bertorelli, R., Rocchia, W., Masetti, M., Guijarro, A., Lodola, A., Armirotti, A., Garau, G., Bandiera, T., Reggiani, A., Mor, M., Cavalli, A., Piomelli, D., 2012. A catalytically silent FAAH-1 variant drives anandamide transport in neurons. *Nat. Neurosci.* 15 (1), 64–69. <https://doi.org/10.1038/nn.2986>.
- Funk, C.D., 2001. Prostaglandins and leukotrienes: Advances in eicosanoid biology. *Science* 294 (5548), 1871–1875. <https://doi.org/10.1126/science.294.5548.1871>.
- Gabrielli, M., Battista, N., Riganti, L., Prada, I., Antonucci, F., Cantone, L., Lombardi, M., Matteoli, M., Maccarrone, M., Verderio, C., 2015. Active endocannabinoids are secreted on the surface of microglial microvesicles. *SpringerPlus* 4 (2), 1–32. <https://doi.org/10.1186/s1293-1801-4-S1-L29>.
- Gaffal, E., Cron, M., Glodde, N., Tüting, T., 2013. Anti-inflammatory activity of topical THC in DNFB-mediated mouse allergic contact dermatitis independent of CB1 and CB2 receptors. *Allergy: Eur. J. Allergy Clin. Immunol.* 68 (8), 994–1000. <https://doi.org/10.1111/all.12183>.
- Gaffal, Evelyn, Kemter, A.M., Scheu, S., Dantas, R.L., Vogt, J., Baune, B., Tüting, T., Zimmer, A., Alferink, J., 2020. Cannabinoid receptor 2 modulates maturation of dendritic cells and their capacity to induce hapten-induced contact hypersensitivity. *Int. J. Mol. Sci.* 21 (2) <https://doi.org/10.3390/ijms21020475>.
- Gallazzo, G., Giancola, F., Stanzani, A., Fracassi, F., Bernardini, C., Forni, M., Pietra, M., Chiocchetti, R., 2018. Localization of cannabinoid receptors CB1, CB2, GPR55, and PPARα in the canine gastrointestinal tract. *Histochem. Cell Biol.* 150 (2), 187–205. <https://doi.org/10.1007/s00418-018-1684-7>.
- Galiègue, S., Mary, S., Marchand, J., Dussossy, D., Carrikre, D., Camyon, P., Bouaboula, M., Shirez, D., Fur, G.L.E., Casellas, P., 1995. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *Biochemistry* 61, 54–61.
- Galli, S.J., Tsai, M., 2012. IgE and mast cells in allergic disease. *Nat. Med.* 18 (5), 693–704. <https://doi.org/10.1038/nm.2755>.
- Galli, S.J., Gaudenzio, N., Tsai, M., 2020. Mast cells in inflammation and disease: recent progress and ongoing concerns. *Annu. Rev. Immunol.* 38, 49–77. <https://doi.org/10.1146/annurev-immunol-071719-094903>.
- Gao, Y., Li, Y., Tan, Y., Liu, W., Ouaddi, S., McCoy, J., Kovacevic, M., Situm, M., Stanimirovic, A., Li, M., Wambier, C., Goren, A., Zou, Y., 2022. Novel cannabidiol aspartame combination treatment (JW-100) significantly reduces ISGA score in atopic dermatitis: results from a randomized double-blinded placebo-controlled interventional study. *J. Cosmet. Dermatol.* 21 (4), 1647–1650. <https://doi.org/10.1111/jocd.14263>.
- Gause, W.C., Rothlin, C., Loke, P., 2020. Heterogeneity in the initiation, development and function of type 2 immunity. *Nat. Rev. Immunol.* 20 (10), 603–614. <https://doi.org/10.1038/s41577-020-0301-x>.
- Giudice, E., Del, Rinaldi, L., Passarotto, M., Facchinetti, F., D'Arrigo, A., Guiotto, A., Carbonare, M.D., Battistin, L., Leon, A., 2007. Cannabidiol, unlike synthetic cannabinoids, triggers activation of RBL-2H3 mast cells. *J. Leukoc. Biol.* 81 (6), 1512–1522. <https://doi.org/10.1189/jlb.1206738>.
- Glaser, S.T., Abumrad, N.A., Fatade, F., Kaczocha, M., Studholme, K.M., Deutsch, D.G., 2003. Evidence against the presence of an anandamide transporter. *Proc. Natl. Acad. Sci. USA* 100 (7), 4269–4274. <https://doi.org/10.1073/pnas.0730816100>.
- Gomez, G., Gonzalez-Espinoza, C., Odom, S., Baez, G., Cid, M.E., Ryan, J.J., Rivera, J., 2005. Impaired FcεRI-dependent gene expression and defective eicosanoid and cytokine production as a consequence of fyn deficiency in mast cells. *J. Immunol.* 175 (11), 7602–7610. <https://doi.org/10.4049/jimmunol.175.11.7602>.
- Gong, H., Tashkin, D.P., Calvaresi, B., 1983. Comparison of bronchial effects of nabilone and terbutaline in healthy and asthmatic subjects. *J. Clin. Pharmacol.* 23 (4), 127–133. <https://doi.org/10.1002/j.1552-4604.1983.tb02715.x>.
- Granberg, M., Fowler, C.J., Jacobsson, S.O.P., 2001. Effects of the cannabimimetic fatty acid derivatives 2-arachidonoylglycerol, anandamide, palmitoylethanolamide and methanandamide upon IgE-dependent antigen-induced β-hexosaminidase, serotonin and TNF α release from rat RBL-2H3 basophilic leukaemia cells. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 364 (1), 66–73. <https://doi.org/10.1007/s002100100424>.
- Grimsey, N.L., Graham, E.S., Dragunow, M., Glass, M., 2010. Cannabinoid Receptor 1 trafficking and the role of the intracellular pool: Implications for therapeutics. *Biochem. Pharmacol.* 80 (7), 1050–1062. <https://doi.org/10.1016/j.bcp.2010.06.007>.
- Grimsey, N.L., Goodfellow, C.E., Dragunow, M., Glass, M., 2011. Cannabinoid receptor 2 undergoes Rab5-mediated internalization and recycles via a Rab11-dependent pathway. *Biochim. Et. Biophys. Acta - Mol. Cell Res.* 1813 (8), 1554–1560. <https://doi.org/10.1016/j.bbamer.2011.05.010>.
- Gu, Z., Singh, S., Niyogi, R.G., Lamont, G.J., Wang, H., Lamont, R.J., Scott, D.A., 2019. Marijuana-derived cannabinoids trigger a CB2/PI3K axis of suppression of the innate response to oral pathogens. *Front. Immunol.* 10 (October), 1–13. <https://doi.org/10.3389/fimmu.2019.02288>.
- Guhl, S., Tapkenhinch, S., Smorodchenko, A., Grützkau, A., Henz, B.M., Zuberbier, T., Hartmann, K., 2003. Ultraviolet irradiation induces apoptosis in human immature, but not in skin mast cells. *J. Invest. Dermatol.* 121 (4), 837–844. <https://doi.org/10.1046/j.1523-1747.2003.12480.x>.
- Guhl, S., Babina, M., Neou, A., Zuberbier, T., Artuc, M., 2010. Mast cell lines HMC-1 and LAD2 in comparison with mature human skin mast cells – drastically reduced levels of tryptase and chymase in mast cell lines. *Exp. Dermatol.* 19 (9), 845–847. <https://doi.org/10.1111/j.1600-0625.2010.01103.x>.
- Gulledge, T.V., Collette, N.M., Mackey, E., Johnstone, S.E., Moazami, Y., Todd, D.A., Moeser, A.J., Pierce, J.G., Cech, N.B., Laster, S.M., 2018. Mast cell degranulation and calcium influx are inhibited by an Echinacea purpurea extract and the alkylamide dodeca-2E,4E-dienoic acid isobutylamide. *J. Ethnopharmacol.* 212 (1), 166–174. <https://doi.org/10.1016/j.jep.2017.10.012>.
- Haj-Dahmane, S., Shen, R.Y., Elmes, M.W., Studholme, K., Kanjiya, M.P., Bogdan, D., Thanos, P.K., Miyauchi, J.T., Tsirka, S.E., Deutsch, D.G., Kaczocha, M., 2018. Fatty acid-binding protein 5 controls retrograde endocannabinoid signaling at central glutamate synapses. *Proc. Natl. Acad. Sci. USA* 115 (13), 3482–3487. <https://doi.org/10.1073/pnas.1721339115>.
- Hartley, J., Nogrady, S., Seaton, A., 1978. Bronchodilator effect of delta1-tetrahydrocannabinol. *Br. J. Clin. Pharmacol.* 5 (6), 523–525. <https://doi.org/10.1111/j.1365-2125.1978.tb01667.x>.
- Haruna, T., Soga, M., Morioka, Y., Imura, K., Furue, Y., Yamamoto, M., Hayakawa, J., Deguchi, M., Arimura, A., Yasui, K., 2017. The Inhibitory Effect of S-777469, a Cannabinoid Type 2 Receptor Agonist, on Skin Inflammation in Mice. *Pharmacology* 99 (5–6), 259–267. <https://doi.org/10.1159/000455916>.
- Harvina, I.T., Levi-Schaffer, F., Draber, P., Friedman, S., Polakovicova, I., Gibbs, B.F., Blank, U., Nilsson, G., Maurer, M., 2014. Molecular targets on mast cells and basophils for novel therapies. *J. Allergy Clin. Immunol.* 134 (3), 530–544. <https://doi.org/10.1016/j.jaci.2014.03.007>.
- Hashimoto, Y., Ohno-Shosaku, T., Kano, M., 2007. Ca²⁺-assisted receptor-driven endocannabinoid release: mechanisms that associate presynaptic and postsynaptic activities. *Curr. Opin. Neurobiol.* 17 (3), 360–365. <https://doi.org/10.1016/j.conb.2007.03.012>.
- Henson, J., Vitetta, L., Quezada, M., Hall, S., 2021. Enhancing endocannabinoid control of stress with cannabidiol. *J. Clin. Med.* 10 (24), 5852. <https://doi.org/10.3390/jcm10245852>.
- Hepp, R., Puri, N., Hohenstein, A.C., Crawford, G.L., Whiteheart, S.W., Roche, P.A., 2005. Phosphorylation of SNAP-23 regulates exocytosis from mast cells. *J. Biol. Chem.* 280 (8), 6610–6620. <https://doi.org/10.1074/JBC.M412126200>.
- Hernandez-Hansen, V., Smith, A.J., Surviladze, Z., Chigae, A., Mazel, T., Kalesnikoff, J., Lowell, C.A., Krystal, G., Sklar, L.A., Wilson, B.S., Oliver, J.M., 2004. Dysregulated FcεRI signaling and altered fyn and SHIP activities in lyn-deficient mast cells. *J. Immunol.* 173 (1), 100–112. <https://doi.org/10.4049/jimmunol.173.1.100>.
- Hillard, C.J., Jarrahian, A., 2003. Cellular accumulation of anandamide: consensus and controversy. *Br. J. Pharmacol.* 140 (5), 802–808. <https://doi.org/10.1038/sj.bjp.0705468>.
- Hillard, C.J., Edgemond, W.S., Jarrahian, A., Campbell, W.B., 1997. Accumulation of N-arachidonylethanolamine (anandamide) into cerebellar granule cells occurs via facilitated diffusion. *J. Neurochem.* 69 (2), 631–638. <https://doi.org/10.1046/j.1471-4159.1997.69020631.x>.
- Hirasawa, N., Sato, Y., Fujita, Y., Ohuchi, K., 2000. Involvement of a phosphatidylinositol 3-kinase-p38 mitogen activated protein kinase pathway in antigen-induced IL-4 production in mast cells. *Biochim. Et. Biophys. Acta (BBA) - Bioenerg.* 1456 (1), 45–55. [https://doi.org/10.1016/S0005-2728\(99\)00104-8](https://doi.org/10.1016/S0005-2728(99)00104-8).
- Ho, W.-S., Barrett, D.A., Randall, M.D., 2008. 'Entourage' effects of N-palmitoylethanolamide and N-oleoylethanolamide on vasorelaxation to anandamide occur through TRPV1 receptors. *Br. J. Pharmacol.* 155 (6), 837–846. <https://doi.org/10.1038/bjp.2008.324>.
- Hossny, E., Ebisawa, M., El-Gamal, Y., Arasi, S., Dahdah, L., El-Owaidy, R., Galvan, C.A., Lee, B.W., Levin, M., Martinez, S., Pawankar, R., Tang, M.L.K., Tham, E.H., Fiocchi, A., 2019. Challenges of managing food allergy in the developing world. *World Allergy Organ. J.* 12 (11), 100089. <https://doi.org/10.1016/j.waojou.2019.100089>.

- Howlett, A.C., 2005. Cannabinoid receptor signaling. *Handb. Exp. Pharmacol.* 168, 53–79. <https://doi.org/10.1007/3-540-26573-2.2>.
- Howlett, A.C., Barth, F., Bonner, T.I., Cabral, G., Casellas, P., Devane, W.A., Felder, C.C., Herkenham, M., Mackie, K., Martin, B.R., Mechoulam, R., Pertwee, R.G., 2002. International union of pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol. Rev.* 54 (2), 161–202. <https://doi.org/10.1124/pr.54.2.161>.
- Hsieh, C., Brown, S., Derleth, C., Mackie, K., 2002. Internalization and recycling of the CB1 cannabinoid receptor. *J. Neurochem.* 73 (2), 493–501. <https://doi.org/10.1046/j.1471-4159.1999.0730493.x>.
- Hsu, K.-L., Tsuboi, K., Adibekian, A., Pugh, H., Masuda, K., Cravatt, B.F., 2012. DAGL β inhibition perturbs a lipid network involved in macrophage inflammatory responses. *Nat. Chem. Biol.* 8 (12), 999–1007. <https://doi.org/10.1038/nchembio.1105>.
- Ibsen, M.S., Finlay, D.B., Patel, M., Javitch, J.A., Glass, M., Grimsey, N.L., 2019. Cannabinoid CB1 and CB2 receptor-mediated arrestin translocation: species, subtype, and agonist-dependence. *Front. Pharmacol.* 10 (APR), 1–18. <https://doi.org/10.3389/fphar.2019.00350>.
- Irrera, N., D'ascola, A., Pallio, G., Bitto, A., Mazzon, E., Mannino, F., Squadrito, V., Arcoraci, V., Minutoli, L., Campo, G.M., Avenoso, A., Bongiorno, E.B., Vaccaro, M., Squadrito, F., Altavilla, D., 2019. β -Caryophyllene mitigates collagen antibody induced arthritis (CAIA) in mice through a cross-talk between CB2 and PPAR- γ receptors. *Biomolecules* 9 (8). <https://doi.org/10.3390/biom9080326>.
- Iuvone, T., De Filippis, D., Di Spiezio Sardo, A., D'Amico, A., Simonetti, S., Sparice, S., Esposito, G., Bifulco, G., Insabato, L., Nappi, C., Guida, M., 2008. Selective CB2 up-regulation in women affected by endometrial inflammation. *J. Cell. Mol. Med.* 12 (2), 661–670. <https://doi.org/10.1111/j.1582-4934.2007.00085.x>.
- Jackson, A.R., Nagarkatti, P., Nagarkatti, M., 2014. Anandamide attenuates Th-17 cell-mediated delayed-type hypersensitivity response by triggering IL-10 production and consequent microRNA induction. *PLoS ONE* 9 (4), e93954. <https://doi.org/10.1371/journal.pone.0093954>.
- Jacobsson, S.O.P., Fowler, C.J., 2001. Characterization of palmitoylethanolamide transport in mouse Neuro-2a neuroblastoma and rat RBL-2H3 basophilic leukaemia cells: comparison with anandamide. *Br. J. Pharmacol.* 132 (8), 1743–1754. <https://doi.org/10.1038/sj.bjp.0704029>.
- Jing, H., Reed, A., Ulanovskaya, O.A., Grigoleit, J.-S., Herbst, D.M., Henry, C.L., Li, H., Barbas, S., Germain, J., Masuda, K., Cravatt, B.F., 2021. Phospholipase C γ 2 regulates endocannabinoid and eicosanoid networks in innate immune cells. *Proc. Natl. Acad. Sci.* 118 (41), e212971118. <https://doi.org/10.1073/pnas.2112971118>.
- (St) John, A.L., Rathore, A.P.S., Ginhoux, F., 2022. New perspectives on the origins and heterogeneity of mast cells. *Nat. Rev. Immunol.* <https://doi.org/10.1038/s41577-022-00731-2>.
- Jonsson, K.-O., Persson, E., Fowler, C.J., 2006. The cannabinoid CB2 receptor selective agonist JWH133 reduces mast cell oedema in response to compound 48/80 in vivo but not the release of β -hexosaminidase from skin slices in vitro. *Life Sci.* 78 (6), 598–606. <https://doi.org/10.1016/j.lfs.2005.05.059>.
- Jordan, C.J., Xi, Z.X., 2019. Progress in brain cannabinoid CB 2 receptor research: from genes to behavior. *Neurosci. Biobehav. Rev.* 98 (October 2018), 208–220. <https://doi.org/10.1016/j.neubiorev.2018.12.026>.
- Jüttler, E., Petrovita, I., Tarabin, V., Prinz, S., Dong-Si, T., Fink, G., Schwaninger, M., 2004. The cannabinoid dexamibinol is an inhibitor of the nuclear factor-kappa B (NF- κ B). *Neuropharmacology* 47 (4), 580–592. <https://doi.org/10.1016/j.neuropharm.2004.05.009>.
- Kaczocha, M., Haj-Dahmane, S., 2022. Mechanisms of endocannabinoid transport in the brain. *Br. J. Pharmacol.* 179 (17), 4300–4310. <https://doi.org/10.1111/bph.15469>.
- Kaczocha, M., Glaser, S.T., Deutsch, D.G., 2009. Identification of intracellular carriers for the endocannabinoid anandamide. *Proc. Natl. Acad. Sci. USA* 106 (15), 6375–6380. <https://doi.org/10.1073/pnas.0901515106>.
- Kaczocha, M., Vivieca, S., Sun, J., Glaser, S.T., Deutsch, D.G., 2012. Fatty acid-binding proteins transport N-acyl ethanolamines to nuclear receptors and are targets of endocannabinoid transport inhibitors. *J. Biol. Chem.* 287 (5), 3415–3424. <https://doi.org/10.1074/jbc.M111.304907>.
- Kalesnikoff, J., Baur, N., Leitges, M., Hughes, M.R., Damen, J.E., Huber, M., Krystal, G., 2002. SHP negatively regulates IgE + antigen-induced IL-6 production in mast cells by inhibiting NF- κ B activity. *J. Immunol.* 168 (9), 4737–4746. <https://doi.org/10.4049/jimmunol.168.9.4737>.
- Kamata, T., Yamashita, M., Kimura, M., Murata, K., Inami, M., Shimizu, C., Sugaya, K., Wang, C.R., Taniguchi, M., Nakayama, T., 2003. src homology 2 domain-containing tyrosine phosphatase SHP-1 controls the development of allergic airway inflammation. *J. Clin. Invest.* 111 (1), 109–119. <https://doi.org/10.1172/JCI15719>.
- Kaplan, B.L.F., 2013. The role of CB1 in immune modulation by cannabinoids. *Pharmacol. Ther.* 137 (3), 365–374. <https://doi.org/10.1016/j.pharmthera.2012.12.004>.
- Karsak, M., Gaffal, E., Date, R., Wang-Eckhardt, L., Rehne, J., Petrosino, S., Starowicz, K., Steuder, R., Schlicker, E., Cravatt, B., Mechoulam, R., Buettner, R., Werner, S., Di Marzo, V., Tüting, T., Zimmer, A., 2007. Attenuation of allergic contact dermatitis through the endocannabinoid system. *Science* 316 (5830), 1494–1497. <https://doi.org/10.1126/science.1142265>.
- Kennerly, D.A., 1987. Diacylglycerol metabolism in mast cells. Analysis of lipid metabolic pathways using molecular species analysis of intermediates. *J. Biol. Chem.* 262 (34), 16305–16313. [https://doi.org/10.1016/s0021-9258\(18\)49255-1](https://doi.org/10.1016/s0021-9258(18)49255-1).
- Keppel Hesselink, J.M., 2015. The terms 'autacoid', 'hormone' and 'chalone' and how they have shifted with time. *Auton. Autacoid Pharmacol.* 35 (4), 51–58. <https://doi.org/10.1111/aap.12037>.
- Khoury, M., Cohen, I., Bar-Sela, G., 2022. The two sides of the same coin—medical cannabis, cannabinoids and immunity: pros and cons explained. *Pharmaceutics* 14 (2), 1–23. <https://doi.org/10.3390/pharmaceutics14020389>.
- Kim, H.J., Kim, B., Park, B.M., Jeon, J.E., Lee, S.H., Mann, S., Ahn, S.K., Hong, S.P., Jeong, S.K., 2015. Topical cannabinoid receptor 1 agonist attenuates the cutaneous inflammatory responses in oxazolone-induced atopic dermatitis model. *Int. J. Dermatol.* 54 (10), e401–e408. <https://doi.org/10.1111/ijd.12841>.
- Kim, M., Kwon, Y., Jung, H.S., Kim, Y., Jeoung, D., 2019. Fc ϵ RI-HDAC3-MCP1 signaling axis promotes passive anaphylaxis mediated by cellular interactions. *Int. J. Mol. Sci.* 20 (19). <https://doi.org/10.3390/ijms20194964>.
- Kim, M.S., Rådinger, M., Gilfillan, A.M., 2008. The multiple roles of phosphoinositide 3-kinase in mast cell biology. *Trends Immunol.* 29 (10), 493–501. <https://doi.org/10.1016/j.it.2008.07.004>.
- Kim, Y., Kim, K., Park, D., Lee, E., Lee, H., Lee, Y.S., Choe, J., Jeoung, D., 2012. Histone deacetylase 3 mediates allergic skin inflammation by regulating expression of MCP1 protein. *J. Biol. Chem.* 287 (31), 25844–25859. <https://doi.org/10.1074/jbc.M112.348284>.
- Koo, N., Kim, K.-M., 2009. Distinct effects on M2-type pyruvate kinase are involved in the dimethylsulfoxide-induced modulation of cellular proliferation and degranulation of mast cells. *Arch. Pharmacol. Res.* 32 (11), 1637–1642. <https://doi.org/10.1007/s12272-009-2118-9>.
- Kovacs, F.E., Knop, T., Urbanski, M.J., Freiman, I., Freiman, T.M., Feuerstein, T.J., Zentner, J., Szabo, B., 2012. Exogenous and endogenous cannabinoids suppress inhibitory neurotransmission in the human neocortex. *Neuropsychopharmacology* 37 (5), 1104–1114. <https://doi.org/10.1038/npp.2011.262>.
- Kundu, D., Kennedy, L., Meadows, V., Baiocchi, L., Alpini, G., Francis, H., 2020. The dynamic interplay between mast cells, aging/cellular senescence, and liver disease. *Gene Expr.* 20 (2), 77–88. <https://doi.org/10.3727/105221620X15960509906371>.
- Lallena, M.-J., Diaz-Meco, M.T., Bren, G., Payá, C.V., Moscat, J., 1999. Activation of I κ B Kinase β by Protein Kinase C Isoforms. *Mol. Cell. Biol.* 19 (3), 2180–2188. <https://doi.org/10.1128/MCB.19.3.2180>.
- Landry, R.P., Martinez, E., Deleo, J.A., Romero-Sandoval, E.A., 2012. Spinal cannabinoid receptor type 2 agonist reduces mechanical allodynia and induces mitogen-activated protein kinase phosphatases in a rat model of neuropathic pain. *J. Pain.* 13 (9), 836–848. <https://doi.org/10.1016/j.jpain.2012.05.013>.
- Lau, A.H.Y., Chow, S.S.M., 2003. Effects of cannabinoid receptor agonists on immunologically induced histamine release from rat peritoneal mast cells. *Eur. J. Pharmacol.* 464 (2), 229–235. [https://doi.org/10.1016/S0014-2999\(03\)01430-4](https://doi.org/10.1016/S0014-2999(03)01430-4).
- Le, Q., Gomez, G., Zhao, W., Hu, J., Xia, H.-Z., Fukuoka, Y., Katunuma, N., Schwartz, L., 2011. Processing of human prototypase in mast cells involves cathepsins L, B, and C. *J. Immunol.* (Baltim., Md.: 1950) 187, 1912–1918. <https://doi.org/10.4049/jimmunol.1001806>.
- Lee, S.F., Newton, C., Widen, R., Friedman, H., Klein, T.W., 2001. Differential expression of cannabinoid CB2 receptor mRNA in mouse immune cell subpopulations and following B cell stimulation. *Eur. J. Pharmacol.* 423 (2–3), 235–241. [https://doi.org/10.1016/S0014-2999\(01\)01122-0](https://doi.org/10.1016/S0014-2999(01)01122-0).
- Leuti, A., Fazio, D., Fava, M., Piccoli, A., Oddi, S., Maccarrone, M., 2020. Bioactive lipids, inflammation and chronic diseases. *Adv. Drug Deliv. Rev.* 159, 133–169. <https://doi.org/10.1016/j.addr.2020.06.028>.
- Levi-Montalcini, R., Skaper, S.D., Dal Toso, R., Petrelli, L., Leon, A., 1996. Nerve growth factor: from neurotrophin to neurokinin. *Trends Neurosci.* 19 (11), 514–520. [https://doi.org/10.1016/S0166-2236\(96\)10058-8](https://doi.org/10.1016/S0166-2236(96)10058-8).
- Li, K., Feng, J., Li, Y., Yuece, B., Lin, X., Yu, L., Li, Y., Feng, Y., Storr, M., 2013. Anti-inflammatory role of cannabidiol and O-1602 in cerulein-induced acute pancreatitis in mice. *Pancreas* 42 (1), 123–129. <https://doi.org/10.1097/MPA.0b013e318259f6f0>.
- Li, Q., Guo, H., Cai, Maslov, L.N., Qiao, X., Wen, Zhou, J., Jing, Zhang, Y., 2014. Mitochondrial permeability transition pore plays a role in the cardioprotection of CB2 receptor against ischemia-reperfusion injury. *Can. J. Physiol. Pharmacol.* 92 (3), 205–214. <https://doi.org/10.1139/cjpp-2013-0293>.
- Li, Y., Leung, P.S.C., Gershwin, M.E., Song, J., 2022. New mechanistic advances in Fc ϵ RI - mast cell - mediated allergic signaling. *Clin. Rev. Allergy Immunol.* 431–446. <https://doi.org/10.1007/s12016-022-08955-9>.
- Liedhegner, E.S., Vogt, C.D., Sem, D.S., Cunningham, C.W., Hillard, C.J., 2014. Sterol carrier protein-2: binding protein for endocannabinoids. *Mol. Neurobiol.* 50 (1), 149–158. <https://doi.org/10.1007/s12035-014-8651-7>.
- Liu, J., Wang, L., Harvey-White, J., Osei-Hyiaman, D., Razdan, R., Gong, Q., Chan, A.C., Zhou, Z., Huang, B.X., Kim, H.-Y., Kunos, G., 2006. A biosynthetic pathway for anandamide. *Proc. Natl. Acad. Sci.* 103 (36), 13345–13350. <https://doi.org/10.1073/pnas.0601832103>.
- Liu, Q.R., Pan, C.H., Hishimoto, A., Li, C.Y., Xi, Z.X., Llorente-Berzal, A., Viveros, M.P., Ishiguro, H., Arinami, T., Onaivi, E.S., Uhl, G.R., 2009. Species differences in cannabinoid receptor 2 (CNR2 gene): Identification of novel human and rodent CB2 isoforms, differential tissue expression and regulation by cannabinoid receptor ligands. *Genes, Brain Behav.* 8 (5), 519–530. <https://doi.org/10.1111/j.1601-183X.2009.00498.x>.
- Liu, Qing Rong, Canseco-Alba, A., Zhang, H.Y., Tagliaferro, P., Chung, M., Dennis, E., Sanabria, B., Schanz, N., Escosteguy-Neto, J.C., Ishiguro, H., Lin, Z., Sgro, S., Leonard, C.M., Santos-Junior, J.G., Gardner, E.L., Egan, J.M., Lee, J.W., Xi, Z.X., Onaivi, E.S., 2017. Cannabinoid type 2 receptors in dopamine neurons inhibits psychomotor behaviors, alters anxiety, depression and alcohol preference. *Sci. Rep.* 7 (1). <https://doi.org/10.1038/s41598-017-17796-y>.
- Liu, T., Zhang, L., Joo, D., Sun, S.C., 2017. NF- κ B signaling in inflammation. *Signal Transduct. Target. Ther.* 2 (April). <https://doi.org/10.1038/sigtrans.2017.23>.
- Liu, Y.J., Fan, H.B., Jin, Y., Ren, C.G., Jia, X.E., Wang, L., Chen, Y., Dong, M., Zhu, K.Y., Dong, Z.W., Ye, B.X., Zhong, Z., Deng, M., Liu, T.X., Ren, R., 2013. Cannabinoid receptor 2 suppresses leukocyte inflammatory migration by modulating the JNK/c-Jun/Alox5 pathway. *J. Biol. Chem.* 288 (19), 13551–13562. <https://doi.org/10.1074/jbc.M113.453811>.

- Loh, W., Tang, M.L.K., 2018. The epidemiology of food allergy in the global context. *Int. J. Environ. Res. Public Health* 15 (9). <https://doi.org/10.3390/ijerph15092043>.
- Lorentz, A., Baumann, A., Vitte, J., Blank, U., 2012. The SNARE machinery in mast cell secretion. *Front. Immunol.* 3. <https://doi.org/10.3389/fimmu.2012.00143>.
- Lu, H.C., MacKie, K., 2016. An introduction to the endogenous cannabinoid system. In: *In Biol. Psychiat.*, Vol. 79. Elsevier USA, pp. 516–525. <https://doi.org/10.1016/j.biopsych.2015.07.028>.
- Lynch, N.R., Hagel, I.A., Palenque, M.E., Di Prisco, M.C., Escudero, J.E., Corao, L.A., Sandia, J.A., Ferreira, L.J., Botto, C., Perez, M., 1998. Relationship between helminthic infection and IgE response in atopic and nonatopic children in a tropical environment. *J. Allergy Clin. Immunol.* 101 (2), 217–221. [https://doi.org/10.1016/S0091-6749\(98\)70386-0](https://doi.org/10.1016/S0091-6749(98)70386-0).
- Maccarrone, M., 2017. Metabolism of the endocannabinoid anandamide: open questions after 25 years. *Front. Mol. Neurosci.* 10 (May), 1–10. <https://doi.org/10.3389/fnmol.2017.00166>.
- Maccarrone, M., Fiorucci, L., Erba, F., Bari, M., Finazzi-Agrò, A., Ascoli, F., 2000. Human mast cells take up and hydrolyze anandamide under the control of 5-lipoxygenase and do not express cannabinoid receptors. *FEBS Lett.* 468 (2), 176–180. [https://doi.org/10.1016/S0014-5793\(00\)01223-0](https://doi.org/10.1016/S0014-5793(00)01223-0).
- Maccarrone, M., Bab, I., Bíró, T., Cabral, G.A., Dey, S.K., Di Marzo, V., Konje, J.C., Kunos, G., Mechoulam, R., Pacher, P., Sharkey, K.A., Zimmer, A., 2015. Endocannabinoid signaling at the periphery: 50 years after THC. *Trends Pharmacol. Sci.* 36 (5), 277–296. <https://doi.org/10.1016/j.tips.2015.02.008>.
- Madera-Salcedo, I.K., Danelli, L., Tiwari, N., Dema, B., Pacreau, E., Vibhushan, S., Birnbaum, J., Agabriel, C., Liabeuf, V., Klingebiel, C., Menasche, G., Macias-Silva, M., Benhamou, M., Charles, N., González-Espinosa, C., Vitte, J., Blank, U., 2018. Tomosyn functions as a PKC δ -regulated fusion clamp in mast cell degranulation. *Sci. Signal.* 11 (537). <https://doi.org/10.1126/scisignal.aan4350>.
- Maggirwar, S.B., Khalsa, J.H., 2021. The link between cannabis use, immune system, and viral infections. *Viruses* 13 (6), 1099. <https://doi.org/10.3390/v13061099>.
- Maier, J.V., Brema, S., Tuckermann, J., Herzer, U., Klein, M., Stassen, M., Moorthy, A., Cato, A.C.B., 2007. Dual specificity phosphatase 1 knockout mice show enhanced susceptibility to anaphylaxis but are sensitive to glucocorticoids. *Mol. Endocrinol.* 21 (11), 2663–2671. <https://doi.org/10.1210/me.2007-0067>.
- Malbec, O., Roget, K., Schiffer, C., Iannascoli, B., Dumas, A.R., Arock, M., Daéron, M., 2007. Peritoneal cell-derived mast cells: an in vitro model of mature serosal-type mouse mast cells. *J. Immunol.* 178 (10), 6465–6475. <https://doi.org/10.4049/jimmunol.178.10.6465>.
- Mancini, I., Brusa, R., Quadrato, G., Foglia, C., Scandroglio, P., Silverman, L., Tushian, D., Reggiani, A., Beltramo, M., 2009. Constitutive activity of cannabinoid-2 (CB2) receptors plays an essential role in the protean agonism of (+)AM1241 and L768242. *Br. J. Pharmacol.* 158 (1), 382–391. <https://doi.org/10.1111/j.1476-5381.2009.00154.x>.
- Manetz, T.S., Gonzalez-Espinosa, C., Arudchandran, R., Xirasagar, S., Tybulewicz, V., Rivera, J., 2001. Vav1 regulates phospholipase cgamma activation and calcium responses in mast cells. *Mol. Cell. Biol.* 21 (11), 3763–3774. <https://doi.org/10.1128/MCB.21.11.3763-3774.2001>.
- Marazzi, J., Kleyer, J., Paredes, J.M.V., Gertsch, J., 2011. Endocannabinoid content in fetal bovine sera - unexpected effects on mononuclear cells and osteoclastogenesis. *J. Immunol. Methods* 373 (1–2), 219–228. <https://doi.org/10.1016/j.jim.2011.08.021>.
- Maresz, K., Carrier, E.J., Ponomarev, E.D., Hillard, C.J., Dittel, B.N., 2005. Modulation of the cannabinoid CB2 receptor in microglial cells in response to inflammatory stimuli. *J. Neurochem.* 95 (2), 437–445. <https://doi.org/10.1111/j.1471-4159.2005.03380.x>.
- Marsicano, G., Goodenough, S., Monory, K., Hermann, H., Eder, M., Cannich, A., Azad, S.C., Cascio, M.G., Ortega-Gutiérrez, S., Van der Stelt, M., López-Rodríguez, M.L., Casanova, E., Schütz, G., Ziegler, W., Di Marzo, V., Behl, C., Lutz, B., 2003. CB1 cannabinoid receptors and on-demand defense against excitotoxicity. *Science* 302 (5642), 84–88. <https://doi.org/10.1126/science.1088208>.
- Martín-Fontecha, M., Eiwegger, T., Jartti, T., Rueda-Zubiaurre, A., Tisinger, K., Stepanov, J., Puhakka, T., Rückert, B., Ortega-Gutiérrez, S., López-Rodríguez, M.L., Akdis, M., Akdis, C.A., Palomares, O., 2014. The expression of cannabinoid receptor 1 is significantly increased in atopic patients. *e2 J. Allergy Clin. Immunol.* 133 (3), 926–929. <https://doi.org/10.1016/j.jaci.2013.12.1032>.
- Maximov, A., Tang, J., Yang, X., Pang, Z.P., Südhof, T.C., 2009. Complexin controls the force transfer from SNARE complexes to membranes in fusion. *Science* 323 (5913), 516–521. <https://doi.org/10.1126/science.1166505>.
- Melicoff, E., Sansores-Garcia, L., Gomez, A., Moreira, D.C., Datta, P., Thakur, P., Petrova, Y., Siddiqi, T., Murthy, J.N., Dickey, B.F., Heidelberger, R., Adachi, R., 2009. Synaptotagmin-2 controls regulated exocytosis but not other secretory responses of mast cells. *J. Biol. Chem.* 284 (29), 19445–19451. <https://doi.org/10.1074/jbc.M109.002550>.
- Mendizabal-Zubiaga, J., Melser, S., Bénard, G., Ramos, A., Reguera, L., Arrabal, S., Elezgarai, I., Gerrikagoitia, I., Suarez, J., Rodríguez De Fonseca, F., Puente, N., Marsicano, G., Grandes, P., 2016. Cannabinoid CB1 receptors are localized in striated muscle mitochondria and regulate mitochondrial respiration. *Front. Physiol.* 7, 476. <https://doi.org/10.3389/fphys.2016.00476>.
- Miller, M.R., Mannowet, N., Iavarone, A.T., Safavi, R., Gracheva, E.O., Smith, J.F., Hill, R.Z., Bautista, D.M., Kirichok, Y., Lishko, P.V., 2016. Unconventional endocannabinoid signaling governs sperm activation via the sex hormone progesterone. *Science* 352 (6285), 555–559. <https://doi.org/10.1126/science.1246887>.
- Mimura, T., Ueda, Y., Watanabe, Y., Sugiura, T., 2012. The cannabinoid receptor-2 is involved in allergic inflammation. *Life Sci.* 90 (21–22), 862–866. <https://doi.org/10.1016/j.lfs.2012.04.005>.
- Moiseeva, E.P., Leyland, M.L., Bradding, P., 2012. CADM1 isoforms differentially regulate human mast cell survival and homotypic adhesion. *Cell. Mol. Life Sci.* 69 (16), 2751–2764. <https://doi.org/10.1007/s00018-012-0948-y>.
- Monino-Romero, S., Erkert, L., Schmidthalder, K., Diesner, S.C., Sallis, B.F., Pennington, L., Jardtzy, T., Oettgen, H.C., Bohle, B., Fiebiger, E., Szépfalusi, Z., 2018. The soluble isoform of human FcεRI is an endogenous inhibitor of IgE-mediated mast cell responses. *Allergy* 74 (2), 236–245. <https://doi.org/10.1111/all.13567>.
- Monticelli, S., Leoni, C., 2017. Epigenetic and transcriptional control of mast cell responses. *F1000Research* 6 (0), 1–11. <https://doi.org/10.12688/f1000research.12384.1>.
- Motakis, E., Gohl, S., Ishizu, Y., Itoh, M., Kawaji, H., de Hoon, M., Lassmann, T., Carninci, P., Hayashizaki, Y., Zuberbier, T., Forrest, A.R.R., Babina, M., 2014. Redefinition of the human mast cell transcriptome by deep-CAGE sequencing. *Blood* 123 (17), e58–e67. <https://doi.org/10.1182/blood-2013-02-483792>.
- Mukai, K., Tsai, M., Stark, P., Marichal, T., Galli, S.J., 2016. IgE and mast cells in host defense against parasites and venoms. *Semin. Immunopathol.* 38 (5), 581–603. <https://doi.org/10.1007/s00281-016-0565-1>.
- Mukai, K., Tsai, M., Saito, H., Galli, S.J., 2018. Mast cells as sources of cytokines, chemokines, and growth factors. *Immunol. Rev.* 282 (1), 121–150. <https://doi.org/10.1111/immr.12634>.
- Munro, S., Thomas, K.L., Abu-Shaar, M., 1993. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 365 (6441), 61–65. <https://doi.org/10.1038/365061a0>.
- Nakata, K., Yoshimaru, T., Suzuki, Y., Inoue, T., Ra, C., Yakura, H., Mizuno, K., 2008. Positive and negative regulation of high affinity IgE receptor signaling by src homology region 2 domain-containing phosphatase 1. *J. Immunol.* 181 (8), 5414–5424. <https://doi.org/10.4049/jimmunol.181.8.5414>.
- Nam, G., Jeong, S.K., Park, B.M., Lee, S.H., Kim, H.J., Hong, S.-P., Kim, B., Kim, B.-W., 2016. Selective cannabinoid receptor-1 agonists regulate mast cell activation in an oxazolone-induced atopic dermatitis model. *Ann. Dermatol.* 28 (1), 22. <https://doi.org/10.5021/ad.2016.28.1.22>.
- Navarrete, C., García-Martín, A., Correa-Sáez, A., Prados, M.E., Fernández, F., Pineda, R., Mazonne, M., Álvarez-Benito, M., Calzado, M.A., Muñoz, E., 2022. A cannabidiol aminoquinone derivative activates the PP2A/B5α/HIF pathway and shows protective effects in a murine model of traumatic brain injury. *J. Neuroinflamm.* 19 (1), 177. <https://doi.org/10.1186/s12974-022-02540-9>.
- Nicolussi, S., Viveros-Paredes, J.M., Gachet, M.S., Rau, M., Flores-Soto, M.E., Blunder, M., Gertsch, J., 2014. Guineensine is a novel inhibitor of endocannabinoid uptake showing cannabimimetic behavioral effects in BALB/c mice. *Pharmacol. Res.* 80, 52–65. <https://doi.org/10.1016/j.phrs.2013.12.010>.
- Nogueras-Ortiz, C., Yudowski, G.A., 2016. The multiple waves of cannabinoid 1 receptor signaling. *Mol. Pharmacol.* 90 (5), 620–626. <https://doi.org/10.1124/mol.116.104539>.
- O'Sullivan, S.E., Kendall, D.A., 2010. Cannabinoid activation of peroxisome proliferator-activated receptors: potential for modulation of inflammatory diseases. *Immunobiology* 215 (8), 611–616. <https://doi.org/10.1016/j.imbio.2009.09.007>.
- O'Sullivan, S., Sairise Elizabeth, 2016. An update on PPAR activation by cannabinoids. In: *British Journal of Pharmacology*, Vol. 173. John Wiley and Sons Inc., pp. 1899–1910. <https://doi.org/10.1111/bph.13497>.
- Oddi, S., Fezza, F., Pasquariello, N., De Simone, C., Rapino, C., Dainese, E., Finazzi-Agrò, A., Maccarrone, M., 2008. Evidence for the intracellular accumulation of anandamide in adiposomes. *Cell. Mol. Life Sci.* 65 (5), 840–850. <https://doi.org/10.1007/s00018-008-7494-7>.
- Oddi, Sergio, Fezza, F., Pasquariello, N., D'Agostino, A., Catanzaro, G., De Simone, C., Rapino, C., Finazzi-Agrò, A., Maccarrone, M., 2009. Molecular identification of albumin and Hsp70 as cytosolic anandamide-binding proteins. *Chem. Biol.* 16 (6), 624–632. <https://doi.org/10.1016/j.chembiol.2009.05.004>.
- Ohno-Shosaku, T., Shosaku, J., Tsubokawa, H., Kano, M., 2002. Cooperative endocannabinoid production by neuronal depolarization and group I metabotropic glutamate receptor activation. *Eur. J. Neurosci.* 15 (6), 953–961. <https://doi.org/10.1046/j.1460-9568.2002.01929.x>.
- Oláh, A., Szabó-Papp, J., Soeberdt, M., Knie, U., Dähnhardt-Pfeiffer, S., Abels, C., Bíró, T., 2017. Echinacea purpurea-derived alkylamides exhibit potent anti-inflammatory effects and alleviate clinical symptoms of atopic eczema. *J. Dermatol. Sci.* 88 (1), 67–77. <https://doi.org/10.1016/j.jdermsci.2017.05.015>.
- Opitz, C.A., Rimmerman, N., Zhang, Y., Mead, L.E., Yoder, M.C., Ingram, D.A., Walker, J. M., Rehman, J., 2007. Production of the endocannabinoids anandamide and 2-arachidonoylglycerol by endothelial progenitor cells. *FEBS Lett.* 581 (25), 4927–4931. <https://doi.org/10.1016/J.FEBSLET.2007.09.032>.
- Oubrain, S., Wang, R., Hausknecht, K.A., Shen, R.Y., Haj-Dahmane, S., 2021. Tonic endocannabinoid signaling gates synaptic plasticity in dorsal raphe nucleus serotonin neurons through peroxisome proliferator-activated receptors. *Front. Pharmacol.* 12 (June), 1–14. <https://doi.org/10.3389/fphar.2021.691219>.
- Palomares, O., Akdis, M., Martín-Fontecha, M., Akdis, C.A., 2017. Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells. *Immunol. Rev.* 278 (1), 219–236. <https://doi.org/10.1111/immr.12555>.
- Parolaro, D., 1999. Presence and functional regulation of cannabinoid receptors in immune cells. *Life Sci.* 65 (6), 637–644. [https://doi.org/10.1016/S0024-3205\(99\)00286-6](https://doi.org/10.1016/S0024-3205(99)00286-6).
- Parravicini, V., Gadina, M., Kovarova, M., Odom, S., Gonzalez-Espinosa, C., Furumoto, Y., Saitoh, S., Samelson, L.E., O'Shea, J.J., Rivera, J., 2002. Fyn kinase initiates complementary signals required for IgE-dependent mast cell degranulation. *Nat. Immunol.* 3 (8), 741–748. <https://doi.org/10.1038/ni817>.
- Passalacqua, G., Canonica, G.W., 2016. Allergen immunotherapy. *Immunol. Allergy Clin. North Am.* 36 (1), 1–12. <https://doi.org/10.1016/j.jiac.2015.08.001>.

- Paumet, F., Le Mao, J., Martin, S., Galli, T., David, B., Blank, U., Roa, M., 2000. Soluble NSF attachment protein receptors (SNAREs) in RBL-2H3 mast cells: functional role of syntaxin 4 in exocytosis and identification of a vesicle-associated membrane protein 8-containing secretory compartment. *J. Immunol.* 164 (11), 5850–5857. <https://doi.org/10.4049/jimmunol.164.11.5850>.
- Peng, Y., Power, M.R., Li, B., Lin, T.-J., 2005. Inhibition of IKK down-regulates antigen + IgE-induced TNF production by mast cells: a role for the IKK-I κ B-NF- κ B pathway in IgE-dependent mast cell activation. *J. Leukoc. Biol.* 77 (6), 975–983. <https://doi.org/10.1189/jlb.0204115>.
- Perkins, N.D., 2007. Integrating cell-signalling pathways with NF- κ B and IKK function. *Nat. Rev. Mol. Cell Biol.* 8 (1), 49–62. <https://doi.org/10.1038/nrm2083>.
- Pertwee, R.G., Howlett, A.C., Abood, M.E., Alexander, S.P.H., Di Marzo, V., Elphick, M.R., Greasley, P.J., Hansen, H.S., Kunos, G., Mackie, K., Mechoulam, R., Ross, R.A., 2010. International union of basic and clinical pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. *Pharmacol. Rev.* 62 (4), 588–631. <https://doi.org/10.1124/pr.110.003004>.
- Pertwee, Roger G., 2015. Endocannabinoids and their pharmacological actions. In: *Handbook of Experimental Pharmacology*, Vol. 231. Springer New York LLC, pp. 1–37. https://doi.org/10.1007/978-3-319-20825-1_1.
- Petrosino, S., Schiano Moriello, A., 2020. Palmitoylethanolamide: a nutritional approach to keep neuroinflammation within physiological boundaries—a systematic review. *Int. J. Mol. Sci.* 21 (24), 9526. <https://doi.org/10.3390/ijms21249526>.
- Petrosino, S., Schiano Moriello, A., Cerrato, S., Fusco, M., Puigdemont, A., De Petrocellis, L., Di Marzo, V., 2016. The anti-inflammatory mediator palmitoylethanolamide enhances the levels of 2-arachidonoyl-glycerol and potentiates its actions at TRPV1 cation channels. *Br. J. Pharmacol.* 173 (7), 1154–1162. <https://doi.org/10.1111/bph.13084>.
- Petrosino, S., Schiano Moriello, A., Verde, R., Allarà, M., Imperatore, R., Ligresti, A., Mahmoud, A.M., Peritore, A.F., Iannotti, F.A., Di Marzo, V., 2019. Palmitoylethanolamide counteracts substance P-induced mast cell activation in vitro by stimulating diacylglycerol lipase activity. *J. Neuroinflamm.* 16 (1), 274. <https://doi.org/10.1186/s12974-019-1671-5>.
- Pickel, V.M., Chan, J., Kash, T.L., Rodríguez, J.J., Mackie, K., 2004. Compartment-specific localization of cannabinoid 1 (CB1) and μ -opioid receptors in rat nucleus accumbens. *Neuroscience* 127 (1), 101–112. <https://doi.org/10.1016/j.neuroscience.2004.05.015>.
- Platzter, B., Rüter, F., van der Mee, J., Fiebigel, E., 2011. Soluble IgE receptors—elements of the IgE network. *Immunol. Lett.* 141 (1), 36–44. <https://doi.org/10.1016/j.imlet.2011.08.004>.
- Plum, T., Wang, X., Rettel, M., Krijgsvel, J., Feyerabend, T.B., Rodewald, H.-R., 2020. Human mast cell proteome reveals unique lineage, putative functions, and structural basis for cell ablation. *e5 Immunity* 52 (2), 404–416. <https://doi.org/10.1016/j.immuni.2020.01.012>.
- Pritchard, D.I., 1993. Immunity to helminths: is too much IgE parasite—rather than host-protective? *Parasite Immunol.* 15 (1), 5–9. <https://doi.org/10.1111/j.1365-3024.1993.tb00566.x>.
- Pulvirenti, N., Nasca, M.R., Micali, G., 2007. Topical adelmidrol 2% emulsion, a novel aliamide, in the treatment of mild atopic dermatitis in pediatric subjects: A pilot study. *Acta Dermatovenereol. Croat.* 15 (2), 80–83.
- Rahaman, O., Ganguly, D., 2021. Endocannabinoids in immune regulation and immunopathologies. *Immunology* 164 (2), 242–252. <https://doi.org/10.1111/imm.13378>.
- Rakhshan, F., Day, T.A., Blakely, R.D., Barker, E.L., 2000. Carrier-mediated uptake of the endogenous cannabinoid anandamide in RBL-2H3 Cells. *J. Pharmacol. Exp. Ther.*, 292(3), 960 LP – 967. (<http://jpet.aspetjournals.org/content/292/3/960.abstract>).
- Rankin, L., Fowler, C.J., 2020. The basal pharmacology of palmitoylethanolamide. *Int. J. Mol. Sci.* 21 (21), 7942. <https://doi.org/10.3390/ijms21217942>.
- Rhee, M.-H., Nevo, I., Avidor-Reiss, T., Levy, R., Vogel, Z., 2000. Differential superactivation of adenylyl cyclase isozymes after chronic activation of the CB₁ cannabinoid receptor. *Mol. Pharmacol.* 57 (4), 746–752. <https://doi.org/10.1124/mol.57.4.746>.
- Ruiz, C.M., Gomes, J.C., 2000. Effects of ethanol, acetaldehyde, and acetic acid on histamine secretion in guinea pig lung mast cells. *Alcohol* 20 (2), 133–138. [https://doi.org/10.1016/S0741-8329\(99\)00065-8](https://doi.org/10.1016/S0741-8329(99)00065-8).
- Saitoh, S., Arudchandran, R., Manetz, T.S., Zhang, W., Sommers, C.L., Love, P.E., Rivera, J., Samelson, L.E., 2000. LAT is essential for Fc ϵ R1-mediated mast cell activation. *Immunity* 12 (5), 525–535. [https://doi.org/10.1016/S1074-7613\(00\)80204-6](https://doi.org/10.1016/S1074-7613(00)80204-6).
- Salojin, K.V., Zhang, J., Delovitch, T.L., 1999. TCR and CD28 are coupled via ZAP-70 to the activation of the Vav/Rac-1/PAK-1/p38 MAPK signaling pathway. *J. Immunol.* (Baltimore, Md.: 1950) 163 (2), 844–853.
- Samayawardhena, L.A., Pallen, C.J., 2010. PTP α activates lyn and fyn and suppresses Hck to negatively regulate Fc ϵ R1-dependent mast cell activation and allergic responses. *J. Immunol.* 185 (10), 5993–6002. <https://doi.org/10.4049/jimmunol.1001261>.
- Samson, M.-T., Small-Howard, A., Shimoda, L.M.N., Koblan-Huberson, M., Stokes, A.J., Turner, H., 2003. Differential roles of CB1 and CB2 cannabinoid receptors in mast cells. *J. Immunol.* 170 (10), 4953–4962. <https://doi.org/10.4049/jimmunol.170.10.4953>.
- Sanchez, E., Gonzalez, E.A., Moreno, D.S., Cardenas, R.A., Ramos, M.A., Davalos, A.J., Manlio, J., Rodarte, A.I., Petrova, Y., Moreira, D.C., Chavez, M.A., Tortoriello, A., Lara, A., Gutierrez, B.A., Burns, A.R., Heidelberg, R., Adachi, R., 2019. Syntaxin 3, but not syntaxin 4, is required for mast cell-regulated exocytosis, where it plays a primary role mediating compound exocytosis. *J. Biol. Chem.* 294 (9), 3012–3023. <https://doi.org/10.1074/jbc.RA118.005532>.
- Santiago, M., Sachdev, S., Arnold, J.C., McGregor, I.S., Connor, M., 2019. Absence of entourage: terpenoids commonly found in cannabis sativa do not modulate the functional activity of Δ 9-THC at human CB1 and CB2 receptors. *Cannabis Cannabinoid Res.* 4 (3), 165–176. <https://doi.org/10.1089/can.2019.0016>.
- Schmid, P.C., Reddy, P.V., Natarajan, V., Schmid, H.H., 1983. Metabolism of N-acyl ethanolamine phospholipids by a mammalian phosphodiesterase of the phospholipase D type. *J. Biol. Chem.* 258 (15), 9302–9306. [https://doi.org/10.1016/s0021-9258\(17\)44667-9](https://doi.org/10.1016/s0021-9258(17)44667-9).
- Scuderi, C., Esposito, G., Blasio, A., Valenza, M., Arietti, P., Steardo Jr, L., Carnuccio, R., De Filippis, D., Petrosino, S., Iuvone, T., Marzo, V., Di, Steardo, L., 2011. Palmitoylethanolamide counteracts reactive astrogliosis induced by β -amyloid peptide. *J. Cell. Mol. Med.* 15 (12), 2664–2674. <https://doi.org/10.1111/j.1582-4934.2011.01267.x>.
- Scuderi, C., Valenza, M., Stecca, C., Esposito, G., Carratù, M.R., Steardo, L., 2012. Palmitoylethanolamide exerts neuroprotective effects in mixed neuroglial cultures and organotypic hippocampal slices via peroxisome proliferator-activated receptor- α . *J. Neuroinflamm.* 9 (1), 49. <https://doi.org/10.1186/1742-2094-9-49>.
- Serra-Pages, M., Olivera, A., Torres, R., Picado, C., de Mora, F., Rivera, J., 2012. E-prostanoid 2 receptors dampen mast cell degranulation via cAMP/PKA-mediated suppression of IgE-dependent signaling. *J. Leukoc. Biol.* 92 (6), 1155–1165. <https://doi.org/10.1189/jlb.0212109>.
- Sharir, H., Abood, M.E., 2010. Pharmacological characterization of GPR55, a putative cannabinoid receptor. *Pharmacol. Ther.* 126 (3), 301–313. <https://doi.org/10.1016/j.pharmthera.2010.02.004>.
- Sido, Jessica M., Nagarkatti, P.S., Nagarkatti, M., 2016. Production of endocannabinoids by activated T cells and B cells modulates inflammation associated with delayed-type hypersensitivity. *Eur. J. Immunol.* 46 (6), 1472–1479. (<https://doi.org/10.1002/eji.201546181>).
- Sido, Jessica M., Jackson, A.R., Nagarkatti, P.S., Nagarkatti, M., 2016. Marijuana-derived Δ 9-tetrahydrocannabinol suppresses Th1/Th17 cell-mediated delayed-type hypersensitivity through microRNA regulation. *J. Mol. Med.* 94 (9), 1039–1051. <https://doi.org/10.1007/s00109-016-1404-5>.
- Sido, Jessica Margaret, Yang, X., Nagarkatti, P.S., Nagarkatti, M., 2015. Δ 9-Tetrahydrocannabinol-mediated epigenetic modifications elicit myeloid-derived suppressor cell activation via STAT3/S100A8. *J. Leukoc. Biol.* 97 (4), 677–688. <https://doi.org/10.1189/jlb.1A1014-479R>.
- Siebenhaar, F., Redegeld, F.A., Bischoff, S.C., Gibbs, B.F., Maurer, M., 2018. Mast cells as drivers of disease and therapeutic targets. *Trends Immunol.* 39 (2), 151–162. <https://doi.org/10.1016/j.it.2017.10.005>.
- Sigel, E., Baur, R., Rácz, I., Marazzi, J., Smart, T.G., Zimmer, A., Gertsch, J., 2011. The major central endocannabinoid directly acts at GABA A receptors. *Proc. Natl. Acad. Sci. USA* 108 (44), 18150–18155. <https://doi.org/10.1073/pnas.1113444108>.
- Skaper, S.D., Buriani, A., Dal Toso, R., Petrelli, L., Romanello, S., Facci, L., & Leon, A. (1996). The ALIamide palmitoylethanolamide and cannabinoids, but not anandamide, are protective in a delayed postglutamate paradigm of excitotoxic death in cerebellar granule neurons. *Proceedings of the National Academy of Sciences of the United States of America*, 93(9), 3984–3989. <https://doi.org/10.1073/pnas.93.9.3984>.
- Small-Howard, A.L., Shimoda, L.M.N., Adra, C.N., Turner, H., 2005. Anti-inflammatory potential of CB1-mediated cAMP elevation in mast cells. *Biochem. J.* 388 (2), 465–473. <https://doi.org/10.1042/BJ20041682>.
- Smith, A., Kaufman, F., Sandy, M.S., Cardenas, A., 2020. Cannabis exposure during critical windows of development: epigenetic and molecular pathways implicated in neuropsychiatric disease. *Curr. Environ. Health Rep.* 7 (3), 325–342. <https://doi.org/10.1007/s40572-020-00275-4>.
- Soethoudt, M., Grether, U., Fingerle, J., Grim, T.W., Fezza, F., de Petrocellis, L., Ullmer, C., Rothenhäusler, B., Perret, C., van Gils, N., Finlay, D., MacDonald, C., Chicca, A., Gens, M.D., Stuart, J., de Vries, H., Mastrangelo, N., Xia, L., Alachouzos, G., van der Stelt, M., 2017. Cannabinoid CB2 receptor ligand profiling reveals biased signalling and off-target activity. *Nat. Commun.* 8 (1), 13958. <https://doi.org/10.1038/ncomms13958>.
- Stadel, R., Ahn, K.H., Kendall, D.A., 2011. The cannabinoid type-1 receptor carboxyl-terminus: more than just a tail. *J. Neurochem.* 117 (1), 1–18. <https://doi.org/10.1111/j.1471-4159.2011.07186.x>.
- Ständer, S., Schmelz, M., Metz, D., Luger, T., Rukwied, R., 2005. Distribution of cannabinoid receptor 1 (CB1) and 2 (CB2) on sensory nerve fibers and adnexal structures in human skin. *J. Dermatol. Sci.* 38 (3), 177–188. <https://doi.org/10.1016/j.jdermsci.2005.01.007>.
- Starkl, P., Watzgenboeck, M.L., Popov, L.M., Zahalka, S., Hladik, A., Lakovits, K., Radhouani, M., Haschemi, A., Marichal, T., Reber, L.L., Gaudenzio, N., Sibilano, R., Stulik, L., Fontaine, F., Mueller, A.C., Amieva, M.R., Galli, S.J., Knapp, S., 2020. IgE effector mechanisms, in concert with mast cells, contribute to acquired host defense against staphylococcus aureus. *e9 Immunity* 53 (4), 793–804. <https://doi.org/10.1016/j.immuni.2020.08.002>.
- Stempel, A.V., Stumpf, A., Zhang, H.-Y., Özdoğan, T., Pannasch, U., Theis, A.-K., Otte, D.-M., Wojtalla, A., Rácz, I., Ponomarenko, A., Xi, Z.-X., Zimmer, A., Schmitz, D., 2016. Cannabinoid type 2 receptors mediate a cell type-specific plasticity in the hippocampus. *Neuron* 90 (4), 795–809. <https://doi.org/10.1016/j.neuron.2016.03.034>.
- Su, S.H., Wu, Y.F., Lin, Q., Hai, J., 2017. Cannabinoid receptor agonist WIN55,212-2 and fatty acid amide hydrolase inhibitor URB597 ameliorate neuroinflammatory responses in chronic cerebral hypoperfusion model by blocking NF- κ B pathways. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 390 (12), 1189–1200. <https://doi.org/10.1007/s00210-017-1417-9>.
- Sugawara, K., Tsuruta, D., Zimmer, A., Funk, W., Gibbs, B.F., Kromminga, A., Zimmer, A., Paus, R., Maritime, C., Kingdom, U., 2012. Endocannabinoids limit

- excessive mast cell maturation and activation in human skin. *J. Allergy Clin Immunol* 129 (3). <https://doi.org/10.1016/j.jaci.2011.11.009>.
- Sugawara, K., Zakány, N., Hundt, T., Emelianov, V., Tsuruta, D., Schäfer, C., Kloepper, J. E., Bíró, T., Paus, R., 2013. Cannabinoid receptor 1 controls human mucosal-type mast cell degranulation and maturation in situ. *e8 J. Allergy Clin. Immunol.* 132 (1), 182–193. <https://doi.org/10.1016/j.jaci.2013.01.002>.
- Suzuki, K., Verma, I.M., 2008. Phosphorylation of SNAP-23 by IκB kinase 2 Regulates Mast Cell Degranulation. *Cell* 134 (3), 485–495. <https://doi.org/10.1016/j.cell.2008.05.050>.
- Tanasescu, R., Constantinescu, C.S., 2010. Cannabinoids and the immune system: an overview. *Immunobiology* 215 (8), 588–597. <https://doi.org/10.1016/j.imbio.2009.12.005>.
- Tashkin, D.P., Shapiro, B.J., Reiss, S., Olsen, J.L., Lodge, J.W., 1976. Bronchial effects of aerosolized delta-9-tetrahydrocannabinol. In: *The Therapeutic Potential Of Marihuana*, Vol. 31. Springer, US, pp. 97–109. https://doi.org/10.1007/978-1-4613-4286-1_8.
- Tiwari, N., Wang, C.C., Brochetta, C., Scanduzzi, L., Hong, W., Blank, U., 2009. Increased formation of VAMP-3-containing SNARE complexes in mast cells from VAMP-8 deficient cells. *Inflamm. Res.* 58 (SUPPL. 1), 13–14. <https://doi.org/10.1007/s00011-009-0645-y>.
- Tiwari, Neeraj, Wang, C.C., Brochetta, C., Ke, G., Vita, F., Qi, Z., Rivera, J., Soranzo, M. R., Zabucchi, G., Hong, W., Blank, U., 2008. VAMP-8 segregates mast cell-preformed mediator exocytosis from cytokine trafficking pathways. *Blood* 111 (7), 3665–3674. <https://doi.org/10.1182/blood-2007-07-103309>.
- Tonks, N.K., 2006. Protein tyrosine phosphatases: from genes, to function, to disease. *Nat. Rev. Mol. Cell Biol.* 7 (11), 833–846. <https://doi.org/10.1038/nrm2039>.
- Tóth, A., Blumberg, P.M., Boczán, J., 2009. Anandamide and the vanilloid receptor (TRPV1). *Vitam. Horm. Vol. 81* (Issue C), 389–419. [https://doi.org/10.1016/S0083-6729\(09\)81015-7](https://doi.org/10.1016/S0083-6729(09)81015-7).
- Turcotte, C., Blanchet, M.R., Laviolette, M., Flaman, N., 2016. The CB2 receptor and its role as a regulator of inflammation. *Cell. Mol. Life Sci.* 73 (23), 4449–4470. <https://doi.org/10.1007/s00018-016-2300-4>.
- Ueda, N., Yamakana, K., Terasawa, Y., Yamamoto, S., 1999. An acid amidase hydrolyzing anandamide as an endogenous ligand for cannabinoid receptors. *FEBS Lett.* 454 (3), 267–270. [https://doi.org/10.1016/S0014-5793\(99\)00820-0](https://doi.org/10.1016/S0014-5793(99)00820-0).
- Valastro, C., Campanile, D., Marinaro, M., Franchini, D., Piscitelli, F., Verde, R., Di Marzo, V., Di Bello, A., 2017. Characterization of endocannabinoids and related acylethanolamides in the synovial fluid of dogs with osteoarthritis: a pilot study. *BMC Vet. Res.* 13 (1), 309. <https://doi.org/10.1186/s12917-017-1245-7>.
- Valenza, M., Facchinetti, R., Steardo, L., Scuderi, C., 2022. Palmitoylethanolamide and white matter lesions: evidence for therapeutic implications. *Biomolecules* 12 (9), 1191. <https://doi.org/10.3390/biom12091191>.
- Van Sickle, M.D., Duncan, M., Kingsley, P.J., Mouihate, A., Urbani, P., Mackie, K., Stella, N., Makriyannis, A., Piomelli, D., Davison, J.S., Marnett, L.J., Di Marzo, V., Pittman, Q.J., Patel, K.D., Sharkey, K.A., 2005. Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science* 310 (5746), 329–332. <https://doi.org/10.1126/science.1115740>.
- Vannacci, A., Zagli, G., Marzocca, C., Pierpaoli, S., Passani, M.B., Mannaioni, P.F., Masini, E., 2002. Down-regulation by cannabinoids of the immunological activation of human basophils and guinea pig mast cells. *Inflamm. Res.* 51 (1), 9–10. <https://doi.org/10.1007/PL00022463>.
- Velten, L., Haas, S.F., Raffel, S., Blaszkiewicz, S., Islam, S., Hennig, B.P., Hirche, C., Lutz, C., Buss, E.C., Nowak, D., Boch, T., Hofmann, W.-K., Ho, A.D., Huber, W., Trumpp, A., Essers, M.A.G., Steinmetz, L.M., 2017. Human haematopoietic stem cell lineage commitment is a continuous process. *Nat. Cell Biol.* 19 (4), 271–281. <https://doi.org/10.1038/ncb3493>.
- Vincent, L., Vang, D., Nguyen, J., Benson, B., Lei, J., Gupta, K., 2016. Cannabinoid receptor-specific mechanisms to alleviate pain in sickle cell anemia via inhibition of mast cell activation and neurogenic inflammation. *Haematologica* 101 (5), 566–577. <https://doi.org/10.3324/haematol.2015.136523>.
- Voehringer, D., Shinkai, K., Locksley, R.M., 2004. Type 2 immunity reflects orchestrated recruitment of cells committed to IL-4 production. *Immunity* 20 (3), 267–277. [https://doi.org/10.1016/S1074-7613\(04\)00026-3](https://doi.org/10.1016/S1074-7613(04)00026-3).
- Walter, L., Franklin, A., Witting, A., Möller, T., Stella, N., 2002. Astrocytes in culture produce anandamide and other acylethanolamides. *J. Biol. Chem.* 277 (23), 20869–20876. <https://doi.org/10.1074/jbc.M110813200>.
- Walter, L., Franklin, A., Witting, A., Wade, C., Xie, Y., Kunos, G., Mackie, K., Stella, N., 2003. Nonpsychotropic cannabinoid receptors regulate microglial cell migration. *J. Neurosci.* 23 (4), 1398–1405. <https://doi.org/10.1523/jneurosci.23-04-01398.2003>.
- Wang, X., Yamamoto, T., Kadowaki, M., Yang, Y., 2021. Identification of key pathways and gene expression in the activation of mast cells via calcium flux using bioinformatics analysis. *Biocell* 45 (2), 395–415. <https://doi.org/10.32604/BIOCCELL.2021.012280>.
- Weston, M.C., Peachell, P.T., 1998. Regulation of human mast cell and basophil function by cAMP. *Gen. Pharmacol.* 31 (5), 715–719. [https://doi.org/10.1016/S0306-3623\(98\)00080-9](https://doi.org/10.1016/S0306-3623(98)00080-9).
- Williams, S.J., Hartley, J.P., Graham, J.D., 1976. Bronchodilator effect of delta1-tetrahydrocannabinol administered by aerosol of asthmatic patients. *Thorax* 31 (6), 720–723. <https://doi.org/10.1136/thx.31.6.720>.
- Woodward, D.F., Liang, Y., Krauss, A.H.P., 2008. Prostaglandin-ethanolamides and their pharmacology. *Br. J. Pharmacol.* 153 (3), 410–419. <https://doi.org/10.1038/sj.bjp.0707434>.
- Xiao, W., Nishimoto, H., Hong, H., Kitaura, J., Nunomura, S., Maeda-Yamamoto, M., Kawakami, Y., Lowell, C.A., Ra, C., Kawakami, T., 2005. Positive and Negative Regulation of Mast Cell Activation by Lyn via the FcεRI. *J. Immunol.* 175 (10), 6885–6892. <https://doi.org/10.4049/jimmunol.175.10.6885>.
- Yang, X., Hegde, V.L., Rao, R., Zhang, J., Nagarkatti, P.S., Nagarkatti, M., 2014. Histone modifications are associated with Δ9-tetrahydrocannabinol-mediated alterations in antigen-specific T cell responses. *J. Biol. Chem.* 289 (27), 18707–18718. <https://doi.org/10.1074/jbc.M113.545210>.
- Yates, M.L., Barker, E.L., 2009. Inactivation and biotransformation of the endogenous cannabinoids anandamide and 2-arachidonoylglycerol. *Mol. Pharmacol.* 76 (1), 11–17. <https://doi.org/10.1124/mol.109.055251>.
- Zhang, H.Y., Gao, M., Shen, H., Bi, G.H., Yang, H.J., Liu, Q.R., Wu, J., Gardner, E.L., Bonci, A., Xi, Z.X., 2017. Expression of functional cannabinoid CB2 receptor in VTA dopamine neurons in rats. *Addict. Biol.* 22 (3), 752–765. <https://doi.org/10.1111/adb.12367>.
- Zhang, T., Finn, D.F., Barlow, J.W., Walsh, J.J., 2016. Mast cell stabilisers. *Eur. J. Pharmacol.* 778, 158–168. <https://doi.org/10.1016/j.ejphar.2015.05.071>.
- Zhang, Y.F., Liu, Q.M., Gao, Y.Y., Liu, B., Liu, H., Cao, M.J., Yang, X.W., Liu, G.M., 2019. Attenuation of allergic responses following treatment with resveratrol in anaphylactic models and IgE-mediated mast cells. *Food Funct.* 10 (4), 2030–2039. <https://doi.org/10.1039/c9fo00077a>.
- Zheng, S., Papalex, E., Butler, A., Stephenson, W., Satija, R., 2018. Molecular transitions in early progenitors during human cord blood hematopoiesis. *Mol. Syst. Biol.* 14 (3), 1–20. <https://doi.org/10.15252/msb.20178041>.
- Zhu, Z., Oh, S.Y., Cho, Y.S., Zhang, L., Kim, Y.-K., Zheng, T., 2010. Tyrosine phosphatase SHP-1 in allergic and anaphylactic inflammation. *Immunol. Res.* 47 (1–3), 3–13. <https://doi.org/10.1007/s12026-009-8134-5>.
- Zoerner, A.A., Stichtenoth, D.O., Engeli, S., Batkai, S., Winkler, C., Schaumann, F., Janke, J., Holz, O., Tsikas, D., Jordan, J., Hohlfeld, J.M., 2011. Allergen challenge increases anandamide in bronchoalveolar fluid of patients with allergic asthma. *Clin. Pharmacol. Ther.* 90 (3), 388–391. <https://doi.org/10.1038/clpt.2011.94>.
- Zygmunt, P.M., Petersson, J., Andersson, D.A., Chuang, H.H., Sjørgård, M., Di Marzo, V., Julius, D., Högestätt, E.D., 1999. Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. *Nature* 400 (6743), 452–457. <https://doi.org/10.1038/22761>.