INTERNAL DISEASES

LYSOPHOSPHATIDIC ACID AND ITS RECEPTORS: ROLE IN BRONCHIAL ASTHMA PATHOGENESIS

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ABSTRACT

Lysophosphatidic acid (LPA) is a biologically active lipid mediator that regulates a number of signaling pathways involved in the pathogenesis of bronchial asthma. Attention to studying the relationship of LPA with LPA receptors (LPARs) and ion channels with transient receptor potential (TRP) is caused by their role in the initiation and development of bronchial obstruction, which suggests the development of new effective strategies for the treatment of bronchial asthma through blocking LPA synthesis and/or regulation of the activity of the ligand-receptor relationship.
The aim of the review. *To summarize ideas on the role of lysophosphatidic acid and its receptors in the pathogenesis of bronchial asthma based on the analysis of articles published in English in 2020–2023 from the PubMed database.*
Conclusion. *The review summarizes recent literature data on the chemical structure, biosynthetic pathways and LPA receptors. It presents the information on the role of LPA, LPARs and TRP channels in the pathogenesis of bronchial asthma; summarizes the bronchial asthma therapeutic strategies targeting LPA, LPARs, and TRP channels. The review highlights not only a new perspective on understanding the mechanisms of initiation of asthmatic reactions, but also possible ways to manage them at the stage of correction of their development.*

Key words: *lysophosphatidic acid, lysophosphatidic acid receptors, transient receptor potential channels, bronchial asthma*

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РОЛЬ ЛИЗОФОСФАТИДНОЙ КИСЛОТЫ И ЕЁ РЕЦЕПТОРОВ В ПАТОГЕНЕЗЕ БРОНХИАЛЬНОЙ АСТМЫ

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РЕЗЮМЕ

Лизофосфатидная кислота (LPA, lysophosphatidic acid) является биологически активным липидным медиатором, регулирующим ряд сигнальных путей, вовлечённых в патогенез бронхиальной астмы (БА). Интерес к изучению взаимоотношений LPA с LPA-рецепторами (LPARs, lysophosphatidic acid receptors)и ионными каналами с транзиторным рецепторным потенциалом (TRP, transient receptor potential) обусловлен их ролью в инициации и развитии бронхиальной обструкции, что предполагает разработку новых эффективных стратегий лечения БА через блокирование синтеза LPA и/или регуляции активности лиганд-рецепторного взаимоотношения.

Цель обзора. *Обобщить представления о роли лизофосфатидной кислоты и её рецепторов в патогенезе бронхиальной астмы на основании анализа статей, опубликованных на английском языке в период с 2020 по 2023 г. в базе данных PubMed.*

Заключение. *В данном обзоре обобщены последние литературные данные о химической структуре, путях биосинтеза и рецепторах LPA. Представлена информация о роли LPA, LPARs и TRP-каналов в патогенезе БА. Обобщены терапевтические стратегии БА, нацеленные на LPA, LPARs и TRP-каналы. Данный обзор подчёркивает не только новый взгляд на понимание механизмов инициации астматических реакций, но и возможные способы управления ими на этапе коррекции их развития.*

Ключевые слова: *лизофосфатидная кислота, рецепторы лизофосфатидной кислоты, ионные каналы с транзиторным рецепторным потенциалом, бронхиальная астма*

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INTRODUCTION

Lysophospholipids are bioactive lipid mediators localised in cell membranes [1]. They affect cell proliferation, differentiation, survival, migration, adhesion, invasion and morphogenesis, and are associated with neurogenesis, angiogenesis, fibrogenesis and oncogenesis [2]. In recent years, the signalling function of lysophospholipids, in particular lysophosphatidic acid (LPA), has been actively studied in various diseases and pathological conditions. However, not much attention has been paid to the study of the role of LPA in the pathogenesis of bronchopulmonary diseases, particularly bronchial asthma [3-5].

LPA is known to interact with LPA receptors 1-6 (LPARs), peroxisome proliferator-activated nuclear receptors (PPARs), actin-binding proteins (ABPs) and, as recently discovered, ion channel receptors with transient receptor potential (TRP), resulting in the activation of multiple signalling pathways [2, 4, 6, 7].

The role of LPA receptors in the pathogenesis of asthmatic reactions has been actively studied [3], but in recent years the focus of research has shifted significantly to the interaction of LPA with TRP-channel receptors [8, 9]. Malfunction of these channels is known to have a significant impact on the pathogenesis of bronchial obstruction, which makes them potential targets in bronchial asthma treatment [10-18]. LPA has been identified as a ligand for TRP receptors and its ability to modulate the activity of TRPM2 (TRP cation channel, subfamily M, member 2), TRPV1 (TRP cation channel, subfamily V, member 1) and TRPA1 (TRP cation channel, subfamily A, member 1) has been described [3, 19].

After the mechanism of interaction of LPA with LPARs and TRP receptors in the bronchopulmonary system has been established a new perspective on understanding the mechanisms of initiation of asthmatic reactions and possible ways to manage them is being discovered, which suggests fundamentally new possibilities in the development of an effective therapeutic strategy for bronchial asthma at the stage of correction of the development of asthmatic reactions.

Controlling LPA signalling through influencing LPAR1-6 is a relevant pharmacological objective [20]. However, LPA signalling via its receptors is also associated with stimulation of fibrosis development, triggering atherogenesis, oncogenesis and metastasis [21]. Therefore, the use of LPA agonists faces the dilemma of utilising therapeutically effective mechanisms of action of this lipid molecule while avoiding the development of undesirable effects [20], hence the relevance of studying other LPA receptors as therapeutic targets.

This article summarizes recent literature data on the chemical structure, biosynthetic pathways and LPA receptors. The focus is on the role of LPA, LPARs and TRP channels in the pathogenesis of bronchial asthma. Possible therapeutic strategies for bronchial asthma targeting LPAs, LPARs and TRP-channels are summarized and discussed.

The PubMed database was systematically searched for articles published in English in 2020–2023. Five articles published before 2020, which did not include the keywords of this review, were also analyzed to provide more detail on the information provided. The review included information sources that addressed issues relevant to the aim of this review. Information requests included the following set of keywords: 'lysophosphatidic acid', 'asthma', 'transient receptor potential channels', 'lysophosphatidic acid receptors' (Table 1).

The titles of the articles found on request were reviewed and if they matched the literature review topic, the abstracts of the articles were analyzed. If the abstract complied with the inclusion criteria, the full-text version of the article was searched and analyzed.

TABLE 1

RESULTS OF A SYSTEMATIC SEARCH OF ARTICLES IN THE PUBMED DATABASE (2020–2023)

Key words	Number of articles for the period 2020–2023
"lysophosphatidic acid"	698
"lysophosphatidic acid" and "asthma"	9
"lysophosphatidic acid" and "transient receptor potential channels"	7
"lysophosphatidic acid" and "asthma" and "transient receptor potential channels"	1
"asthma" and "transient receptor potential channels"	67
"lysophosphatidic acid" and "lysophosphatidic acid receptors"	304
"lysophosphatidic acid" and "asthma" and "lysophosphatidic acid receptors"	5
"asthma" and "lysophosphatidic acid receptors"	4

1. LYSOPHOSPHATIDIC ACID

Lysophosphatidic acid is classified as a lysoglycerophospholipid, a phospholipid with only one fatty acid residue, unlike glycerophospholipids that have two fatty acids at the sn-1 and sn-2 positions [6].

Lysophosphatidic acids are represented by different molecular species depending on the presence of saturated or unsaturated fatty acid residues in their structure (LPA16:0, LPA18:0, LPA18:1, LPA18:2, LPA20:4 and LPA22:6). Also, the structure and activity of LPA are determined by the position of fatty acids in the glycerol molecule [1, 6] (Fig. 1).

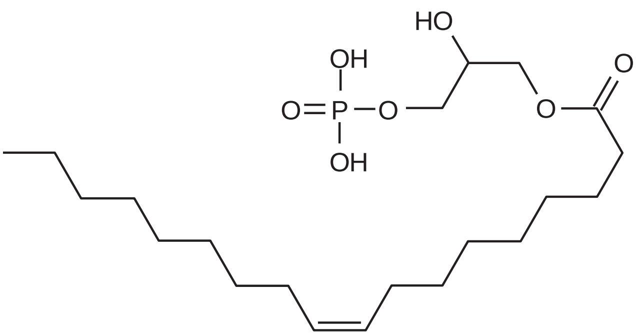

FIG. 1.
Chemical structure of lysophosphatidic acid

LPA biosynthesis is carried out through several pathways [2, 6, 7] (Table 2).

In the first pathway, LPA biosynthesis depends on the activity of phospholipases [22]. This pathway includes cleavage of membrane phospholipids (phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine) or cleavage of diacylglycerol (DAG) and phosphatidic acid formation. Phosphatidic acid is a substrate for phospholipases A1 and A2, which release fatty acids from the sn-1 or sn-2 positions, respectively, forming LPA.

Phospholipase A1 acts both extracellularly and intracellularly. Extracellular phospholipase A1 is involved in triacylglycerol hydrolysis and fatty acid cleavage. Phospholipase A2 is a large superfamily comprising 15 groups and 30 isoforms belonging to four types: secreted (IB, IIA, IIC, IID, IIE, IIF, III, V, X, XIIA and XIIB), cytosolic, calcium-independent and lipoprotein-associated phospholipases A2. Phospholipase A2 hydrolyses unsaturated fatty acids and is involved in the generation of eicosanoids and platelet-activating factor. On the one hand, secreted phospholipase A2 releases omega-3-polyunsaturated fatty acids (PUFAs), which are a substrate for anti-inflammatory and pro-resolving oxylipins. On the other hand, secreted phospholipase A2 is involved in the generation of fatty acids, lysophosphatidic acid, lysophospholipids, prostaglandins, leukotrienes and thromboxanes, which have pro-inflammatory effects [1, 22].

In the second pathway, LPA biosynthesis is mediated by autotaxin (ATX) [6]. Autotaxin (isoforms ATX-α, ATX-β, ATX-γ, ATX-δ and ATX-ε) or lysophospholipase D belongs to the ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2) family. The transcription of the *ENPP2* gene located in the human chromosomal region 8q24 is regulated by several pro-inflammatory and transcription factors [23]. ATX inhibition leads to decreased levels of pro-inflammatory mediators (tumour necrosis factor, interleukin (IL) 1, IL-6) in the experiment [24].

ATX is active in most biological fluids, including serum/plasma, bronchoalveolar lavage (BAL) fluid, cerebrospinal fluid and urine. In platelets, autotaxin can bind to platelet integrins αVβ3 and αIIbβ3. Adipose tissue is considered to be the main source of autotaxin in blood [6].

LPA is also formed from glycerol-3-phosphate with the participation of glycerol-3-phosphate acyltransferase (GPAT). Lastly, LPA can be cleaved to monoacylglycerol and diacylglycerol with the participation of lysophosphatases, to PA – via LPA-acyltransferase, and to G3P – with the participation of lysophospholipases [6].

Lysophosphatidic acid receptors

The physiological role of circulating LPAs is to preferentially transmit signals by interacting with transmembrane G-protein coupled receptors (GPCRs), which include LPA receptors (LPAR1–6) [2, 6]. Furthermore, recent studies revealed that LPA is a ligand for some TRP channels [2, 4, 6, 7]. The LPA receptors are summarised in Table 3.

LPAR1–3 belong to the endothelial differentiation gene (EDG family: LPAR1/EDG2, LPAR2/EDG4 and LPAR3/EDG7. LPAR4 (P2RY9, GPR23), LPAR5 (GPR92) and LPAR6 (P2RY5, GPR87) belong to purinergic receptors (P2Y).

TABLE 2

PATHWAYS AND ENZYMES OF LYSOPHOSPHATIDIC ACID BIOSYNTHESIS

Pathways of LPA biosynthesis	Enzymes involved in LPA biosynthesis
Phosphatidic acid	PLA1, PLA2
Lysoglycerophospholipids (LPC, Lyso-PS and LPE)	ATX/Lyso PLD
Glycerol 3-phosphate (G3P)	GPAT

Recent studies have shown that LPA can also activate P2Y10 [2].

LPAR1 is widely expressed in various organs and tissues, but mainly in the brain, heart, placenta, large and small intestines. Higher expression of LPAR2 mRNA is found in kidney, uterus, and testis; lower expression – in thymus, pancreas, and spleen. The level of LPAR3 mRNA is higher in the heart, lungs, pancreas, brain, prostate and ovaries. LPAR4 mRNA levels are elevated in mouse skin, heart, ovaries, and thymus. Large amount of LPAR5 is expressed in the spleen, large and small intestines. LPAR6 is associated with hair growth, but there are relatively few studies on its role and mechanisms in various systems [2].

LPARs activate Gα protein subtypes (Gα12/13, Gαq/11, Gαi/o and Gαs) that modulate downstream signalling pathways. Thus, the ROCK (Rho/Rho-associated protein kinase) signalling pathway is activated via Gα12/13; Gαq/11 activates phospholipase C (PLC) and further downstream cascades, GSK3 (glycogen synthase kinase 3) and CREB; Gαi/0 activates the PLC pathways, CREB and GSK3, and stimulates extracellular signal-regulated kinases 1/2 (ERK1/2), Akt/phosphoinositide-3-kinases (PI3K, PI3-kinases) and inhibits cyclic adenosine monophosphate (cAMP) production; GαS modulates adenylate cyclase and protein kinase A (PKA) activity by activating the cAMP signalling pathway [25].

TABLE 3

LYSOPHOSPHATIDIC ACID RECEPTORS

LPA receptors	Signalling pathway/effector
LPAR1/EDG2	Gα12/13–Rho–ROCK Gαi/o–Ras–Erk 1/2 Gαi/o–PI3K–Akt-mTOR Gαi/o–PLC–CREB и GSK3 Gαq/11-PLC–CREB и GSK3
LPAR2/EDG4	Gα12/13–Rho–ROCK Gαi/o–Ras–Erk 1/2 Gαi/o–PI3K–Akt-mTOR Gαi/o–PLC–CREB и GSK3 Gαq/11–PLC–CREB и GSK3
LPAR3/EDG7	Gαq/11–PLC–CREB и GSK3 Gαi/o–Ras–Erk 1/2 Gαi/o–PI3K–Akt-mTOR Gαi/o–PLC–CREB и GSK3
LPAR4 (P2RY9, GPR23)	Gα12/13–Rho–ROCK Gαq/11–PLC–CREB и GSK3 Gαi/o – Ras – Erk 1/2 Gαi/o–PI3K–Akt-mTOR Gαi/o–PLC–CREB и GSK3 Gαs–AC–RKA
LPAR5 (GPR92)	Gα12/13–Rho–ROCK Gαq/11–PLC–CREB и GSK3 Gαs–AC–RKA
LPAR6 (P2RY5, GPR87)	Gα12/13–Rho–ROCK Gαi/o–Ras–Erk 1/2 Gαi/o–PI3K–Akt-mTOR Gαi/o–PLC–CREB и GSK3 Gαs–AC–RKA
P2RY10	–
TRPV1	Direct interaction with K710 at the COOH end
TRPA1	LPAR5-PLD Direct interaction with intracellular KK672-673 and KR977-978
TRPM2	LPAR1-Gαi/o-MAP kinases-PARP-1-ADP-ribose

The main effect of LPA is its ability to modulate the actin cytoskeleton through the activation of small GTPases of the Ras superfamily via Gαi/o (stimulation of extracellular Erk1/2 signals) and Rho via Gα12/13 (stimulation of ROCK) [26]. These receptors signal through MARK, PLC and tyrosine kinases and initiate the synthesis of a number of transcription factors that interact with DNA sites and initiate proliferation, cell migration or intercellular interactions.

LPA mediates many functions through LPARs, in particular $Ca2^{+}$ mobilisation, survival, proliferation, adhesion, cell migration, immune function, by reducing chemokine production and inhibiting cell migration, and myelination [2].

TRP channels

As mentioned above, lysophosphotidic acid actively interacts with TRP-channels, which play an essential role in sensory physiology (smell, taste, vision, touch, thermo-sensing, osmosensing), pathophysiology of pain and inflammation, and act as signalling conductors in cells [27-29]. The function of these channels is to alter the cell membrane potential and fluctuate the intracellular concentration of free calcium $[Ca2^{+}]i$ in response to stimulating environmental influences [30]. TRP channels integrate TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPML (mucolipin), TRPP (polycystin) receptors [28-33]. TRPA1, TRPV1, TRPV2, TRPV4, TRPM3 and TRPM8 are thermosensory TRP-channels that are activated by changes in temperature, particularly ambient temperature [27, 32]. TRPVs are activated by heat, while TRPA1 and TRPM8 are activated by cold [33, 34].

TRP-channels are expressed in neuronal cells as well as in cells of the respiratory tract [14, 27]. To date, it has been established that LPA is able to directly or indirectly activate TRPM2, TRPV1 and TRPA1 [3, 35]. For instance, TRPM2 and TRPA1 are activated indirectly. Extracellular LPA elevation activates LPAR5, phospholipase D (PLD, phospholipase D) leading to increased intracellular LPA levels and TRPA1 activation. Activation of LPAR5 via Gαi/o stimulates PARP-1 (poly(ADP-ribose) polymerase 1), ADP-ribose, and TRPM2. TRPA1 and TRPV1 are directly activated [3, 35].

Thus, literature data demonstrate that LPA realizes its mechanism of action through interaction with LPARs and TRP channels, activating a number of signaling pathways. LPARs and TRP-channels are widely represented in the bronchopulmonary system, which makes it important to further study the effects of LPA in BA, despite the fact that clinical trials of TRP modulators have not been successful so far [14].

2. WHEEZING AND TRP-CHANNELS

Epidemiological studies of recent years convincingly demonstrate that the combination of high, low temperatures and humidity is accompanied by the development of wheezing in BA patients [12], which is mediated by the participation of TRP-channels in the reception of physicochemical stimuli of the environment [10], in particular, thermosensory TRPA1, TRPV1, TRPV2, TRPV4, TRPM3 and TRPM8 [27, 33].

Strong evidence has been presented for the important role of TRPA1, TRPC6, TRPM2, TRPM5, TRPM7, TRPM8, TRPV2, TRPV4 in airway function and pathogenesis of related diseases [13, 15-17].

For example, C-fibres, non-neuronal cells, airway cells, smooth muscle cells, epithelial cells and fibroblasts express TRPA1 [36]. Cigarette smoke, car exhaust, air pollution, reactive oxygen intermediates (ROIs), and various temperature conditions are among the known TRPA1 agonists [37, 38]. Activation of sensory nerves via TRPA1 initiates coughing, mucus secretion, airway hyperresponsiveness, inflammation and development of wheezing [15, 17, 37, 39].

Vanilloid receptors (TRPV1-6) are localised in nociceptive neurons, airway sensory fibres, on bronchial epithelial cells, mast cells, macrophages and human airway smooth muscle cells [14, 15, 28].

TRPV1 is present in airway sensory fibres lining the trachea, bronchi and alveoli, and is also expressed in bronchial epithelial cells and in intrapulmonary arterioles. The relationship between TRPV1 and bronchopulmonary diseases has been demonstrated *in vitro* and *in vivo*. Activation of TRPV1 by agonists leads to the release of neurokinin A, substance P and CGRP, which contribute to smooth muscle contraction, mucus hypersecretion, coughing and the development of asthma-like symptoms [13]. Of significance, a role for TRPV1, which is mainly expressed in neurons, in IL-33 secretion by airway epithelium in response to exposure to the house dust mite allergen HDM and fungal allergens has recently been described [14]. Bronchospasm and asthma-like symptoms that develop in response by exposure to cold air and high humidity are associated with the involvement of not only TRPV1 but also TRPV2 and TRPV4 in osmoreception [16, 40]. TRPV1 and TRPV4 seem to contribute most significantly to the development and exacerbation of BA [18].

TRPA1 channels often act in concert with TRPV1 [41]. These data suggest that the interaction between TRPA1 and TRPV1 may be essential in regulating the function and excitability of pulmonary sensory neurons during airway inflammation. TRPV1 can also oligomerize with other TRP family subunits, including TRPV3 [41].

TRPV1-4 are channels showing a predominance of $Ca2^{+}$ influx over Na^{+} influx, with TRPV5 and TRPV6 being $Ca2^{+}$ – only permeable channels [18]. In a review by J.H. Nam and W.K. Kim the relationship between TRP channels and immune cells involved in the pathogenesis of allergic diseases, as well as therapeutic agents targeting these channels are discussed [30]. An increase in intracellular $Ca2^{+}$ concentration causes the release of histamine, anaphylactic chemotaxis factor of eosinophils and neutrophils from mast cells and leads to contraction of bronchial musculature. This intracellular $Ca2^{+}$ signalling is provided by TRP-channels involved in almost all types of immune cells, in particular mast cells, T-cells and B-cells involved in the pathogenesis of allergic inflammation characteristic of allergic BA [30].

3. LYSOPHOSPHATIDIC ACID, LPARS AND TRP-CHANNELS IN THE PATHOGENESIS OF WHEEZING

LPA synthesis is enhanced by inflammation, particularly localised in the bronchopulmonary system [5, 42-46]. *In vitro* studies have revealed that LPA activates eosinophils, lymphocytes, mast, dendritic, epithelial and smooth muscle cells in the airways.

LPA levels have been demonstrated to be significantly elevated in the BAL of patients with BA [5]. Of interest, LPA has been identified as a regulator of the epithelial-mesenchymal transition involved in the conversion of fibroblasts to myofibroblasts and the development of airway remodelling [47].

The functions of LPA in the bronchopulmonary system are conditioned by its reactions with LPARs [2, 5, 46] and TRP-channels [4, 8]. As previously mentioned, central to the effects of LPA is its ability to activate the small GTPases Ras (Erk1/2 stimulation) and Rho-kinases via Gα12/13 (ROCK stimulation) [26].

The Rho-kinase of the ROCK signalling pathway is known to play a key role in maintaining the expression of muscle contractions during smooth muscle activation. Rho-kinase inhibition is currently being studied as a component of combined treatment of wheezing in BA [48]. Accordingly, the LPA – LPARs – ROCK signalling pathway requires to be studied closely.

LPA via LPAR1-3 activates p38 MAPK and JNK kinases and induces IL-8 production, which increases inflammation and promotes airway remodelling in BA [5]. These data are evidence that LPA plays an important role in allergic airway inflammation and that blockade of LPARs may have therapeutic potential in BA [5].

LPA is able to activate TRPA1, TRPM2 and TRPV1 [3, 17]. Currently, only sporadic works have focused on the interaction between LPA and TRPA1 in various pathologies [9]. TRPM2 are expressed in pulmonary endothelium and are involved in the regulation of barrier function, cell death, cell migration and angiogenesis [16]. Although LPA is able to activate TRPM2 [3], their interaction in BA has not been studied [17].

Recently, it has been described that LPA can activate TRPV1 [3, 19]. M. Benítez-Angeles et al. reported that LPA directly interacts with TRPV1 through the K710 residue in the C-terminal of TRPV1 [19].

Interestingly, LPA has been implicated in the pathogenesis of wheezing through interaction with LPAR and TRPV1 [3, 4]. A series of works by N.G. Jendzjowsky et al. was devoted to the study of the role of carotid bodies in the occurrence of wheezing [3]. Carotid corpuscles respond to changes in partial pressure of oxygen, carbon dioxide, pH, temperature, and have also demonstrated the ability to react in response to bacterial infection [49] and exposure to allergens [3]. N.G. Jendzjowsky et al. have revealed that the increase in blood LPA caused by allergen exposure activates carotid cells and causes wheezing via LPAR and TRPV1 [3]. This signalling pathway involves PKCε (protein kinase C epsilon) binding LPAR1 and TRPV1 to each other. In their recent work, N.G. Jendzjowsky et al. also have revealed that repeated exposure to allergen increases carotid body sensitivity to LPA as a consequence of LPARs hyperexpression in carotid bodies. These experimental data demonstrate the ability of allergens to sensitise carotid cells, highlighting their role in the development of BA and the involvement of the LPAR1 – PKCε – TRPV1 pathway in the pathogenesis of asthmatic reactions [3]. However, it is worth noting that this mechanism has not yet been confirmed in humans.

In summary, the presented data evidence the therapeutic potential of LPA, TRP-channels and LPARs, which play a definite role in the development of airway inflammation and bronchospasm in BA.

4 MODERN THERAPEUTIC APPROACHES TO THE REGULATION OF LPA ACTIVITY

LPAR antagonists

LPA as a potent signalling molecule affects numerous physiological and pathological processes; therefore, the control of LPA signalling is of growing pharmacotherapeutic interest worldwide [20]. The action of LPA is mediated through the activation of several types of molecular targets, including LPAR1-6, which are now targeted by most drug development methods in a wide range of pathologies [20]. LPA signalling through its receptors, however, is also associated with the development of pathological responses that include, for example, stimulation of fibrosis or the development of atherogenesis, which should be taken under consideration in drug development [20, 21].

In a brilliant review by S. Llona-Minguez et al. the results of 30 years of studies conducted in the pharmaceutical industry in relation to LPA and its receptors have been summarised [50]. The co-authors of the review note that LPAR1 and LPAR1/LPAR3 antagonists have attracted the most attention for pharmaceutical development (Kirin Ki16425). Of the two potential LPAR antagonist molecules (BMS-986020 for the treatment of idiopathic pulmonary fibrosis and SAR-100842 for the treatment of systemic sclerosis), the study of SAR-100842 was discontinued [6]. S. Llona-Minguez et al. also analyse a number of developmental issues: for example, the lack of potent and selective low molecular weight LPAR3 and LPAR5 agonists, LPAR4 antagonists and the lack of LPAR6 modulators [50]. The authors also identified a wide range of conditions in which selective LPA modulators may be effective (fibrosis, thrombosis, cancer metastasis, urinary tract diseases, and several others), while emphasising the inherent risk of side effects and the need to develop new LPA modulators with selectivity in mind. Also S. Llona-Minguez et al. emphasize the need to detail the structure of LPA receptors and to develop the design of new drugs on this basis [50].

Y.J. Lee et al. indicate the prospect of developing LPAR2 antagonists for the BA treatment [51]. The authors of this study compared the effects of an antagonist (H2L5186303) and an agonist (GRI977143) of LPAR2 in an experimental protocol for ovalbumin-induced allergic BA (OVA).

H2L5186303 demonstrated reduced airway hyperresponsiveness, decreased levels of inflammatory cytokines, mucin production and eosinophil counts. The authors of this study suggest that the development of LPAR2 antagonists will achieve greater therapeutic efficacy in BA compared to the action of agonists in this pathology [51].

M. Kondo et al. also demonstrated on the model of allergic BA that administration of LPAR2 antagonist (H2L5186303) effectively suppressed allergic inflammation [5]. The authors revealed that the increase in IL-13 production as a result of LPA stimulation was inhibited by treatment with LPAR2 antagonists. The authors of this study also demonstrated that LPA exacerbates allergic bronchial inflammation by promoting Th2 differentiation and IL-33 production, whereas the LPAR2 antagonist controls IL-33 production. According to the conclusion of M. Kondo et al. blockade of LPAR2 may be an effective therapeutic strategy in BA [5].

N.G. Jendzjowsky et al. demonstrated that administration of LPA receptor antagonist (BrP-LPA) effectively blocks bronchoconstriction in experiment [3].

Drugs inhibiting synthesis or enhancing degradation of LPA

Many therapeutic agents are currently available that inhibit LPA synthesis by affecting the reduction of autotoxin activity or enhancing LPA degradation [43, 51-53].

There is currently sufficient evidence that the ATX-LPA axis is involved in the processes of cancer initiation and metastasis, the development of atherosclerosis, obesity, arthritis, glaucoma, acute and chronic liver failure, fibrosis of the liver, kidneys and lungs and many other diseases and pathological conditions [21, 23, 44, 54, 55]. Some researchers continue to support and develop the idea that this axis plays an important role in the development of airway inflammation [21], particularly in BA [5, 45]. For example, the role of the ATX-LPA axis in lung development, lung function in norm and pathology is brilliantly summarised in a recent study by S. Zulfikar et al. [21].

One possible method to affect the LPA signalling pathway is through ATX inhibition [45, 52, 56, 57]. ATX inhibitors may be effective for the treatment of chronic inflammation [44, 52, 58]. New imidazo[1,2-a]pyridine derivatives are considered as potent allosteric inhibitors of ATX. Their promising antifibrotic efficacy was demonstrated in a mouse lung model [59]. J.W. Cuozzo et al. found inhibition of LPA production through the interaction of compound 1 (X-165) with autotaxin under experimental conditions. This compound has also demonstrated efficacy in a mouse model of fibrosis [53].

It is conceivable that ATX is a relatively safe therapeutic target, but to date there is insufficient information about its safety in humans [45]. No ATX inhibitors are currently approved by the US Food and Drug Administration (FDA), with only two drugs in clinical trials, BBT-877 and BLD-0409 [52]. ATX inhibitor researchers concur that there is a need to optimise their kinetic properties and to develop inhibitors with multiple targets. For example, in LPA-mediated diseases, ATX, PLA, and PPAR may serve as targets [52].

TRPV receptor antagonists

As mentioned above, LPA is able to activate TRP-channels (TRPA1, TRPM2 and TRPV1); some of them are involved in the pathogenesis of wheezing [3]. These experimental data demonstrate the ability of allergens to sensitise carotid cells and activate the LPAR1 – PKCε – TRPV1 pathway, which plays an important role in the pathogenesis of asthmatic reactions. Since administration of a TRPV1 receptor antagonist (AMG9810) blocks the development of wheezing, vanniloid receptors may be an important target for therapy of BA [3].

Thus, there are now a number of LPAR antagonists, inhibitors of LPA synthesis, and drugs that enhance LPA degradation that are effective in BA. In addition, there is evidence that TRPV1 receptor antagonists are promising for the treatment of wheezing.

CONCLUSION

LPA controls many physiological processes in the cell and is one of the mediators whose expression is enhanced in inflammation localised in the bronchopulmonary system. LPA receptors have been revealed to be activated by a number of downstream signalling pathways through interactions with LPARs, nuclear receptors and TRP-channels. Although LPARs are potent activators of signalling pathways, the study of TRP-channels also deserves close attention because of their involvement in the pathogenesis of bronchial obstruction.

As evident from the literature provided, some ATX and LPA antagonists reduce airway inflammation and hyperresponsiveness underlying the pathogenesis of BA. A number of studies also point to the promise of developing LPA receptor antagonists (particularly LPAR2) for the treatment of BA. In addition, there is emerging evidence that TRPV1 receptor antagonists are promising for the management of wheezing. Recent studies also reveal that LPA is involved in the pathogenesis of wheezing through interactions with LPAR and TRPV1, which offers interesting prospects for the development of inhibitors with multiple targets. A number of researchers have indeed emphasised the need not only to optimise the kinetic properties of ATX inhibitors, but also to develop inhibitors with multiple targets for their action. For example, in LPA-mediated diseases, ATX, PLA and PPAR may serve as multiple targets. Based on the analysed literature, we can also assume that such multiple targets for the development of LPA inhibitors may be LPAR and TRP-channels, which will allow to effectively influence the main links in the wheezing pathogenesis. The purpose of this review was to draw researcher attention to this area, which undoubtedly requires further study.

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Conflict of interest

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