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Chapter

Cannabinoid Receptors as Regulators of Neutrophil Activity in Inflammatory Diseases

Mariana Conceição Souza and Elaine Cruz Rosas

Abstract

Cannabinoids are compounds present in *Cannabis sativa* (phytocannabinoids), endogenously produced (endocannabinoids) or synthesized, that bind to G protein-coupled receptors named cannabinoid receptors B1 and B2. They were first described as psychotropic compounds; however, cannabinoids are also potent immunoregulatory agents. Cannabinoids can modulate neutrophil activity in sterile and infectious inflammatory diseases. Concerning sterile inflammatory diseases as arthritis, ischemic diseases, and colitis, the use of CB2 agonist impairs the intracellular signaling pathways involved in the production of inflammatory mediators and expression of adhesion molecules. As a consequence, neutrophils did not release metalloproteinases either to adhere to endothelial cells, resulting in reduced tissue damage. A similar anti-inflammatory CB2 agonist mechanism of action in sepsis and mycobacterial infection models is observed. However, it is not clear if inflammation resolution promoted by cannabinoid treatment during infection is also related to microbial viability. Despite the growing literature showing the effects of cannabinoids on neutrophils, there are still some gaps that should be filled before proposing cannabinoid-based drugs to treat neutrophil-dependent diseases.

Keywords: cannabinoid agonist, inflammation, infection, endocannabinoids, phytocannabinoids, synthetic cannabinoids

1. Introduction

Neutrophils have been classically recognized as the most relevant cell during acute inflammatory responses and, more recently, in chronic inflammation [1]. On the one hand, neutrophils produce bactericidal molecules and coordinate the accumulation of pro-resolving cells. On the other hand, neutrophil over activation leads to tissue damage. In this context, several approaches have been proposed to regulate the accumulation and the activity of neutrophils in pathological conditions.

In parallel, the findings concerning the importance of the endocannabinoid system as the endogenous immunoregulatory mechanism raise questions on how it could be therapeutically used to treat inflammatory diseases. In this chapter, we discuss how the endocannabinoid system can be used to modulate the activity of neutrophils in sterile and infectious inflammatory diseases.

2. Cannabinoid system

Cannabis sativa (marijuana) is one of the oldest plants that produced psychoactive effects on humans. In addition, it has been used in medicine in controlling pain, convulsion, inflammation, and asthma [2, 3]. Cannabinoids are a group of lipophilic and pharmacologically active compounds present in *C. sativa*. The first component from cannabis identified was the tetrahydrocannabinol (Δ9-THC) and and, as other cannabinoids, binds to G protein-coupled receptors (GPCRs) named cannabinoid receptors [4, 5].

Cannabinoid receptor agonists are responsible for several biological effects, such as analgesic, antiemetic, antitumor, and anti-inflammatory [6–13], and are classified into three groups based on their origin: endogenous cannabinoids (endocannabinoids—**Figure 1a** and **b**), phytocannabinoids (**Figure 1c** and **d**), and synthetic cannabinoids (**Figure 1e** and **f**) [5].

Endocannabinoids (eCBs) are eicosanoids derived from polyunsaturated chain fatty acids, such as arachidonic acid, and comprise amides, esters, and ether [14]. Anandamide (AEA) was the first endocannabinoid described in the mammalian

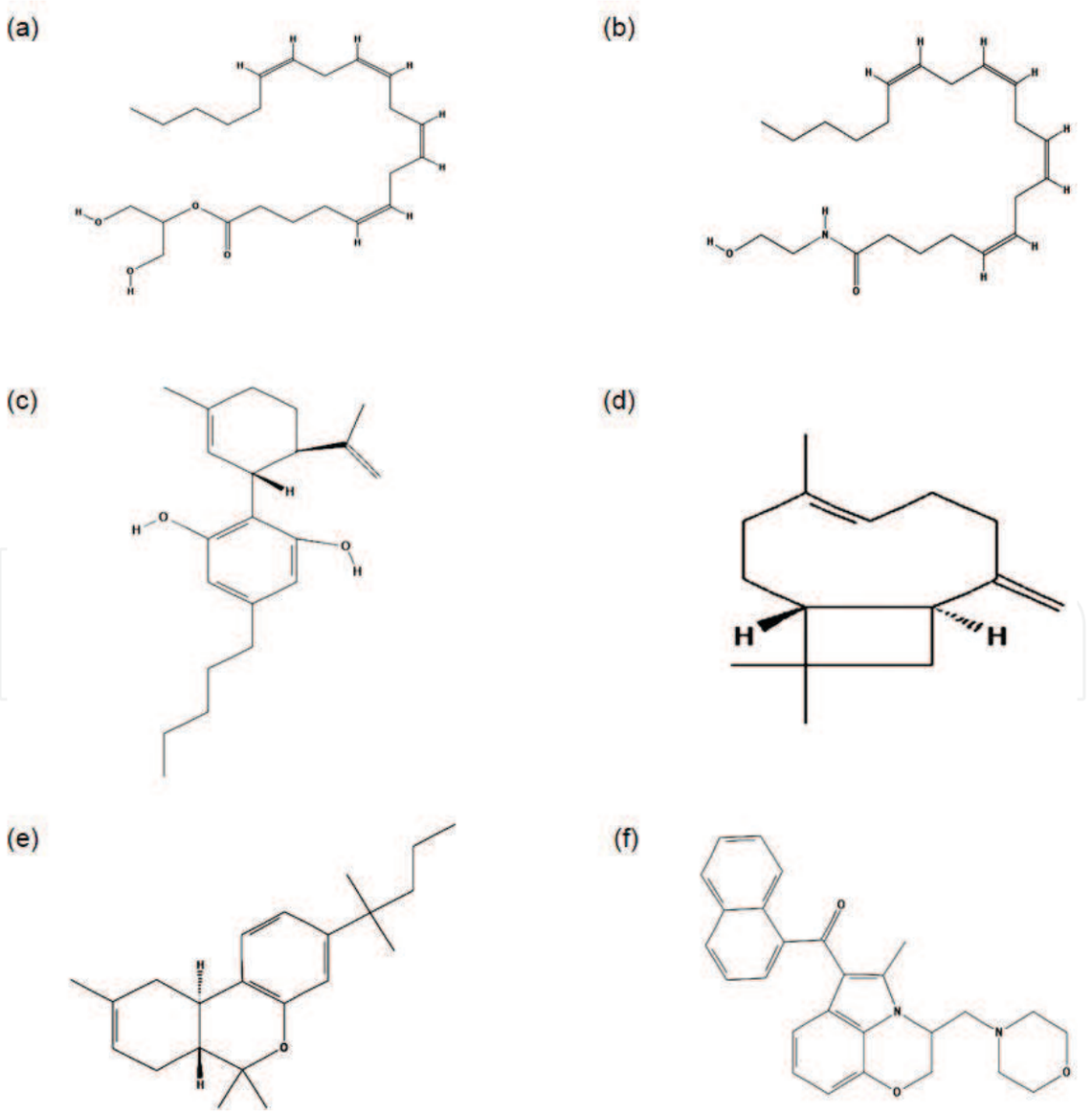

Figure 1.
Chemical structure of some representatives of the cannabinoid agonists. (a) 2-AG, (b) AEA, (c) cannabidiol, (d) β-caryophyllene, (e) JWH-133, and (f) WIN 55212-2.

brain and other tissues [15], followed by 2-arachidonoylglycerol (2-AG) [16, 17]. The AEA and 2-AG represent the major substances of this class. The eCBs together with the cannabinoid receptors and the enzymes that regulate their biosynthesis and degradation constitute the "endocannabinoid system" [18]. Beyond the well-known psychotropic effects, the endocannabinoid system plays an essential immunomodulatory role by modulating the release of cytokines and on acute or chronical diseases through two main ways, neuro- and immunomodulation [19, 20].

The group of phytocannabinoids consists of active substances initially extracted from *Cannabis sativa*, whose pharmacological activity is associated with the terpene phenolic class. Phytocannabinoids are classified into two groups: psychoactive cannabinoids, such as Δ9-THC, and non-psychoactive such as cannabidiol and cannabinol [21, 22]. More recently, other molecules have been isolated from different plant species, which exert effects through cannabinoid receptors, such as the alkylamides derived from *Echinacea angustifolia* and *Otanthus maritimus* and sesquiterpene, as β-caryophyllene, found in some plant species from *Copaifera* genus [23–27].

The characterization of the chemical structure of Δ9-THC and endocannabinoids allowed the development of synthetic cannabinoids. From THC, it was possible to synthesize several compounds that have similar chemical structures with different levels of affinity for cannabinoid receptors [5, 28]. Synthetic cannabinoids have been used as a pharmacological tool for *in vivo* or *in vitro* studies to explore the therapeutic potential of the cannabinoid system. However, it has already been described that metabolites form dipyrone and paracetamol exert its analgesic effects by inhibiting endocannabinoid biosynthesis and binding of cannabinoid receptors, respectively [29].

The cannabinoid receptors CB1 and CB2 are the main receptors of the cannabinoid system. Both belong to the family of GPCRs, specifically inhibitory G protein (Gi) [30]. The binding of agonists to cannabinoid receptors inhibits adenylate cyclase (AC) and modulates activation of different members of the MAPK family, including ERK1/ERK2, p38, and JNK1/2 (**Figure 2**) [30–37]. By inhibiting AC, the reduction of the second messenger cyclic adenosine monophosphate (cAMP) leads to the opening of rectifying potassium channels. CB1 also mediates the inhibition of N-type and P/Q-type calcium currents [22, 38]. Besides CB1 and CB2, the existence of a third cannabinoid receptor (CB3) has been suggested [39], and there are two orphan G protein-coupled receptors (GPCRs) which overlap with CB1 and CB2, named GPR18 and GPR55 [40]. In addition to activation via GPCRs, cannabinoids can perform their actions by activating PPARs, including PPARγ [41–43].

CB1 is expressed in the central nervous system, especially by neurons [44] and modulates physiological processes, such as motor behavior, learning, memory and cognition, and pain perception [45]. This receptor is associated with the psychotropic effects of cannabinoid agonists, such as THC [46, 47].

CB2 is the peripheral receptor for cannabinoid agonists. It is mainly expressed in immune tissues such as the spleen and thymus as well as in blood cell subpopulations such as CD4 and CD8 lymphocytes, neutrophils, monocytes, natural killer (NK) cells, and B lymphocytes [47]. Nevertheless, CB2 is also found at low levels in neuronal and nonneuronal cells of the brain, but it does not produce psychoactive effects [47–49].

The CB2 expression intensity in immune cells depends on cell populations and activation state [50, 51]. Macrophages from different tissues increase CB2 expression after stimulation with interferon (IFN)-γ, which suggests that macrophages activated during an inflammatory process are more sensitive to the action of cannabinoid agonists than those in the resting state [52]. The first evidence that cannabinoids might modulate cytokine production was in the mid-1980s when murine

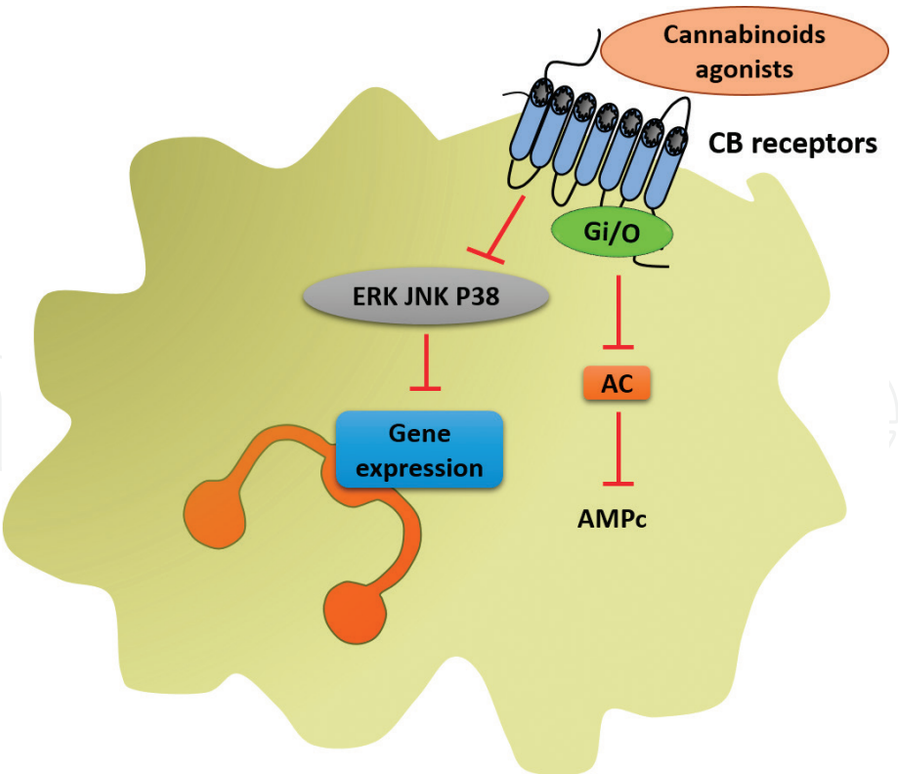

Figure 2.
Neutrophil activated expresses cannabinoid receptors (CB receptors). The cannabinoid receptors CB1 and CB2 belong to the family of GPCRs, specifically inhibitory G protein (Gi/o). The binding of agonists to cannabinoid receptors inhibits the activation of different members of the MAPK family (ERK1/2, p38, and JNK1/2), gene expression, as well as reduces cyclic adenosine monophosphate (cAMP) levels by inhibiting adenylate cyclase (AC) activity.

cells treated with agonist cannabinoid reduced the levels of type I interferons (IFN-α and IFN-β) after stimulation with LPS or polyinosinic-polycytidylic acid (polyI:C). Many subsequent studies have shown that cannabinoids inhibited the production of cytokines in innate and adaptive immune responses, both in animal models and in human cell cultures (to review [53]). In such a way, CB2 has become an important target, especially in inflammatory conditions. The CB2 receptor modulates immune cell functions, both *in vitro* and in animal models of inflammatory diseases. In this context, some studies have reported that mice lacking the CB2 receptor have an exacerbated inflammatory phenotype (to review [19]). Besides, CB2 agonists have an inhibitory effect on leukocyte migration and in the production of pro-inflammatory mediators *in vivo* and *in vitro*, showing a high anti-inflammatory potential [54]. Due to the lack of psychotropic effects, CB2 agonists are considered a promising therapeutic strategy for the treatment of chronic inflammatory diseases. Preclinical studies showed the action of CB2 agonists on different experimental models of inflammation, such as colitis, arthritis, cerebral ischemia, and sepsis [10, 53, 55–59], and in these studies, they showed that the action of CB2 agonists modulated the neutrophil activity.

3. Neutrophils, cannabinoid system, inflammation, and infection

3.1 Neutrophils and cannabinoid system

Neutrophils play a crucial role in inflammatory processes, which are present in the pathology of different diseases. The neutrophil recruitment to the inflammatory site is an essential stage in the inflammatory responses; these cells are released from

the bone marrow to the periphery immediately after the first signal of inflammation. The mobilization of neutrophils from the bone marrow is conducted by the hematopoietic cytokine granulocyte colony-stimulating factor (G-CSF), which mobilizes neutrophils indirectly by shifting the balance between ligands to CXCR4 (CXCL12) and CXCR2 (CXCL1 and CXCL2) [60]. Neutrophil-active chemoattractant, as chemokines CXCL1 and CXCL2, is produced and released within the bone marrow and in inflamed tissue. In this context, chemokines from inflamed foci might make their way to the bone marrow and modulate neutrophil egress. Thus, CXCL1 and CXCL2 can act locally by inducing neutrophil recruitment from blood to peripheral tissue and systemically by inducing neutrophil mobilization from the bone marrow to the bloodstream [61].

Once in the peripheral blood, neutrophils can be rapidly recruited into inflamed or infected tissues. A panel of diverse stimuli, especially pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), activates macrophages, mast cells, or stromal cells to produce and release pro-inflammatory mediators as interleukin (IL)-1β, tumor necrosis factor (TNF), CXCL8, CXCL1, CXCL2, and lipid mediators, such as leukotriene B_4 (LTB_4) and endocannabinoids [61, 62]. In inflammatory loci, neutrophils find antigen, molecules, and/or immune complexes that trigger different actions, such as phagocytosis, production of reactive oxygen species (ROS), and release of enzyme-rich granules (as collagenases, gelatinases, neutrophil myeloperoxidase (MPO), and elastase [63]). Neutrophils enter the tissue through surface molecules which interact with vascular endothelial cells. This process is accompanied by a regulated rearrangement of the cytoskeleton of neutrophils that lead to actin polymerization [64], which is mainly governed by members of the Rho family GTPases including RhoA, Rac1, and Cdc42 [65].

Concerning cannabinoid receptor expression, it was observed that neutrophil from healthy donors expresses low levels of CB2 [66]. In addition, it was shown that the CB2 receptor plays a crucial role in neutrophil differentiation, and it has been implicated in the development of leukemia [67, 68].

The role of the cannabinoid system in neutrophil migration is controversial. The activation of CB2 receptors by 2-AG did not induce polarization and migration of human blood neutrophils [69]. However, pretreatment of neutrophils with 2-AG inhibited the fMLP- and CXCL8-induced migration without affecting the polarization of the cells [69]. In contrast, McHugh and coworkers showed that 2-AG does not inhibit the migration of human neutrophils toward fMLP and does not show chemotactic effects by itself [70]. Furthermore, Balenga and coworkers showed that 2-AG induces migration of neutrophils toward inflammatory sites, through cross talk with activated GPR55 [62].

Despite the uncertainty regarding the involvement of CB2 agonist with the neutrophil migration and action, some studies show that there is a relationship between neutrophils and cannabinoid system in the pathogenesis of inflammatory or infection diseases (**Table 1**). In the next section, we will discuss the cannabinoid system and its action on the neutrophil participation in inflammatory and infection conditions [54, 62, 69–85].

3.2 Neutrophils, cannabinoid system, and inflammation

The action of CB2 agonists on their receptors impairs the secretion of pro-inflammatory cytokines and chemokines and reduces the recruitment of neutrophils. As discussed previously, neutrophils play a significant role in inflammatory diseases, including acute, chronic, autoimmune, infectious, and noninfectious conditions. The relation between neutrophil and cannabinoid system in inflammatory disease was discussed in this section.

Drugs	Mechanism of action on neutrophils	Reference
Endocannabinoids		
N-arachidonoyl-ethanolamine (AEA)	Decreases neutrophil migration in vitro	70
	Decreases neutrophil migration in vivo	71
2-arachidonoylgycerol (2-AG)	Decreases neutrophil migration in vitro	69
	Increases neutrophil motility	62, 72
Phytocannabinoids		
cannabidiol	Neutrophil deactivation in vitro	70, 73, 74
	Decreases neutrophil migration in vivo	74, 75, 76, 77
Delta 9-tetrahydrocannabidiol (THC)	Decreases neutrophil migration in vivo	77, 78, 79
beta-caryophyllene	Decreases neutrophil migration in vivo	54, 80, 81, 82
	Decreases neutrophil migration in vitro	83
Synthetic cannabinoid		
HU-308	Decreases neutrophil migration in vivo	77
JWH-133	Neutrophil deactivation in vitro	84
WIN55212-2	Decreases neutrophil migration in vivo and in vitro	71

Table 1.
Cannabinoid agonists, which exert action on neutrophils.

Increased macro- and microscopic colon damage scores, a high number of macrophage and neutrophil and MPO activity, characterizes experimental colitis. The activation of CB receptors by their ligands produces a protective effect in experimental colitis by decreasing prostaglandin, ROS and nitric oxide production, and reduction of leukocyte accumulation as neutrophils, resulting in diminished of colon tissue inflammation. Besides, mice lacking functional CB receptors are less resistant to colon inflammation than wild-type animals [53, 86]. The synthetic non-psychotropic cannabinoids as JWH-133, cannabinoid from the plant as cannabigerol [87] and β-caryophyllene [54], and synthetic atypical cannabinoid O-1602 (non-CB1 and CB2 ligands) [88] have been able to inhibit neutrophil recruitment in colitis models. Thus, during inflammation, the CB2 receptor activation by endocannabinoids or synthetic cannabinoid provides a mechanism for the reestablishment of regular GI transit (to review [89]).

Neutrophils are also essential cells in the development of arthritis. Neutrophils are abundant in inflamed joints, and these cells are essential to the initiation and progression of rheumatoid arthritis (RA). Neutrophil effector mechanisms include the release of pro-inflammatory cytokines, reactive oxygen and nitrogen species

(ROS and RNS), and granules containing derivative enzymes, which can cause further damage to the tissue and amplify the inflammatory response [90]. In such way, it has already been described that in RA there is an increase of CB2 expression and elevated endocannabinoid levels, observed in the synovial tissue and fluid from a patient with this disease [91]. Synovial fibroblasts and macrophages are mainly responsible for endocannabinoid production. These cells also are essential in the production of chemokines (CXCR1 or 2 ligands, such as CXCL8), the C5a fragment of the complement system, and LTB_4 which are responsible for neutrophil mobilization to the synovial cavity [61]. In this context, the activation of CB2 receptors inhibits the production of pro-inflammatory mediators, like chemokines, which reduces the leukocyte migration, like neutrophils, to the synovial cavity and metalloproteinase release [92]. Moreover, the activation of CB2 receptors inhibits IL-1β-induced activation of extracellular signal-regulated kinases 1 and 2 and p38 mitogen-activated protein kinase in RA fibroblast [92].

The role of cannabinoid in neutrophils was also studied in ischemic models. Endocannabinoids act via the CB2 receptor in the modulation of the inflammatory response and myocardial remodeling after infarction. CB2 receptor plays an essential role in the formation of infarction border zone, collagen deposition, and organization of stable scar during remodeling. Duerr and coworkers [93] showed increased numbers of neutrophils in the heart ischemic area of CB2 receptor-deficient (Cnr2−/−) mice when compared with healthy mice. These results suggest that CB2 receptor modulates neutrophil migration to inflammatory infarction site [93]. In accordance, activation of the cannabinoid CB2 receptor by JWH-133 protects against atherosclerotic plaque formation and may also decrease neutrophil MMP-9 release, which reduces the vulnerability of ischemic stroke plaque in arteries. Together, the studies suggest that CB2 agonists represent a promising anti-atherosclerotic treatment [84].

Even though CB1 is the most prominent receptor in the CNS, CB2 modulates neuroinflammation. CB2 activation by JWH-133 reduced the number of neutrophils in the ischemic brain. Furthermore, CB2 activation *in vitro* inhibits adherence of neutrophils to brain endothelial cells. JWH-133 also interfered with the migration of neutrophils induced by the endogenous chemokine CXCL2 through activation of the MAP kinase p38. This effect on neutrophils is probably responsible for the neuroprotection mediated by JWH-133 [56].

3.3 Neutrophils, cannabinoid system, and infection

The relation between neutrophil and infection is well established [94]. On one hand, the exacerbation of neutrophil activation could lead to tissue damage. On the other hand, neutrophils control microorganism growth. In this context, it is essential to study the effect of cannabinoids on neutrophils during infections and evaluate if and how the cannabinoid system modulates neutrophil activity.

The interest in the relationship among cannabinoids and infections exists since the 1960s when studies regarding "hippie subculture" observed the increase of sexually transmitted infections by marijuana consumers [95]. By this time, the studies focused on consumer behavior and how it could increase susceptibility to infections but did not evaluate the effect of cannabinoids on host response to infections [96]. Nowadays, it is known that endocannabinoid system regulates and is regulated by host microbiota, a balance that protects the host from the infection-triggered inflammatory response [29]. However, the increase of studies showing the immunoregulatory role of the endocannabinoid system raises questions about if cannabinoids could modulate microbial viability and/or neutrophil response during infections.

Studies concerning the modulation of neutrophil activity by cannabinoids during infections are mostly addressed to experimental bacterial infection as sepsis model. Neutrophil activity during experimental sepsis is well characterized in studies *in vivo* (to review [97–99]). By using LPS sepsis model, Smith and coworkers showed that treatment with cannabinoid receptor agonists reduced the migration of neutrophils in the peritoneal cavity by inhibiting neutrophil chemoattractant production [59]. The authors conclude that CB2 was responsible for impairing neutrophil migration. In accordance, studies performed in CB2-deficient mice submitted to sepsis induced by cecal ligation and puncture showed increased production of neutrophil chemotactic chemokines and increased numbers of neutrophil in the bone marrow and lung tissue. Interestingly, despite the increase in neutrophil numbers, neutrophils from CB2-deficient mice were not able to activate the MAPK pathway neither control bacterial load [57, 100]. Furthermore, in mycobacteria model of infection, it was observed that CB2 agonism impairs neutrophil adhesion to endothelial cells probably by inhibiting actin polymerization [83].

There are few and controverting data concerning CB1 effects on neutrophils during infection. Leite-Avalca and coworkers showed that CB1 antagonist given to mice submitted to CLP increased the survival rate but not change neutrophil accumulation in the peritoneal cavity [101]. Nevertheless, Kianian and coworkers showed that antagonism of CB1 reduced the adhesion of leukocytes to intestinal submucosal venules [102]. It is noteworthy that in the sepsis model, the activation of CB1 increases the systemic arterial pressure and the flow and decreases the arterial oxygenation; however, it decreases the inflammatory cytokine production [103, 104]. In such a way, an indirect effect of CB1 on leukocyte behavior during sepsis cannot be ruled out.

The results regarding the immunomodulatory effects of cannabinoids in infection are in accordance with the host-directed therapy approach that aims to activate protective responses against microbes in addition to antimicrobial therapy [105]. However, it should be mentioned that antibiotics perturb gut microflora, which could result in the endocannabinoid system unbalance and, thus, in neuropsychiatric disorders [29]. Indeed, further studies are necessary to propose to activate the endocannabinoid system, especially the CB2 pathway, during infections.

4. Conclusion

An increasing amount of data concerning the immunoregulatory role of cannabinoids, especially the CB2 agonists, has been raising the interest in developing new therapeutic strategies for inflammatory diseases. It is already known that the mechanism of action of well-established anti-inflammatory drugs, like paracetamol, depends on the activation of the endocannabinoid system [29]. However, despite all studies showing that cannabinoids can modulate neutrophil biology, there is a long way to go to achieve cannabinoid-based drugs to treat neutrophil-dependent diseases such as arthritis and infection-induced acute lung injury.

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Conflict of interest

The authors declare no conflicts of interest.

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