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Review

Cannabinoids and cannabinoid-like compounds: Biochemical characterization and pharmacological perspectives

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Abstract: Publication interest in cannabinoids, including phytocannabinoids, endogenous cannabinoids, synthetic cannabinoids and cannabinomimetic compounds, is due to the therapeutic potential of these compounds in inflammatory pathology. Since recent years, scientific interest was focused on compounds with cannabinomimetic activity. The therapeutic use of phytocannabinoids and endocannabinoids is somewhat limited due to unresolved issues of dosing, toxicity and safety in humans, while cannabinoid-like compounds combine similar therapeutic effects with a high confirmed safety. Targets for endocannabinoids and phytocannabinoids are endocannabinoid receptors 1 and 2, G protein-coupled receptors (GPCRs), peroxisome proliferator-activated receptors (PPARs), and transient receptor potential ion channels (TRPs). Non-endocannabinoid N-acylethanolamines do not interact with cannabinoid receptors and exhibit agonist activity towards non-cannabinoid receptors, such as PPARs, GPCRs and TRPs. This literature review includes contemporary information on the biological activity, metabolism and pharmacological properties of cannabinoids and cannabinoid-like compounds, as well as their receptors. We established that only a few studies were devoted to the relationship of non-endocannabinoid N-acylethanolamines with non-cannabinoid receptors, such as PPARs, GPCRs, and also with TRPs. We have focused on issues that were insufficiently covered in the published sources in order to identify gaps in existing knowledge and determine the prospects for scientific research.

Keywords: N-acylethanolamine, anandamide, oleoylethanolamine, palmitoylethanolamine, delta(Δ)9-tetrahydrocannabinol, cannabidiol, GPCRs, PPARs, TRPs.

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Introduction

Interest in cannabinoids and cannabinoid-like compounds is due to their therapeutic potential for inflammatory diseases that are currently widespread worldwide [1–9].

Cannabinoids include natural cannabinoids, endogenous cannabinoids, synthetic cannabinoids, and cannabinomimetic compounds [6].

Natural cannabinoids, or phytocannabinoids, are found in plants of the hemp family (cannabis, derived from the Latin *Cannabis sativa* L.) [6]. The most studied phytocannabinoids are delta(Δ)9-tetrahydrocannabinol (THC) and cannabidiol (CBD), along with secondary cannabinoids [10].

Endogenous cannabinoids, or endocannabinoids, are lipids that are synthesized in the human body. First of all, these include N-arachidonoylethanolamine (AEA), also known as anandamide (ANA), and 2-arachidonoylglycerol (2-AG) [5, 6, 11, 12].

Compounds with cannabinomimetic activity include derivatives of saturated or monounsaturated fatty acids, such as N-palmitoylethanolamine (PEA), N-oleoylethanolamine (OEA), stearoylethanolamine, etc. [13].

Cannabinoids are also represented by synthetic substances with a structure and action similar to phytocannabinoids (classical cannabinoids) and by synthetic substances that differ from plant cannabinoids in structure, albeit similar in action (nonclassical cannabinoids) [6]. The latter include aminoalkylindoles, eicosanoids, quinolines, arylsulfonamides, etc. [13].

According to the international lipid classification displayed on the *LIPID MAPS* website (https://www.lipidmaps.org/), endocannabinoids include N-acylethanolamines (NAE) of saturated, monoenoic, and polyunsaturated fatty acids synthesized in the human body. Some cannabinomimetic compounds also belong to the class of NAE [14, 15]. For instance, NAE includes AEA, which contains a polyunsaturated fatty acid, as well as PEA and OEA, which contain saturated or monounsaturated fatty acids. As for 2-AG, it belongs to the monoacylglycerol group (MAG) and is a true endocannabinoid, while AEA is a byproduct of the main NAE: PEA and OEA. At the same time, the physiological role of PEA and OEA is less studied, compared with 2-AG.

Potential targets for endocannabinoids and phytocannabinoids are endocannabinoid receptors 1 and 2 (CB1, CB2) [16], orphan G

protein-coupled receptors, GPCRs) [17-19], peroxisome proliferator-activated receptors (PPARs) [20], and transient receptor potential ion channels (TRPs) [10, 11, 21, 22]. However, amides of saturated or monounsaturated fatty acids, such as PEA and OEA, are considered non-endocannabinoid NAE, since they do not interact with cannabinoid receptors and exhibit agonist activity towards non-cannabinoid receptors, such as PPARs, GPCRs, and TRPs [18].

CB1, CB2, and other GPCRs, along with PPARs and TRPs, are expressed in the digestive and respiratory tracts, skin, and many other organs and systems [16]. Consequently, the therapeutic potential of phytocannabinoids, endocannabinoids, and compounds with cannabinomimetic properties is actively studied in bronchopulmonary inflammatory diseases [1, 7], inflammatory diseases of bowel [4, 5] and skin [6, 8, 9], Alzheimer's disease [2], multiple sclerosis [3], chronic pain [23], obesity [24], and a number of other pathologies.

It should be noted that the therapeutic use of phytocannabinoids and endocannabinoids is rather limited due to the unresolved issues of their dosing, toxicity and safety for humans [21]. The non-endocannabinoid NAE (PEA and OEA) combine similar therapeutic effects with a higher confirmed safety [25]. These N-acylethanolamines have anti-inflammatory, analgesic and anorexic effects via non-endocannabinoid receptors [18].

The PubMed database was initially searched for articles published in English between January 1, 2017 and January 1, 2022. We used the following keywords: N-acylethanolamine, anandamide, oleoylethanolamine, palmitoylethanolamine, delta(Δ)9-tetrahydrocannabinol, cannabidiol, GPCRs, PPARs, TRPs (*Table 1*).

Publication interest in cannabinoids is steadily increasing. E.g., a search query with this keyword conducted in the PubMed database yielded 9,832 results over the past five years, while 2,431 (25%) of them were associated with the last year. Scientific interest in N-acylethanolamines is also constantly growing. A PubMed search with the N-acylethanolamine keyword revealed 230 articles between 2017 and 2022, 62 of which (27%) were from the last year. At the same time, a small number of studies was published on the relationship of PEA and OEA with GPCRs, PPARs and TRPs, as well as of all NAEs with GPCRs (GPR55 and GPR119).

Our review summarizes the latest data on the biological activity, metabolism, and anti-inflammatory effects of endocannabinoid and non-endocannabinoid N-acylethanolamines, as well as their receptors. We established that only a small number of studies was devoted to the relationship of non-endocannabinoid NAEs with non-cannabinoid receptors, such as PPARs, GPCRs, and TRPs. Emphasis was placed on issues that were insufficiently covered in the published sources in order to identify gaps in existing knowledge and determine the prospects for scientific research.

Endocannabinoids and their receptors

The endocannabinoid system consists of cannabinoid receptors (CB1 and CB2), endogenous cannabinoid neurotransmitters (AEA and 2-AG), and also includes transmembrane and intracellular transport systems, along with enzymes responsible for the synthesis and decomposition of neurotransmitters. These enzymes are represented by fatty acid amide hydrolase (FAAH) for AEA and monoacylglycerol lipase (MAGL) for 2-AG [26]. Alternative ways of endocannabinoid degradation include their oxidation with the cyclooxygenase, lipoxygenase and cytochrome P450 [5].

Table 1. Results of a systematic search of 2017-2022 publications on the research topic in the PubMed database

Keywords	*Number of articles for the period of 2017-2022*
"N-acylethanolamine" and CB1 and CB2	7
"Palmitoylethanolamide" and CB1 and CB2	21
"Anandamide" and CB1 and CB2	144
"Oleoylethanolamine" and CB1 and CB2	3
“Δ9-tetrahydrocannabinol” and CB1 and CB2	23
“Cannabidiol” and CB1 and CB2	159
"N-acylethanolamine" and peroxisome proliferator-activated receptor	25
"Palmitoylethanolamide" and peroxisome proliferator-activated receptor	70
"Anandamide" and peroxisome proliferator-activated receptor	30
"Oleoylethanolamine" and peroxisome proliferator-activated receptor	5
“Δ9-tetrahydrocannabinol” and peroxisome proliferator-activated receptor	5
“Cannabidiol” and peroxisome proliferator-activated receptor	43
"N-acylethanolamine" and transient receptor potential channels	1
"Palmitoylethanolamide" and transient receptor potential channels	4
"Anandamide" and transient receptor potential channels	62
"Oleoylethanolamine" and transient receptor potential channels	2
“Δ9-tetrahydrocannabinol” and transient receptor potential channels	1
“Cannabidiol” and transient receptor potential channels	52
"N-acylethanolamine" and GPR55	4
"Palmitoylethanolamide" and GPR55	12
"Anandamide" and GPR55	17
"Oleoylethanolamine" and GPR55	1
“Δ9-tetrahydrocannabinol” and GPR55	3
“Cannabidiol” and GPR55	58
"N-acylethanolamine" and GPR119	1
"Palmitoylethanolamide" and GPR119	2
"Anandamide" and GPR119	2
"Oleoylethanolamine" and GPR119	1
“Δ9-tetrahydrocannabinol” and GPR119	3
“Cannabidiol” and GPR119	5

Table 2. Endocannabinoids and their receptors

Endocannabinoids/Receptors	*AEA*	*2-AG*
CB1	partial agonist	agonist
CB2	partial agonist	primary endogenous agonist
GPCRs	agonist	agonist
TRPA1	agonist	agonist
TRPV1	agonist	agonist
TRPV2	agonist	agonist
TRPV3	agonist	agonist
TRPV4	agonist	agonist
TRPM8	agonist	agonist
PPAR-α	agonist	agonist
PPAR-β/δ	agonist	agonist
PPAR-γ	agonist	agonist

Table 3. Phytocannabinoids and their receptors

Phytocannabinoids/Receptors	*THC*	*CBD*
CB1	partial agonist	agonist / antagonist low affinity
CB2	partial agonist	antagonist low affinity
GPRs	agonist	inverse agonist
TRPA1	agonist	agonist
TRPV1	agonist	partial agonist
TRPV2	agonist	agonist
TRPV3	agonist	agonist
TRPV4	agonist	agonist
TRPM8	agonist	antagonist
PPAR-α	-	agonist
PPAR-β/δ	-	agonist
PPAR-γ	agonist	possible agonist
5-HT1A	-	partial agonist at low concentration inverse agonist at higher concentration
D2 dopamine receptor	-	partial agonist

Table 4. Non-endocannabinoid N-acylethanolamines and their receptors

N-acylethanolamines/Receptors	*PEA*	*OEA*
CB1	agonist	-
CB2	-	-
GPR55	agonist	-
GPR19	agonist	agonist
GPR40	-	agonist
TRPA1	-	-
TRPV1	agonist	agonist
TRPV2	-	-
TRPV3	-	-
TRPV4	-	-
TRPM8	-	-
PPAR-α	agonist	-
PPAR-β/δ	-	-
PPAR-γ	-	-

Structurally, AEA and 2-AG are eicosanoids: 2-AG is involved in regulating the circulatory system, pain and inflammation (immune inflammation and neuroinflammation), while AEA is involved in thermoregulation and nociception.

Endocannabinoids and their receptors are presented in *Table 2*.

Endocannabinoids 2-AG and AEA are agonists of both cannabinoid receptors CB1 and CB2.

The CB1 expression (central type) prevails in the nociceptive areas of the central nervous system, albeit it is also detected in the liver, pancreas, muscle tissue and adipose tissue [27]. CB1 receptor is responsible for the adaptive regulation of intracellular signal cascades, synaptic and cellular plasticity processes [28-30]. This receptor participates in the mechanisms of forming the anxiety, pain, addiction, inflammation, as well as regulation of metabolism [16].

CB2 (peripheral type) is expressed mainly on the immune system cells [30-32]. CB2 is involved in the implementation of the anti-inflammatory effect via reducing the production of proinflammatory cytokines and increasing the production of anti-inflammatory cytokines [33]. CB2 agonists inhibit recruitment of leukocytes and reduce the content of tumor necrosis factor-alpha (TNF-α), interleukins (IL-1β, IL-6, IL-18), monocyte chemoattractant protein-1 (MCP-1) and active forms of oxygen [31]. CB2 agonism leads to the activation of 5'-AMP-activated protein kinase (AMPK), stimulating oxidative phosphorylation and thereby the development of anti-inflammatory effect.

The latest scientific data indicate the existence of other receptors for cannabinoids associated with G proteins. These G protein-coupled receptors (GPCRs) are located in the central nervous system, intestines, liver, bones, skeletal muscles and adipose tissue: G protein-coupled receptor 18 (GPR18), G protein-coupled receptor 55 (GPR55), G-protein coupled receptor 119 (GPR119) and many others [17, 18].

GPR55 receptors are involved in glucose homeostasis, anti-inflammatory and analgesic effects [34, 35]. They are localized in several areas of the brain associated with the development of pain, as well as in the spinal cord [36]. The role of the GPR55 in the pathogenesis of neuropathic pain remains controversial, since some data indicate that their activation causes nociception [34, 37], while other data imply the absence of such effect [38].

GPR119 consists of 335 amino acids and participates mainly in glucose homeostasis [35]. It is expressed in the spinal cord and some areas of the brain, but its involvement in the development of pain is unknown [34, 35]. The study by A. Zúñiga-Romero et al. established that both GPR55 and GPR119 can be important targets for the treatment of neuropathic pain [34].

AEA and 2-AG endocannabinoids are also capable of interacting with other GPCRs (GPR3, GPR6, GPR12, GPR18), as well as with TRPs (TRPV1, TRPV2, TRPV3, TRPV4, TRPM8, TRPA1) and PPARs (PPAR-α, PPAR-β/δ, PPAR-γ) [5, 6, 12]. Besides, they exhibit affinity to serotonin receptors (5-HT1A, 5-HT3), as well as to adenosine and glycine receptors [39]. Anandamide was the first discovered endogenous agonist of TRPV1 and antagonist of TRPM8 [20, 40].

PPARs (PPAR-α, PPAR-β/δ и PPAR-γ) play an important role in the regulation of cellular processes (differentiation, proliferation, apoptosis) and inflammatory responses [41-43]. These receptors are classified as nuclear transcription factors with anti-inflammatory activity [44, 45].

PPAR-α isomer is expressed largely in the liver, kidneys, heart, skeletal muscles, brown adipose tissue, as well as in epithelial cells, macrophages, lymphocytes and dendritic cells of the respiratory tract [46]. Activation of PPAR-α reduces the production of proinflammatory mediators (TNF-α, IL-1, IL-6, IL-8) and modulates the expression of adhesion molecules and chemotactic factors involved in the pathogenesis of inflammation [47]. PPAR-α is also capable of inducing the production of anti-inflammatory IL-10 [47].

PPAR-β/δ isomer (PPAR-δ, PPAR-β, hNUC1, FAAR) is most pronounced in the brain, liver, skin, adipose tissue, keratinocytes

and skeletal muscles [48, 49]. It participates in oxidation of fatty acids and regulates the level of glucose in the blood, along with participating in the wound healing processes [50].

PPAR-γ is expressed virtually in all tissues and cells, but mainly in adipose tissue, colon and spleen [51]. This receptor is a regulator of cellular homeostasis, energy metabolism [41] and a participant of inflammatory responses [44, 45].

Superfamily of transient receptor potential (TRP) ion channels combines conventional receptors of the following categories: canonical (TRPC 1-7), vanilloid (TRPV 1-6), polycystic (TRPP 1-3), mucolipin (TRPML 1-3), ankyrin 1 (TRPA 1), and melastatin (TRPM 1-8) [52, 53]. TRP channels are expressed mainly in neuronal cells, as well as in bronchial epithelium and endothelia, smooth muscle cells, and unmyelinated nociceptive C-type fibers of the lungs [54]. Thermosensitive TRPs (TRTRV1, TRPV2, TRPV4, TRPM3, TRPM8 и TRPA1) constitute the subfamily of TRPs, the representatives of which are activated when temperature changes [55].

Therefore, CB1, CB2, GPCRs (GPR3, GPR6, GPR12, GPR18), TRPs (TRPV1, TRPV2, TRPV3, TRPV4, TRPM8, TRPA1), PPARs (PPAR-α, PPARβ/δ, PPAR-γ), 5-HT1A, 5-HT3, as well as adenosine and glycine receptors, are the targets for endocannabinoids.

Anti-inflammatory effects of endocannabinoids

The complex modes of the action of cannabinoids include their anti-inflammatory and antioxidant effects [23, 27, 28], as well as their ability to modulate immunological processes [22]. The levels of circulating endocannabinoids increase with a number of diseases, the pathogenetic mechanism of which is systemic inflammation [56]. Thus, modulation of endocannabinoid system can have therapeutic potential for multiple pathological conditions [57].

Although the most studied functions of endocannabinoids are associated with the central nervous system and immune processes [22], experimental studies of the last decades confirmed that the transmission of cannabinoid signals is involved in the maintenance of skin homeostasis. Hence. The disorders of skin homeostasis regulation contributes to the development of atopic dermatitis, psoriasis, scleroderma and other skin diseases [6, 8, 9]. CB1 and CB2 are located in keratinocytes, hair follicles, sebaceous glands, sensory neurons, immune system cells and skin fibroblasts [6]. In the experimental study, the CB2 agonist caused the epithelization of skin wounds via increasing the proliferation and migration of keratinocytes [58]. Similarly, in another experiment, the activation of the CB2 receptor limited the infiltration of neutrophils and macrophages and stimulated the proliferation of keratinocytes, thereby contributing to faster wound healing [59]. CB2 agonists lead to a reduction in the production of proinflammatory macrophages M1 and an increase in the number of anti-inflammatory macrophages M2 [59]. The recently developed local inhibitor of the endocannabinoid cell membrane transporter (WOL67-531) minimized allergic manifestations and itching of the skin in the model of atopic dermatitis [60].

CB1, CB2, GPR55 and PPAR-α receptors were revealed in the digestive tract of dogs [4]. Galiazzo et al. demonstrated that these receptors play a protective role in inflammatory intestinal diseases [4]. There are data on a change in the expression of the CB1, CB2 and levels of endocannabinoids in diverticulitis, irritable intestine, inflammatory intestine and colon cancer [5]. Endocannabinoids are capable of acting as double agonists of CB2 and PPAR-γ, leveling off chronic inflammation [3].

In our earlier publication, we covered in detail the role of the endocannabinoid signal system in the pathophysiology of bronchial asthma and obesity [7]. In the bronchi of mice, PPAR-α, CB1 and CB2 receptors are localized [20], with which endocannabinoids interact. CB2 plays an important role in the migration of eosinophils into the respiratory tract [61]. Activation of this receptor type on mast cells has a direct anti-inflammatory effect. The CB2 agonist exhibited a strong anti-inflammatory activity mediated via inhibiting the leukocyte chemoattractant leukotriene B4, prostaglandin E2, thromboxane B2, and prostaglandin F2α [62]. A decrease in CB2 expression maintains chronic inflammation with chronic obstructive pulmonary disease and is accompanied by an increase in the level of proinflammatory cytokines (TNF-α and a transforming growth factor-beta (TGF-β) [63].

The dysfunction of TRP channels constitutes the pathogenetic basis of many inflammatory diseases [40, 53, 54]. The sensitivity of nociceptors is associated with the activity of these channels, the number of which increases significantly in the lungs of patients with bronchial asthma [64]. Chronic inflammation of the respiratory tract and mucus hypersecretion is associated with TRPV1 sensitization [64, 65].

Some studies demonstrated high potential of cannabinoids in the treatment of systemic respiratory infection [33]. For example, CB2 activation limited the infiltration of immune cells into the lungs of animals infected with respiratory syncytial virus and reduced the number of neutrophils and monocytes in the bronchoalveolar lavage. The effects were accompanied by a decrease in the IFN-γ, macrophage inflammatory protein-1α (MIP-1α) and an increase in IL-10 [66].

The increased ratio of polyunsaturated fatty acids (PUFA), ω-6/ω-3, leads to an increase in the levels of AEA and 2-AG, CB1 activity in adipose tissue, pancreas, muscles and liver, and a disorder of the energy homeostasis regulation [67]. Activation of this type of receptors with endocannabinoids helps launching the processes of glucose absorption, adipogenesis, induction of lipogenesis processes, and a reduction in brown adipose tissue thermogenesis [7]. The use of CB1 antagonists is a promising strategy for the treatment of obesity [68].

Thus, the presented data demonstrate high anti-inflammatory potential of endocannabinoids.

Phytocannabinoids

Along with endocannabinoids, phytocannabinoids interact with cannabinoid receptors as well. Phytocannabinoids include THC and CBD, as well as secondary cannabinoids, such as cannabigerolic acid (CBGA) and cannabidiolic acid (CBDA) [10, 39]. Other *Cannabis sativa* L. compounds include cannabigerol (CBG), cannabichromene (CBC), tetrahydrocannabivarin (THCV), cannabicitran (CBT), cannabidivarin (CBDV) and cannabigerivarin (CBGV) [69]. The precursor to all plant cannabinoids is CBGA, which is converted to CBDA, cannabichromenic acid, and Δ-9-tetrahydrocannabinolic acid. These acids form free cannabinoids (CBC, CBD and THC). In addition, *Cannabis sativa* L. contains terpenes, which exhibit a synergistic effect when interacting with cannabinoids [70].

Structurally, THC and CBD are classical cannabinoids [71].

Phytocannabinoids and their receptors are summarized in *Table* 3.

THC binds predominantly to CB1 and, to a lesser extent, to CB2 [19, 31]. It actively influences TRPV2 and has a moderate modulating effect on TRPV3, TRPV4, TRPA1, and TRPM8 [20].

CBD exhibits even lower affinity for CB1 and CB2 receptors than THC. At low concentrations, it even acts as a CB1 and CB2 antagonist [21]. At low concentrations, CBD is a partial agonist of 5-HT1A receptors, while at higher concentrations, it is an inverse agonist [71], as well as a probable PPAR-γ agonist [22]. Besides, CBD is an agonist for TRPV1-4 and TRPA1 and antagonist for TRPM8 [11].

Also, GPR55 and GPR18 are potential targets for phytocannabinoids [10]. THC was identified as a non-selective GPR55 agonist, while CBD blocked this receptor [10]. More recent studies have led to the identification of selective non-cannabinoid GPR55 ligands, including several molecular species of endogenous phospholipids and peptides [17].

CBG, CBDA, CBGA, CBDV, and CBGV act differently on CB1 and CB2 [10]. These phytocannabinoids are agonists; however, they can act as inverse agonists under certain conditions.

Anti-inflammatory effects of phytocannabinoids

THC and its butyl analog, along with Δ-8-tetrahydrocannabinol and Δ-9-tetrahydrocannabivarin, have a psychotropic effect. Contrariwise, CBD, lacking such effect, is capable of changing the action of psychotropic cannabinoids [32, 39]. The therapeutic efficacy of THC is associated with toxicity and a high risk of addiction. The pharmacological effects of THC are close to those of endocannabinoids [57].

An experiment involving the models of systemic inflammation (non-specific ulcerative colitis, Crohn's disease) demonstrated that THC was a suppressor of aberrant immune responses [72]. In addition, THC prevents the development of colorectal cancer associated with colitis. The anticarcinogenic and anti-inflammatory effects of THC are due to the activation of CB2 on immune cells and inhibition of the release of proinflammatory cytokines (IFNγ, TNF-α, IL-17, IL-23 and IL-22) [72]. Interacting with CB2, THC activates the formation of TGF-β1, inducing the production of regulatory T cells (Treg), aimed at suppressing the synthesis of IFNγ and TNFα. Suppression of antigen-presenting cells (APCs) by THC blocks the formation of IL-22 and IL-17. Endocannabinoid levels in patients with ulcerative colitis correlate with clinical parameters and depend on cannabis consumption [73].

Available published data suggest that phytocannabinoids may be effective for the treatment of inflammatory skin diseases [71, 74]. It is known that oral preparations for these diseases are effective only at high doses, causing pronounced side effects [74]. Selective CB2 agonists are effective in the treatment of systemic scleroderma and dermatomyositis. Sublingual administration of THC and CBD reduces pain in epidermolysis bullosa [71]. Topical application of phytocannabinoids is effective in atopic and contact dermatitis and psoriasis [74]. In experimental conditions, it was demonstrated that topical application of THC reduced the activity of allergic inflammation via blocking the production of proinflammatory mediators by keratinocytes [71]. Piomelli et al. demonstrated an ability of THC to inhibit the production of IFN-γ, and the release of proinflammatory chemokines and cytokines independently of cannabinoid receptors [26].

CBD exhibits neuroprotective, antiepileptic, anxiolytic, antidepressant, anti-inflammatory, analgesic, and anticarcinogenic properties [32, 75]. In experimental conditions, the effects of CBD depended on the dose, administration route, and the phase of the inflammatory process [39].

CBD suppresses the expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2), both of which are the invasion pathways for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) localized in the epithelium of the oral cavity, lungs and intestines [76]. The benefits of using CB2 agonists to block the inflammatory response in patients infected with SARS-CoV-2 are discussed in some publications, which is associated with the ability of cannabinoid receptors to reduce the production of proinflammatory cytokines and immune cell proliferation [77]. CBD limits the severity and progression of coronavirus disease (COVID-19) by suppressing the expression of two key receptors for SARS-CoV-2 and a wide range of immunomodulatory and anti-inflammatory effects of this phytocannabinoid [78]. Activation of PPAR-γ in resident alveolar macrophages limits pulmonary inflammation and promotes recovery from viral respiratory infections [51]. As a PPAR-γ agonist, CBD also exhibits antiviral activity and is able to inhibit the development of pulmonary fibrosis [78]. TRP channels partially mediate the effects of CBD on reducing inflammation and pain [11].

It should be noted that a limitation to the clinical use of cannabinoids is the development of side effects (drowsiness, dizziness, speech disorders, memory impairment, drug addiction) at dosages that have therapeutic value [32]. It is likely that the conflicting effects observed in clinical trials using endocannabinoids may be due to the high heterogeneity of their receptors and the complexity of cannabinoid signaling [7]. While promising results from CBD have been identified, its effectiveness is limited by uncertainty regarding its regulatory status and safety in humans [21]. Most studies used significant differences in dosing regimens and administration routes [21]. This determines the high demand for non-endocannabinoid N-acylethanolamines (PEA and OEA), which combine similar effects with high safety [25]. These NAE do not bind to cannabinoid receptors, exerting anti-inflammatory, analgesic, and anorexic effects predominantly via PPARs, GPR55, GPR119, and TRPs [18].

Non-endocannabinoid N-acylethanolamines and their receptors

NAE and their receptors are summarized in *Table 4*. PEA is the most common NAE; it cannot be strictly classified as a classical endocannabinoid, albeit it is often studied in combination with AEA due to similar metabolic pathways of biosynthesis [20, 13]. The mechanism of PEA action is primarily mediated by activation of the PPAR-α nuclear receptor [25, 42]. The results of its interaction with GPR55 [79, 80], GPR119, and TRPV1 [13, 81] are presented.

OEA is a monounsaturated analog of AEA, acting independently of the cannabinoid pathway [82, 83]. OEA activates PPAR-α [81]. It was also demonstrated that OEA binds to GPR119 [84], GPR40 [85], and TRPV1 [86].

Anti-inflammatory effects of non-endocannabinoid N-acylethanolamines

The anti-inflammatory activity of PEA was first described by Ganley and Robinson in 1958 [87]. Further studies demonstrated

that PEA had a favorable effect on neuroinflammation and neurodegeneration, and also has analgesic activity [13, 20, 26].

Several *in vitro* and *in vivo* preclinical studies demonstrated that the biological effects of PEA were caused by its impact on the central and peripheral nervous systems [18, 20, 42, 88]. Currently, PEA is widely used to reduce pain and inflammation [89] and is seen as a promising alternative to exogenous CBD [25]. For example, products and supplements containing PEA (Levagen®, Levagen®+, Normast®, Glialia®, Adolene®, Visimast®, and Pelvilin®) are licensed in various countries as dietary supplements or nutraceuticals, or foods for special medical purposes (FSMPs) at the recommended daily dose of 1200 mg [13, 90, 91].

The anti-inflammatory activity of PEA is implemented through its interaction with PPAR-α, a key regulator of inflammation and pain, which was first demonstrated in 2005 by J. LoVerme et al. [92]. PEA is an endogenous PPAR-α agonist; consequently, blocking the decomposition of PEA by inhibitors of N-acylethanolamine acid amidase (NAAA) leads to activation of the PEA/PPAR-α signaling pathway and control of inflammation and pain [93]. Since chronic pain is associated with the release of NAAA in spinal cord cells, inhibition of this amidase represents a novel approach to the treatment of inflammation and pain [93]. Under experimental conditions, PPAR-α antagonists blocked the protective effects of PEA in neuroinflammation and neurodegeneration [88].

PEA caused an increase in PPAR-α activity during the development of inflammation in the experiment ($P < 0.0001$), while the effects of PEA were blocked by the PPAR-α antagonist, GW6471 [94]. Interestingly, in some animal models, the anti-inflammatory activity of PEA was leveled off by the inverse agonist of the cannabinoid CB2 receptor, SR144528, while PEA did not interact with these receptors and retained its effects in mice lacking CB2 [92]. In addition, SR144528 also blocks the effects of the PPAR-α agonist GW7647. It should be noted that sometimes PPAR-α antagonists do not affect PEA activity, even though they are sensitive to AM630, which is an inverse agonist of the CB2 receptor [95]. Therefore, the effects of PEA mediated by CB2 need further studying. For example, in an experiment, PEA reduced itching and inflammation in skin diseases by activating not only PPAR-α, but also CB2 [96]. The involvement of CB2 in the implementation of the anti-inflammatory action of PEA is rather controversial [79].

In a randomized double-blind controlled trial, D.G. Couch et al. demonstrated that PEA reduced the permeability of the human gastrointestinal tract *in vitro*, *ex vivo* and *in vivo* [94]. This study evaluated the effect of PEA on the absorption of lactulose and mannitol in people taking aspirin. *In vivo*, aspirin increased the absorption of lactulose and mannitol, which was reduced by PEA ($p<0.001$). These results are applicable to diseases associated with increased intestinal permeability, such as inflammatory bowel diseases [94]. In an experimental model of colitis, it was demonstrated as well that exogenous administration of PEA reduced the severity of inflammation and intestinal permeability. It is noteworthy that these effects were accompanied by suppression of GPR55 mRNA, but not by changes in the activities of CB1, CB2, and PPAR-α [97].

The anti-inflammatory effect of PEA is also implemented via GPR55 [79, 80]. E.g., PEA prevents the development of atherosclerosis by promoting switching to the anti-inflammatory phenotype of macrophages due to the activation of GPR55 [79]. Recently, the neuroprotective role of GPR55 in stroke was described both *in vitro* and *in vivo* [80]. Taken together, these data suggest that the neuroinflammation-leveling effects of PEA may be partially mediated by GPR55 activation.

B. Marichal-Cancino et al. proposed that PEA inhibited vasopressor responses to sympathetic stimulation and exogenously administered norepinephrine and induced hypotension through interactions with CB1, TRPV1, and possibly GPR55, but not with CB2 [98]. One of the studies discovered that PEA was also able to prevent the reduction in TRPV1 activity during inflammation ($P<0.0001$) [94].

Oleoylethanolamine (OEA) is anorectic N-acylethanolamine produced in the intestines from dietary fats. It modulates lipid metabolism and insulin secretion via the activation of PPAR-α and GPR119 [85]. The role of OEA in appetite regulation, fat metabolism, and energy homeostasis is well documented [81]. Endocannabinoids stimulate appetite, and lipid and glucose anabolism, thereby increasing body weight, while OEA has the opposite effect due to the activation of PPAR-α [81]. The molecular mechanisms underlying appetite suppression by this NAE remain to be clarified.

Supplements containing OEA mitigate risk factors associated with non-alcoholic fatty liver disease by increasing the level of PPAR-α gene expression [99]. Thus, the use of OEA leads to a decrease in serum levels of triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALT/AST ratio, an increase in high-density lipoprotein cholesterol levels and an improvement in appetite. PPAR-α and GPR119 are important for improving metabolism after bariatric surgery conducted for the treatment of obesity in the experiment (vertical sleeve gastrectomy) [84].

This lipid not only regulates nutrition and body weight by stimulating lipolysis [85], but also has an antitumor effect [100]. There is evidence that OEA protects mice from acute ischemic brain injury by enhancing PPAR-α signaling [101]. During cerebral ischemia, a significant amount of NAE accumulates, but the role of this accumulation is not clear [81, 102]. OEA is used for oral administration in stroke using the nanoparticle-based drug delivery system (NDDS) [82, 83].

Further research is needed to specify the biological activities of PEA and OEA, as well as to develop therapeutic preparations to combat inflammatory diseases.

Conclusion

Over the 20-year period that passed since the discovery of endocannabinoids and cannabinoid receptors, numerous studies were carried out to examine the functions of the endocannabinoid system and explore the therapeutic potential of cannabinoids in various pathologies. However, with a wide range of biological effects, cannabinoids have a number of side effects that limit their therapeutic potential. The discovery of endocannabinoid-like molecules that are saturated or monounsaturated NAE and MAG, and have a similar mechanism of action to cannabinoids but lack their side effects, has shifted scientific interest towards investigating these molecules.

Use of cannabinoids and cannabinoid-like compounds in medicine is actively studied, but the relationship between these compounds and their receptors remains to be clarified. For instance, phytocannabinoids and cannabinoid N-acylethanolamines have similar anti-inflammatory, antimicrobial,

antioxidant and neuromodulatory effects in the course of their interaction with the same receptors: CB1, CB2, PPARs, GPCRs and TRPs. At the same time, non-endocannabinoid N-acylethanolamines do not interact with CB1 and CB2. A growing body of evidence suggests that lipid signaling mediators have similar receptors but act differently and have specific signaling.

PEA and OEA could be more therapeutically promising than cannabinoids. Therefore, further studies are needed to elucidate the molecular mechanisms underlying their biological activity.

Conflict of interest

We declare that we have no conflicts of interest.

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