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The Role of Arachidonic Acid Metabolites (Endocannabinoids and Eicosanoids) in the Immune Processes: A Review

Yulia K. Denisenko, Elena G. Lobanova, Tatyana P. Novgorodtseva, Tatyana A. Gvozdenko, Anna V. Nazarenko

Vladivostok Branch of Far Eastern Scientific Center of Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Treatment, Vladivostok, Russia

Email address
denisenko.imkvl@gmail.com (Y. K. Denisenko)

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Abstract
This review is devoted to the modern concepts of arachidonic acid metabolites – endocannabinoids and eicosanoids. We discussed their biosynthetic pathways, the interaction mechanisms and the role in the immune response. The results of our research on the endocannabinoid system and on the role of eicosanoids in the inflammatory process are given. We found that the synthetic ligands of cannabinoid receptors (WIN 55,212-2 and anandamide) dose-dependently inhibit the lipoxygenase pathway of the pro-inflammatory leukotriene B_4 and the ability of the immune cells to express IL-2, IL-8, and TNF-α. The activities of the immune and the endocannabinoid systems have the reciprocal relationship which is characterized by the decrease in the CB_2 receptor expression and the activation of immune mechanisms. The obtained results on the role of endocannabinoid system in the regulation of the immune response are contributing to the understanding of molecular and cell mechanisms of inflammation development.

1. Introduction

Recently, various signaling pathways regulating the immune response have attracted considerable attention from researchers. The special mediators – endocannabinoids and eicosanoids – play an important role in the cellular and molecular mechanisms of the immune system functioning. These mediators belong to a group of biologically active substances of lipid nature, performing a variety of functions in the body [1-6]. Eicosanoids, their enzymes and receptors are known for their role in the development of many chronic diseases [7-10]. Also, there are some limited data on participation of the endocannabinoid system in the immune processes [11-14].

The substrate for the biosynthesis of eicosanoids and endocannabinoids is formed from phospholipids (PL) containing arachidonic acid (AA) (Fig. 1) [15-17].

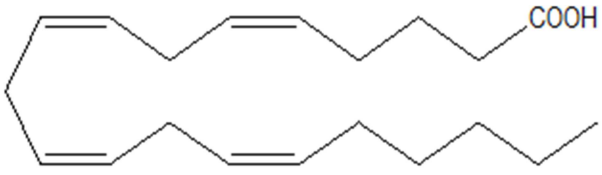


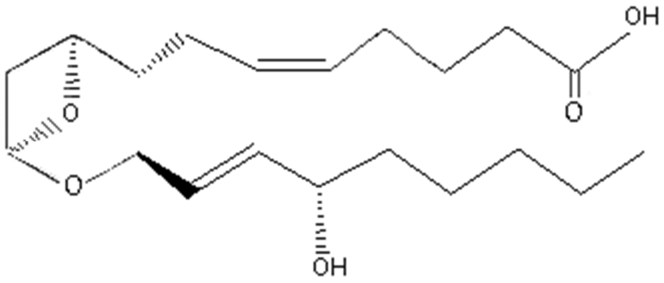
Fig 1. *Arachidonic acid.*

Moreover, endocannabinoids and eicosanoids use the same enzyme systems in metabolism [17]. Taking this into account, we can assume a potential relationship between the signal function of endocannabinoids and eicosanoids, their joint role in the immune processes. However, the attempts to analyze the functions and interactions of these signaling systems led researchers to an ambiguous conclusions. Many questions about the mechanisms of the relationship between the endocannabinoid and eicosanoid-derived second messengers and their functioning in health and disease remain open. This review is devoted to the modern concepts of arachidonic acid metabolites - endocannabinoids and eicosanoids, their biosynthetic pathways, the interaction mechanisms and the role in the immune response.

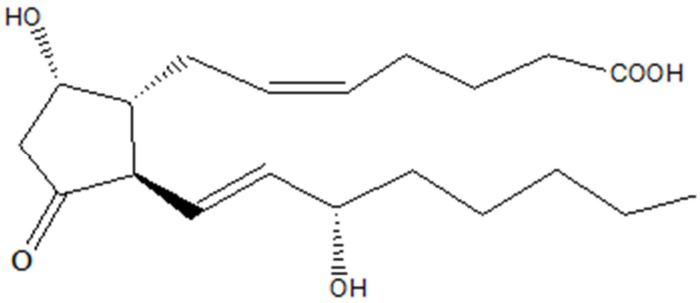
2. Eicosanoid Synthesis

The nature of eicosanoids was determined in 1957, when S. Bergström isolated two new substances from sheep prostate glands and called them prostaglandin F and prostaglandin E (PG). The term prostaglandin was firstly introduced by U. von Euler who won the Nobel Prize in Physiology or Medicine in 1970 for his work on neurotransmitters. In 1964 S. Bergström and D.A. van Dorp proved that the precursor of prostaglandins is an arachidonic acid released from phospholipids [18, 19]. In 1976, Salvador Moncada reported finding of a substance that prevents formation of blood clots and is able to dilate blood vessels. This substance was named prostaglandin I, or prostacyclin.

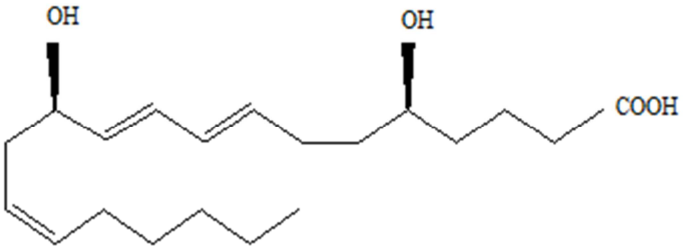
The eicosanoids may be regarded as a large group of molecular mediators, synthesized mainly from arachidonic acid. There are three pathways of AA oxidation: with participation of membrane-bound cyclooxygenase (COX), cytoplasmic lipoxygenases (LOX) and epoxygenases (cytochrome P450-like enzymes) [20, 9, 6, 21]. Depending upon the enzymes involved in the eicosanoid synthesis, we distinguish prostanoids (prostaglandins and thromboxanes - TX), which are metabolized by COX, and leukotrienes (LT), formed under the effect of LOX [22, 23, 24, 25] (Fig. 2).



a) thromboxane A2.



b) prostaglandin D2.



c) leukotriene B_4.

Fig 2. *Eicosanoids: a) thromboxane A_2, b) prostaglandin D_2; c) leukotriene B_4.*

The eicosanoid synthesis via cyclooxygenase begins with the addition of two oxygen molecules to AA and formation of unstable intermediates - endoperoxides. Further, as a result of successive reactions, the endoperoxides can be converted into

prostaglandin-I_2 or prostacyclin (via prostaglandin-I_2-synthase) or into thromboxane A_2 (via thromboxane-A_2-synthase) (Fig. 3). Two isoforms of COX are distinguished: COX-1 and COX-2. It is believed that COX-1 is a constitutive form of COX that regulates the homeostatic functions, whereas the expression of COX-2 occurs during inflammation [25]. The association of COX with an inflammatory response has led to the development of COX-selective inhibitors. Both COX isoforms are inhibited by non-steroidal anti-inflammatory drugs such as aspirin, ibuprofen and indomethacin.

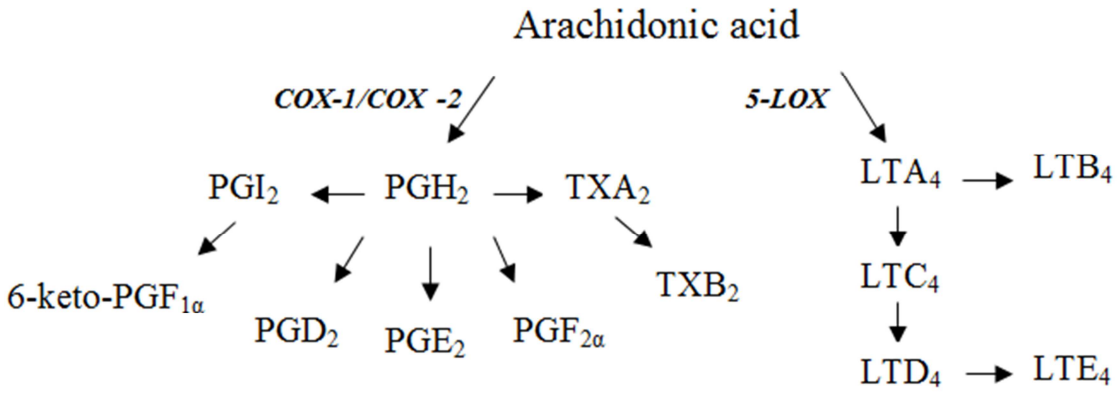


Fig 3. *Cyclooxygenase and lipoxygenase in the arachidonic acid cascade.*

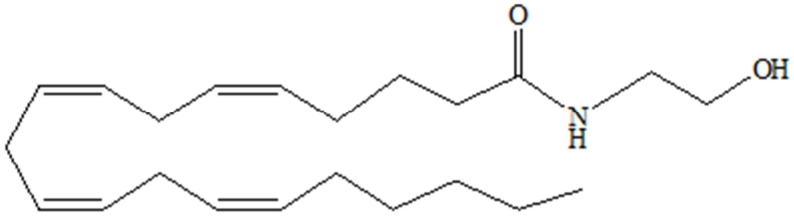
An important role in the AA metabolism is played by 5-lipoxygenase, which forms an unstable compound-leukotrieneA4 [26, 24]. This intermediate compound serves as substrate for two different enzymes: leukotriene A_4 hydrolase and leukotriene C_4 synthase forming leukotrienes B_4 and C_4 respectively. Via gamma-glutamyl transferase leukotriene C_4 is converted to leukotriene D_4, which in its turn is converted to leukotriene E_4 via dipeptidase. In contrast to cyclooxygenase, which is present in the constitutive and inducible forms in most cell types, 5-lipoxygenase is a less common enzyme.

The biologically highly active metabolites of AA include 5,6-, 8,9-, 11,12-and 14,15-epoxyeicosatrienoic and 20-hydroxyeicosatetraenoic acids formed by cytochrome P450 system [21]. Cytochrome P450 is a universal heme-containing monooxygenase, which plays an important role in the oxidation of a number of compounds, both of endogenous (steroids, bile acids, fatty acids, prostaglandins, leukotrienes, biogenic amines) and exogenous origin (drugs, poisons, products of industrial pollution, pesticides, carcinogens, mutagens, and others). Monooxygenase metabolites of AA exert a wide range of actions and often have a multidirectional activity [7].

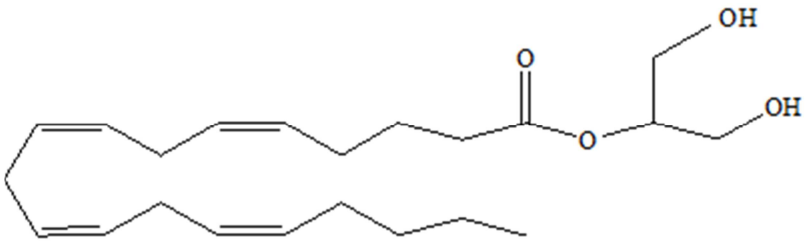
3. Synthesis of Endocannabinoids

Scientific interest in the cannabinoids increased in the 1960s, when Δ9-tetrahydrocannabinol (THC), a component of cannabis, was discovered [27]. In 1988, Devane with coworkers succeeded to detect in the rat brain tissue some specific binding sites for THC, the so-called cannabinoid receptor type 1 (CB_1) [28]. CB_1 was cloned by Matsuda et al. in 1990 [29]. The cannabinoid receptor type 2 (CB_2) was identified in 1993[30]. Subsequently, it was shown that the cannabinoid CB_1 receptors are localized in the structures of the peripheral and central nervous system and involved in the processes of conducting and perception of nociceptive signals. CB_2 receptors are expressed primarily on immune modulating cells, where they mediate an immunomodulatory effect [30-32].

The identification of the cannabinoid receptor ligands was the next stage in the study of the mechanisms of cannabinoids action. In 1992, it was shown that the ethanolamide of arachidonic acid (arachidonoyl ethanolamide) or anandamide is an endogenous ligand of the cannabinoid receptors [28] (Fig. 4a). In 1995, the second cannabinoid receptor ligand, 2-arachidonoylglycerol (2-AG), was discovered [33, 34] (Fig. 4b).



a) anandamide.



b) 2-arachidonoylglycerol (2-AG).

Fig 4. *Endocannabinoids: a) anandamide and b) 2-arachidonoylglycerol (2-AG).*

The main biosynthetic pathway for anandamide begins with N-arachidonoyl phosphatidylethanolamine metabolized by N-acyl-phosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) [35] (Fig. 5).

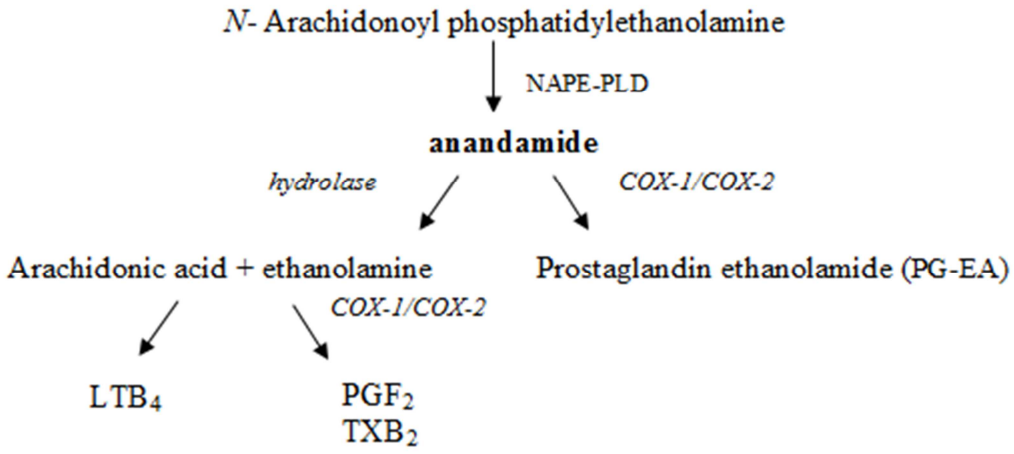


Fig 5. *Metabolism of anandamide.*

The degradation of anandamide and other fatty acid amides leads to the formation of AA, which serves as a substrate for the biosynthesis of eicosanoids [36].

The hydrolysis of AA-containing phospholipids (primarily phosphatidylinositol, the richest in AA content) by phospholipase C leads to the formation of diacylglycerol, which is subsequently metabolized via lipase to2-arachidonoylglyceroland further to AA [2, 34] (Fig. 6).

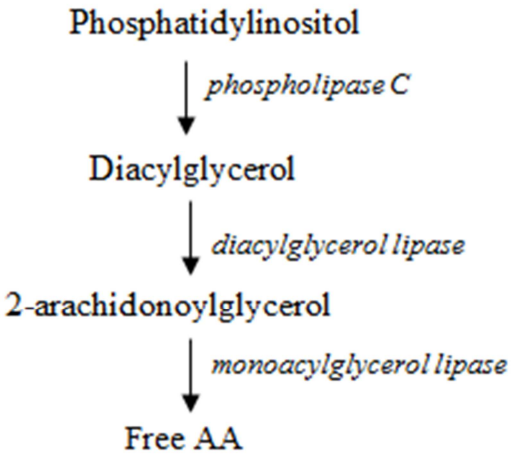


Fig 6. *Synthesis of 2-arachidonoylglycerol.*

4. The Relationship of the Metabolic Pathways in the Biosynthesis of Endocannabinoids and Eicosanoids

Previously, it was believed that the metabolisms of eicosanoids and endocannabinoids occur independently of one another. This suggested an involvement of unrelated enzyme systems. However, phospholipases initiating the biosynthesis of eicosanoids and endocannabinoids are activated by identical secondary messengers (e.g., through an increase in the level of intracellular Ca^{2+}). Very probably, this may cause simultaneous initiation of the formation of signaling molecules [37, 38, 39]. Hampson et al. were the first to demonstrate the ability of LOX-12 to use either arachidonic acid or anandamide as a substrate [40]. The anandamide metabolizes to 12-hydroxyeicosatetraenoic acid ethanolamide (12-HETE-EA) via LOX-12. Besides, LOX-12 uses both AA and anandamide as a substrate with the same efficiency. The ability to metabolize anandamide was revealed also for LOX-15 [41]. Yu et al. have shown the ability ofCOX-2 (but not COX-1) to oxidize fatty acids ethanolamides [42]. The experiments with carrageenan-induced paw edema in rats showed that inhibition of COX-2 results in the accumulation of anandamide. This proved participation of COX-2 in endocannabinoid oxygenation. There is evidence that the converted 2-AG and anandamide are not ligands for the

cannabinoid receptors in COX-2 reactions. Oxidized COX-2- or LOX-endocannabinoids exert biological activity via specific receptors. However, only receptors for prostanoid ligands are characterized [43].The identification of the specific receptors for oxidized endocannabinoids is a main task in clarifying the mechanisms of their action. In future, the determination of their physiological role and functioning at various pathological conditions, and, at last, the identification of the specific receptor blockers for oxidized endocannabinoid ligands will provide new pharmacological directions and ways for therapeutic strategies. The available evidence supports the hypothesis that the oxygenation provides a mechanism for modulating the activity of the endocannabinoid system. A decrease in the level of anti-inflammatory endocannabinoids might be one of mechanisms for the pro-inflammatory action of COX-2.

The first evidence of the affinity of anandamide and cytochrome P450 was obtained in 1993 [44]. It was shown that cytochrome P450 3A and 2D6 are able to metabolize anandamide. There is no data on involvement of cytochrome P450 in degradation of 2-AG.

It is known that cannabinoids, and anandamide in particular, stimulate secretion of arachidonic acid and its metabolites [45, 46]. As noted above, anandamide hydrolysis produces free AA, which can be converted to eicosanoids in cyclooxygenase or lipoxygenase reactions (Fig. 7, path A). Furthermore, endocannabinoids themselves can be exposed to the action of COX or LOX, which also leads to the formation of eicosanoids (Fig. 7, path B) [13]. Consequently, the source of AA for the eicosanoid synthesis may be not only AA-containing phospholipids but also cannabinoids. Perhaps, both reactions play an equivalent role in the synthesis of eicosanoids.

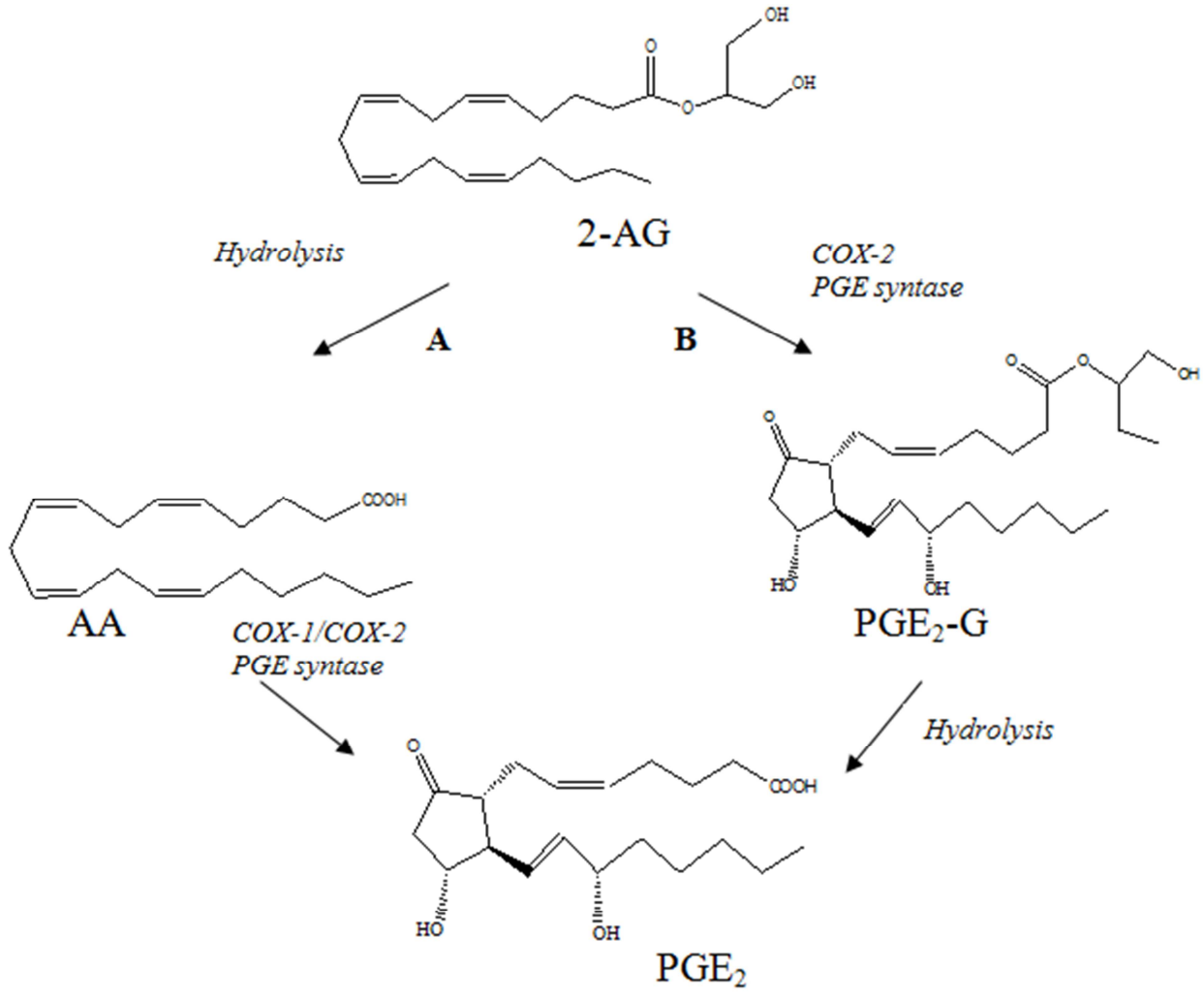


Fig 7. *Metabolism of 2-arachidonoylglycerol (2-AG).*

We have studied the dose-dependent effect of the synthetic cannabinoid receptor ligands WIN 55,212-2 and anandamide on the synthesis of eicosanoids – leukotriene B_4 and thromboxane B_2 – in blood cells in vitro [47]. It has been established that the synthetic ligands of cannabinoid receptors dose-dependently inhibit the lipoxygenase pathway of the pro-inflammatory leukotriene B_4 – and thus suppress the activity of immune system. Low concentrations of WIN 55,212-2 and anandamide (0.1 and 1.0μM, respectively) had no effect on the levels of leukotriene B_4.The administration of 3.0 μM WIN 55,212-2 and anandamide reduced the levels of leukotriene B_4. The greatest inhibitory effect on the

production of pro-inflammatory eicosanoids by blood cells was detected at 10.0 μM concentration. So, the production of leukotriene B_4 was reduced by 83% ($p<0.001$) after 10.0 μM WIN55,212-2 and by 67% ($p<0.001$) after 10.0 μM anandamide. Consequently, 10.0 μM WIN55,212-2 inhibit the synthesis of leukotriene B_4 in blood cells at a greater extent than anandamide. However, WIN 55,212-2 and anandamide had no effect on the synthesis of thromboxane B_2 by blood cells.

The obtained experimental data suggest that the synthetic cannabinoids are able to inhibit the lipoxygenase pathway of eicosanoid biosynthesis, and thus inhibit the formation of the proinflammatory mediator – leukotriene B_4. Apparently, the mechanisms of thromboxane synthesis do not involve the endocannabinoid system. S. Diaz [48] demonstrated the ability of cannabinoids (Δ9-tetrahydrocannabinol) to activate the metabolism of arachidonic acid by the lipoxygenase pathway. Though this effect is realized only at sufficiently high concentrations of the endocannabinoids (32.0μM), which is not realistic to implement under physiological conditions. The controversial data on the effect of endocannabinoids on fatty acid metabolism and eicosanoid synthesis is due to different experimental doses and chemical structure of cannabinoids. In addition, the effect of the synthetic cannabinoid receptor ligands on the synthesis of proinflammatory mediators has a pronounced dose-dependent character. These studies demonstrate the ability of the endocannabinoid system to regulate the activity of the synthesis of pro-inflammatory eicosanoids.

An evident relationship of enzymatic pathways of the biosynthesis of arachidonic acid metabolites suggests their functional overlapping.

5. The Role of Arachidonic Acid Metabolites in Immune Processes

In contrast to cannabinoids, the biological effects of eicosanoids were discovered simultaneously with the establishment of their structure. It is known that the eicosanoids are secondary messengers of hydrophilic hormones. They control smooth muscle contraction (blood vessels, bronchi, uterus), are involved in the release of the products of intracellular synthesis (hormones, mucoids). Eicosanoids affect bone tissue metabolism, the peripheral nervous system, the immune system, the movement and aggregation of cells (leukocytes and thrombocytes), nociceptive processing. They can act as local bioregulators for cells synthesizing them (autocrine effect) and for neighboring cells (paracrine effect) by binding to membrane receptors. In some cases, their action is mediated by cAMP and cGMP [9, 49, 10].

Under pathological conditions, the levels of eicosanoids increase dramatically [10]. In chronic inflammatory diseases (bronchial asthma, rheumatoid arthritis, ulcerative colitis, psoriasis, eczema, etc.) the leukocytes accumulated in the focus of inflammation express great amounts of various enzymes, including phospholipase A_2. This causes a release of AA, rapidly metabolizing to eicosanoids. Eicosanoids, in their turn, cause an increased vascular permeability, exudation of the liquid portion of blood into the extracellular space, and tissular edema, increased blood flow and tissue hyperemia, fever, and an increased migration of leukocytes into the focus of inflammation -all this causes even a greater release of phospholipase A_2, and further maintenance of inflammation.

Eicosanoids play an important role in the development of non-specific systemic inflammatory reaction [8]. So, the leukotrienes are mediators of the allergic and inflammatory processes, and they are synthesized directly by leukocytes. An increased leukotriene synthesis occurs mainly at immediate-type allergic reaction sand begins after the binding of antigen to IgE, presented on these cells' surface[26, 7].The biological action of leukotriene B_4 is mediated by the B-LT-receptor [7].

Prostaglandin D_2 (PGD_2) is the first product of the arachidonic acid oxidation by the cyclooxygenase pathway, which plays a key role in immediate type allergic reactions and inflammation [19]. It is formed primarily in mast cells. The advent of prostaglandin D_2 in the serum indicates the degranulation of mast cells and the development of the early phase of immediate allergic reactions. The intradermal administration of PGD_2 causes vasodilation and increased vascular permeability, which leads to the persistent redness, blister formation and the exit of leukocytes, lymphocytes and monocytes from the vascular bed [50]. The inhalation of PGD2causes bronchoconstriction, indicating an important role of this AA metabolite in the pathogenesis of anaphylactic reactions and systemic mastocytosis.

The biological functions of endocannabinoids are also very diverse. Endocannabinoids regulate the nervous, endocrine, sexual, and immune systems; they are involved in the coordination of movements, in the maintenance of a constant body temperature, and in the formation of memory and appetite processes [51-53, 1, 3, 54-57].

The suppression of the immune response by natural cannabinoids has been shown in several studies [48, 58]. Cannabinoids reduce the overall resistance to bacterial and viral infections, lymphocyte proliferation, antibody synthesis, the activity of natural killer cells and macrophages. At the molecular level, these effects are explained by decreased synthesis of interferon, the tumor necrosis factor-α (TNF-α), and interleukin (IL-2) [12, 59]. Rockwell et al. showed that 2-AG anandamide inhibit the secretion of IL-2 inactivated T-cells. At the same time, it was shown that natural cannabinoids cause an increase rather than a decrease in the supernatant IL-1 activity and increased proliferation of B-lymphocytes [13]. All these data suggest a complex nature of modulation of the immune response by cannabinoids.

CB_2 receptor ligands inhibit the signaling pathway, triggering activation of the toll-like receptor complex CD14 / TLR4 / MD2, that leads to expression of proinflammatory cytokines (IL-1β, IL-6, IL-8 and TNF-α) and induction ofTH1 immune response [17].

Our *in vitro* studies on the effect of WIN 55,212-2 and

anandamide synthetic cannabinoid receptor ligands on cytokines synthesis by the immunecompetent cells [60-62] have shown that cannabinoids inhibit the ability of the immune cells to express IL-2, IL-8, and TNF-α. The revealed effects indicate the immunomodulatory ability of cannabinoids. At the same time, the question remains open: what mechanism is responsible for the regulation of the immune system, whether the immune system is controlled through a direct effect of cannabinoids on the synthesis of pro-inflammatory mediators or through an indirect impact via cannabinoid CB receptors? Because it has been reported that cannabinoids implement their many effects via a receptor-independent pathway [63].

As it was noted above, the endocannabinoid system contains receptors of two main types: CB_1 receptors that are mostly expressed in the brain and spinal cord and are responsible for the motor and cognitive functions, and, secondly, the cannabinoid CB_2 receptors [28, 30]. According to the literature data, it is known that the CB2receptors are mainly localized in the membranes of the immune cells, where they mediate an immunoregulatory effect [11]. Our research has also shown that CB_2 receptors are located on immune cells. But CB_1 receptors have not been found on cells of the immune system. A flow cytometric analysis of the CB_2 receptor in immunecompetent cells showed that the normal content ofCB_2- receptor is not below 90% [64].

To determine the role of the CB_2 receptor in the regulation of the immune response, we simulated the conditions of activation of the immune system. The immune system was stimulated *in vivo* by intracorporeal irradiation of the blood and by enrichment of the blood with an ozone-oxygen mixture. The induction of the immune system cells *in vivo* by intracorporeal irradiation led to a decrease to 60% in the number of cells with the CB_2 receptors [64]. The intravenous administration of an ozone-oxygen mixture resulted in reduction of the number of cells with the CB_2 receptors to 70%. So, the activation of the immune system is accompanied by a decrease in the number of cells expressing the endocannabinoid CB_2 receptor. A reduced expression of the CB_2 receptor in immune cells can be mediated by blockade of endogenous cannabinoids synthesized *de novo*, triggering the limiting of the function of the cannabinoid system and thereby activating the immune system. Under normal conditions, the over expression of the cannabinoid receptor CB_2 leads to the maintenance of the physiological balance in the synthesis of pro-inflammatory and anti-inflammatory mediators. The pooled results of the study suggest that blockade of the CB_2 receptor expression in the development of the immune response is an important mechanism for the regulation of the inflammatory process and prove a reciprocal relationship between the activities of the immune and the endocannabinoid systems. New data on the role of the endocannabinoid system in the regulation of the immune response contribute significantly to the study of cellular and molecular mechanisms in the development of an inflammatory response.

6. Conclusion

Thus, the metabolites of arachidonic acid are involved in the regulatory mechanisms of the immune-metabolic response of the cell; they mediate the intensity of the inflammatory processes. The relationship between the metabolism of endocannabinoids and eicosanoids implies their cross-functioning and an interactive regulation. Further research in this area will enhance understanding of the cellular and molecular mechanisms of signal communication and the intersystem integration of the components of the endocannabinoid and eicosanoid systems and so would help in developing innovative technologies for control of their functions.

Abbreviations

PL, phospholipids; AA, arachidonic acid; PG, prostaglandin; COX, cyclooxygenase; LOX, lipoxygenase; TX, thromboxane; LT, leukotriene; THC, Δ^9-tetrahydrocannabinol; CB_1, cannabinoid receptor type 1; CB_2, cannabinoid receptor type 2; 2-AG, 2-arachidonoylglycerol;TNF-α, tumor necrosis factor-α; IL, interleukin.

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Authors' Contributions

All authors have made substantial contributions to this work. YKD and EGL were responsible for the initial conception and design of the manuscript. YKD wrote the first draft of the manuscript. EGL carried out laboratory investigations. TPN contributed to drafting and final corrections of the manuscript. TPN and TAG supported literature research and participated in critical revision of the manuscript. AVN made final corrections of the manuscript. All the authors read and approved the final manuscript.

References

[1] Battista N, Tommaso M, Bari M, Maccarrone M: The endocannabinoid system: an overview. *Front Behav Neurosci* 2012, 6:9.

[2] Di Marzo V: Endocannabinoids: synthesis and degradation. *Physiol Biochem Pharmacol* 2008, 160:1289–1296.

[3] Fonseca RF, Arco DI, Bermudez-Silva FJ: The endocannabinoid system: physiology and pharmacology. *Alcohol* 2005, 40(1):2-14.

[4] Gertsch J, Leonti M, Raduner S, Racz I, Chen JZ, Xie XQ, Altmann KH, Karsak M, Zimmer A:Beta-caryophyllene is a dietary cannabinoid. *PNAS* 2008, 105(26):9099-9104.

[5] Mechoulam R, Fride E, Di Marzo V: Endocannabinoids. *Eur J Pharmacol* 1998, 359:1-18.

[6] Smith ML, Murphy RC: The eicosanoids: cyclooxygenase, lipoxygenase and epoxygenase pathways. In *Biochemistry of lipids, lipoproteins and membranes.* 4th edition. Edited by Vance DE, Vance JE. Amsterdam: Elsevier Science; 2002:341-371.

[7] Funk CD: Prostaglandins and leukotrienes: advances in eicosanoid biology.*Science*2001, 294:1871-1875.

[8] Gilroy DW: Eicosanoids and the endogenous control of acute inflammatory resolution. *Int J Biochem Cell Biol* 2010, 42(4):524-528.

[9] Samuelsson B, Goldyne M, Granström E, Hamberg M, Hammarström S, Malmsten C: Prostaglandins and thromboxanes. *Annu Rev Biochem* 1978, 47:997-1029.

[10] Tapiero H, Nguyen B, Couvreur G: Polyunsaturated fatty acids (PUFA) and eicosanoids in human health and pathologies. *Biomed. Pharmacother*. 2002, 56:215–222.

[11] Galiègue S, Mary S, Marchand J, Dussossoy D, Carrière D, Carayon P, Bouaboula M, Shire D, Le Fur G, Casellas P: Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *Eur J Biochem* 1995, 232:54-61.

[12] Katona S, Kaminski E, Sanders H, Zajicek J: Cannabinoid influence on cytokine profile in multiple sclerosis. *Clin Exp Immunol* 2005, 140(3):580–585.

[13] Klein TW, Newton C, Friedman H: Cannabinoid receptors and the cytokine network. *Adv Exp Med Biol* 1998, 437: 215-222.

[14] Márquez L, Abanades S, Andreu M: Endocannabinoid system and bowel inflammation. *Med. Clin.(Barc)* 2008, 131(13):513-517.

[15] Sergeeva MG, Varfolomeeva AT: *Arachidonic acidcascade.* Moscow: Public education; 2006.

[16] Brash AR: Arachidonic acid as a bioactive molecule. *J Clin Invest* 2001, 107:1339-1345.

[17] Rouzer CA, Marnett LJ: Endocannabinoid Oxygenation by Cyclooxygenases, Lipoxygenases, and Cytochromes P450: Cross-Talk between the Eicosanoid and Endocannabinoid Signaling Pathways. *Chem Rev* 2011, 111(10):5899–5921.

[18] Bergström S, Danielsson H, Samuelsson B: Enzymic formation of prostaglandin E_2 from arachidonic acid. *Biochim Biophys Acta* 1964, 90:207-210.

[19] Van Dorp DA, Beerthuis RK, Nugeteren DH, Vonkeman H: The biosynthesis of prostaglandins.*Biophys Acta* 1964, 90:204-207.

[20] Giuffrida A, Beltramo M, Piomelli D: Mechanisms of Endocannabinoid Inactivation: Biochemistry and Pharmacology. *J Pharmacol Exp Ther* 2001, 298:7-14.

[21] Spector AA: Arachidonic acid cytochrome P450 epoxygenase pathway. *J Lipid Res* 2009, 50:59–65.

[22] Goldyne ME, Burrish GF, Poubelle P, Borgeat P: Arachidonic acid metabolism among human mononuclear leukocytes. Lipoxygenase-related pathways. *J Biol Chem* 1984, 259:8815–8819.

[23] Lewis RA, Austen KF, Soberman RJ: Leukotrienes and other products of the 5-lipoxygenase pathway. Biochemistry and relation to pathobiology in human diseases. *N Eng. J Med* 1990, 323:645-655.

[24] Murakami M: Regulation of prostaglandin E2 biosynthesis by inducible membrane-associated prostaglandin E2 synthase that acts in concert with cyclooxygenase-2. *J Biol Chem* 2000, 275:783-792.

[25] Smith WL, Garavito RM, DeWitt DL: Prostaglandin endoperoxide H synthases (cyclooxygenases)-1 and -2. *J Biol Chem* 1996, 271:157-160.

[26] Dixon RA: Requirement of a 5-lipoxygenase-activating protein for leukotriene synthesis. *Nature* 1990, 343:282–284.

[27] Gaoni Y, Mechoulam R: Isolation, structure and partial synthesis of an active constituent of hashish. *J Am Chem Soc* 1964, 86:1646-1647.

[28] Devane WA, Dysarz FA 3rd, Johnson MR, Melvin LS, Howlett AC: Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol* 1988, 34:605-613.

[29] Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI: Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 1990, 346:561-564.

[30] Munro S, Thomas KL, Abu-Shaar M: Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 1993, 365:61-65.

[31] Farquhar-Smith WP, Jaggar SI, Rice AS: Attenuation of nerve growth factor-induced visceral hyperalgesia via cannabinoid CB_1 and CB_2-like receptors.*Pain*2002, 97:11-21.

[32] Pertwee RG, Ross RA: Cannabinoid receptors and their ligands. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2002, 66(2,3):101-121.

[33] Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, Gopher A, Almog S, Martin BR, Compton DR, Pertwee RG, Griffin G, Bayerwitch M, Barg J, Vogel Z: Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol* 1995,50:83-90.

[34] Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, Yamashita A, Waku K: 2-Arachidonoylgylcerol: A Possible Endogenous Cannabinoid Receptor Ligand in Brain. *Biochem Biophys Res Commun* 1995, 215:89-97.

[35] Wang J, Ueda N: Biology of endocannabinoid synthesis system. *Prostaglandins & Other Lipid Mediators* 2009, 89:112-119.

[36] Cravatt BF, Demarest K, Patricelli MP, Bracey MH, Giang DK, Martin BR, Lichtman AH: Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. *Proc Natl Acad Sci USA* 2001, 98(16):9371-9376.

[37] Brenowitz SD, Regehr WG: Calcium dependence of retrograde inhibition by endocannabinoids at synapses in to purkinje cells. *J Neurosci* 2003, 23:6373-6384.

[38] Cadas H, Gaillet S, Beltramo M, Venance L, Piomelli D:Biosynthesis of an endogenous cannabinoid precursor in neurons and its control by calcium and cAMP. *J Pancreas* 2004, 5:41-43.

[39] Ueda N, Yamamoto K, Yamamoto S, Tokunaga T, Shirakawa E, Shinkai H, Ogawa M, Sato T, Kudo I, Inoue K, Takizawa H, Nagano T: Lipoxygenase-catalyzed oxygenation of arachidonylethanolamide, a cannabinoid receptor agonist. *Biochim Biophys Acta* 1995, 1254:127-134.

[40] Hampson AJ, Hill WA, Zan-Phillips M, Makriyannis A, Leung E, Eglen RM, Bornheim LM: Anandamide hydroxylation by brain lipoxygenase:metabolite structures and potencies at the cannabinoid receptor. *Biochim Biophys Acta* 1995, 16:173-179.

[41] Forsell PK, Brunnström A, Johannesson M, Claesson HE: Metabolism of anandamide into eoxamides by 15-Lipoxygenase-1 and glutathione transferases. *Lipids* 2012,47(8):781-791.

[42] Yu M, Ives D, Ramesha CS: Synthesis of Prostaglandin E2 Ethanolamide from Anandamide by Cyclooxygenase - 2. *J Biol Chem* 1997, 272 : 21181- 21186.

[43] Narumiya S, Fitzgerald GA: Genetic and pharmacological analysis of prostanoid receptor function. *J Clin Invest* 2001, 108:25 - 30.

[44] Bornheim LM, Kim KY, Chen B, Correia MA: The effect of cannabidiol on mouse hepatic microsomal cytochrome P450 - dependent anandamide metabolism. *Biochem Biophys Res Commun* 1993, 197: 740- 746.

[45] Berdyshev EV, Boichot E, Germain N, Allain N, Anger JP, Lagente V: Influence of fatty acid ethanolamides and Δ9-tetrahydrocannabinol on cytokine and arachidonate release by mononuclear cells. *Eur J Pharmacol* 1997, 330: 231-240.

[46] Racz I, Göthert M, Zimmer A: Anandamide effects on 5-HT3 receptors *in vivo. Europ J Pharmacol* 2008, 596:98-101.

[47] Lobanova EG: Effect of syntheticcannabinoid receptorligandson the expression of eicosanoids *in vitro*. *Bull RAMS* 2012, 32(2) : 5- 8.

[48] Diaz S, Specter S, Volanderhoek JY,Coffey RG:The effect of delta-9-tetrahydrocannabinol on arachidonic acid metabolism in human peripheral blood mononuclear cells. *J Pharmacol Exp Ther* 1994, 268:1289–1296.

[49] Soberman RJ, Christmas P: The organization and consequences of eicosanoid signaling. *Clin Invest* 2003, 111(8):1107-1113.

[50] Snider NT, Kornilov AM, Kent UM, Hollenberg PF: Anandamide Metabolism by Human Liver and Kidney Microsomal Cytochrome P450 Enzymes to Form Hydroxyeicosatetraenoic and Epoxyeicosatrienoic Acid Ethanolamides. *J Pharmacol Exp Ther* 2007, 321: 590-597.

[51] Krylatov AV, Uzhachenko RV, Maslov LN, Ugdyzhekova DS, Bernatskaia NA, Pertwee R, Stefano GB, Makriyannis A: Anandamide and R-(+) metanandamid prevent the development of ischemic and reperfusion arrhythmias in rats by stimulating the CB_2 receptor *Eksp Klin Farmakol* 2002,3:6-9.

[52] Churyukanov MV, Churyukanov VV: Functional organizationand the therapeutic potential of the endogenous cannabinoid system. *Experand clinicalpharmacology* 2004, 67(2): 70- 78.

[53] Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Huffman JW, Layward L: Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* 2000, 404:84-87.

[54] Habayeb OM, Taylor AH, Bell SC, Taylor DJ, Konje JC: Expression of the endocannabinoid system in human first trimester placenta and its role in trophoblast proliferation. *Endocrinology* 2008, 149(10):5052–5060.

[55] Hiley CR: Endocannabinoids and the heart. *J CardioVolasc Pharmacol* 2009, 53(4):267–276.

[56] Pertwee RG: Pharmacological actions of cannabinoids. In: *Cannabinoids. Handbook of Experimental Pharmacology.* Heidelberg, Springer-Verlag; 2005, 168:1-51.

[57] Robson P: Therapeutic aspects of cannabis and cannabinoids.*Br J Psychiatry* 2001, 178:107-115.

[58] Farquhar-Smith WP, Rice AS:Administration of endocannabinoids prevents a referred hyperalgesia associated with inflammation of the urinary bladder. *Anesthesiology* 2001, 94:507-513.

[59] Edgemond WS, Hillard CJ, Falck JR, Kearn CS, Campbell WB: Human platelets and polymorphonuclear leukocytes synthesize oxygenated derivatives of arachidonylethanolamide (anandamide): their affinities for cannabinoid receptors and pathways of inactivation. *Mol Pharmacol*. 1998, 54(1):180-8.

[60] Lobanova (Isachenko) EG, Vitkina TI, Berdyshev EV: The influence of ligands of cannabinoid receptors WIN 55, 212 – 2 and anandamide on TNF-a production, and IL-8 blood leukocytes of healthy individuals and patients with allergy. *Immunopathology, Allergology, Infectology* 2003, 2:86-91.

[61] Lobanova EG: *Effect of cannabinoid receptor ligands on the reactivity of immune cells*. Germany: Lambert Academic Publishing; 2011.

[62] Lobanova EG: Effect of synthetic cannabinoid receptor ligands on the reactivity of immune cells *in vitro*. *Med Immunology* 2009, 11(2-3):261-264.

[63] Bueb JL, Lambert DM, Tschirhart EJ: Receptor-independent effects of natural cannabinoids in rat peritoneal mast cells *in vitro*. *Biochim Biophys Acta* 2001, 1538:252-259.

[64] Lobanova EG: Role of endocannabinoid receptors in the regulation of immune response. *Med Immunology* 2012, 14(3) :189-194.