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# TRP Channels

**Lapasova Zebiniso Khidirovna**

Lecturer of Pathophysiology Department of the Samarkand State Medical University

**Raupov Bakhodir Bakhtiyorovich**

Student of the Samarkand State Medical University

**Abstract.** Lysophosphotidic acid actively interacts with TRP channels, which play an essential role in sensory physiology (smell, taste, vision, touch, thermosensation, osmosensation), the pathophysiology of pain and inflammation, as well asact as signal conductors in cells.

**Key words:** vanilloid receptors, ankyrin, polycystin.

The function of these channels is to change the cell membrane potential and intracellular concentration of free calcium [Ca2+] in response to stimulating influences of the external environment. TRP channels combine TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPML (mucolipin), TRPP (polycystin) receptors. TRPA1, TRPV1, TRPV2, TRPV4, TRPM3 and TRPM8 are thermosensory TRP channels that are activated by changes in temperature, in particular ambient temperature. TRPV are activated by heat, TRPA1 and TRPM8 by cold. TRP channels are expressed in neuronal cells as well as in cells of the respiratory tract. It has been established that LPA is capable of directly or indirectly activating TRPM2, TRPV1 and TRPA1. Thus, TRPM2 and TRPA1 are activated indirectly. Extracellular increase in LPA activates LPAR5, phospholipase D (PLD, phospholipase D), leading to increased levels of intracellular LPA and activation of TRPA1. Activation of LPAR5 through Gαi/o stimulates PARP-1 (poly(ADP-ribose) polymerase 1), ADP-ribose and TRPM2. TRPA1 and TRPV are directly activated. Thus, the data demonstrate that LPA exerts 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 urgent to further study the effects of LPA in bronchial asthma, despite the fact that clinical trials of TRP modulators have not yet been successful.

BRONCHOOBSTRUCTION AND TRP CHANNELS.

Epidemiological studies in recent years convincingly indicate that the combination of high, low temperatures and air humidity is accompanied by the development of bronchial obstruction in patients with bronchial asthma, which is mediated by the participation of TRP channels in the reception of physicochemical stimuli of the external environment, in particular thermosensory TRPA1, TRPV1, TRPV2, TRPV4, TRPM3 and TRPM8. Convincing evidence is presented for the important role of TRPA1, TRPC6, TRPM2, TRPM5, TRPM7, TRPM8, TRPV2, TRPV4 in the function of the respiratory tract and the pathogenesis of related diseases. For example, C-fibers, non-neuronal cells, airway cells, smooth muscle cells, epithelial cells and fibroblasts express TRPA1.

Cigarette smoke, automobile exhaust, air pollution, reactive oxygen species, and various temperature conditions are among the known TRPA1 agonists. Activation of sensory nerves through TRPA1 initiates cough, mucus secretion, airway hyperresponsiveness, inflammation and the development of bronchial obstruction. Vanilloid receptors (TRPV1–6) are localized in nociceptive neurons, sensory fibers of the respiratory tract, on bronchial epithelial cells, mast cells, macrophages and smooth muscle cells of the human respiratory tract. TRPV1 is present in airway sensory fibers lining the trachea, bronchi, and alveoli, and is also expressed in bronchial epithelial cells and in intrapulmonary arteries. The relationship of TRPV1 with 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, cough and the development of asthma-like symptoms. Importantly, a role for TRPV1, which is primarily expressed in neurons, has recently been described in the secretion of IL-33 by airway epithelia in response to house dust mite allergen HDM and fungal allergens. Bronchospasm and asthma-like symptoms that develop in response to exposure to cold air and high humidity are caused by the participation of not only TRPV1, but also TRPV2 and TRPV4 in osmoreception. TRPV1 and TRPV4 appear to be the most significant contributors to the development and exacerbation of asthma. TRPA1 channels often act in concert with TRPV1. These data suggest that the interaction of TRPA1 and TRPV1 may play an important role in regulating the function and excitability of lung sensory neurons during airway inflammation. TRPV1 can also oligomerize with other subunits of the TRP family, including TRPV3. TRPV1–4 are channels demonstrating

the predominance of Ca2+ influx over Na+ influx, while TRPV5 and TRPV6 are permeable only to Ca2+ channels. Reviewed by J.H. Nam and W.K. Kim discusses the relationship between TRP channels and immune cells involved in the pathogenesis of allergic diseases, as well as therapeutic agents targeting these channels. Increased intracellular

Ca2+ concentration causes the release of histamine, an anaphylactic factor for the chemotaxis of eosinophils and neutrophils from mast cells and leads to contraction of the bronchial muscles. This intracellular Ca2+ signaling is mediated by TRP channels, present 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 bronchial asthma.

LYSOPHOSPHATIDE ACID, LPARS AND TRP CHANNELS IN THE PATHOGENESIS OF BRONCHO OBSTRUCTTION.

The synthesis of LPA increases during inflammation, in particular localized in the bronchopulmonary system. In vitro studies have shown that LPA activates eosinophils, lymphocytes, mast cells, dendritic cells, epithelial cells, and airway smooth muscle cells. Interestingly, LPA has been identified as a regulator of epithelial-mesenchymal transition involved in the conversion of fibroblasts to myofibroblasts and the development of remodeling

respiratory tract.

The functions of LPA in the bronchopulmonary system are determined by its reactions with LPAR and TRP channels. As mentioned above, central to the effects of LPA is its ability to activate the small GTPases Ras (stimulation of Erk1/2) and Rho kinase through Gα12/13 (stimulation of ROCK). It is known that Rho-kinase of the ROCK signaling pathway plays a key role in maintaining the expression of muscle contractions during smooth muscle activation. Inhibition of Rho kinase is currently being studied as part of a combination treatment for bronchial obstruction in asthma. Accordingly, the LPA – LPARs – ROCK signaling pathway requires careful study. LPA, through LPAR1-3, activates p38 MAPK

and JNK kinases and induces the production of IL-8, which increases inflammation and promotes airway remodeling in bronchial asthma. These data suggest that LPA plays an important role in allergic airway inflammation and that LPAR blockade may have therapeutic potential in asthma. LPA is able to activate TRPA1, TRPM2 and TRPV1. TRPM2 is expressed in the lung endothelium and is involved in the regulation of function, cell death, cell migration and angiogenesis. Despite the fact that LPA is capable of activating TRPM, their interaction in bronchial asthma has not been studied. Recently, it was described that LPA can activate TRPV1. M. Benítez-Angeles et al. reported that LPA directly interacts with TRPV1 through the K710 residue in the C terminus of TRPV1. Interestingly, LPA is involved in the pathogenesis of bronchial obstruction through interaction with LPAR and TRPV1. Series of works by N.G. Jendzjowsky et al. was devoted to studying the role of carotid bodies in the occurrence of bronchial obstruction. Carotid bodies respond to changes in the partial pressure of oxygen, carbon dioxide

gas, pH, temperature, and also demonstrate the ability to respond in response to bronchial asthma, bacterial infection and exposure to allergens. N.G. Jendzjowsky et al showed that an increase in blood LPA caused by allergen exposure activates carotid bodies and causes bronchial obstruction via LPAR and TRPV1. This signaling pathway includes PKCε (protein kinase C epsilon), which links LPAR1 and TRPV1. In his latest works N.G. Jendzjowsky et al. also showed that repeated allergen exposure increases the sensitivity of carotid bodies to LPA due to overexpression of LPARs in carotid bodies. These experimental data demonstrate the ability of allergens to sensitize carotid bodies, emphasizing their role in the development of bronchial asthma and the involvement of the LPAR1 – PKCε – TRPV1 pathway in the pathogenesis of asthmatic reactions. It is worth noting that this mechanism has not yet been confirmed in humans. Thus, the presented data indicate the therapeutic potential of LPA, TRP channels and LPARs, which play a certain role in the development of

inflammation of the respiratory tract and bronchospasm in bronchial asthma.

## MODERN THERAPEUTIC

### APPROACHES TO REGULATING LPA ACTIVITY.

#### LPAR antagonists.

LPA, as a potent signaling molecule, influences numerous physiological and pathological processes, therefore, controlling LPA signaling has attracted growing pharmacotherapeutic interest worldwide. The action of LPA is mediated by the activation of several types of molecular targets, including LPAR1–6, which are currently the focus of most drug development methods for a wide range of pathologies [20]. However, LPA signaling through its receptors is also associated with the development of pathological reactions, which include, for example, stimulation of fibrosis or the development of atherogenesis, which must be taken into account when developing drugs [20, 21]. In an excellent review by S. Llona-Minguez et al. summarizes the results of 30 years of research conducted in the pharmaceutical industry regarding LPA and its receptors. The review authors note that LPAR1 and LPAR1/LPAR3 antagonists have received the most attention for development in the pharmaceutical industry (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), SAR-100842 was discontinued from study [6]. S. Llona-Minguez et al. also review a number of

development issues: for example, the lack of potent and selective small molecule LPAR3 and LPAR5 agonists, LPAR4 antagonists and the lack of LPAR6 modulators [50].

The authors also highlight the wide range of conditions in which selective LPA modulators may be effective (fibrosis, thrombosis, cancer metastasis, urinary tract disease, and several others), while emphasizing the inherent risk of side effects and the need to develop new LPA modulators that take them into account. selectivity. Also S. Llona Minguez et al. emphasize the need to detail the structure of LPA receptors and develop the design of new drugs on this basis.

Y.J. Lee et al. indicate the promise of developing LPAR2 antagonists for the treatment of bronchial asthma. The authors of this study compared the effects of an antagonist (H2L5186303) and an agonist (GRI977143) of LPAR2 in an experimental protocol for allergic bronchial asthma induced

ovalbumin (OVA). H2L5186303 demonstrated

decreased airway hyperresponsiveness, decreased levels of inflammatory cytokines, production

mucin and eosinophil count. The authors of this study suggest that the development of LPAR2 antagonists will achieve greater therapeutic efficacy in bronchial asthma compared to the action of agonists in this pathology [51]. M. Kondo et al. in a model of allergic bronchial asthma, they also demonstrated that administration of an LPAR2 antagonist (H2L5186303) effectively suppressed allergic inflammation [5]. The authors showed that the increase in IL-13 production due to LPA stimulation was inhibited by treatment with LPAR2 antagonists. The authors of this study also demonstrated that LPA aggravates allergic bronchial inflammation by promoting Th2 differentiation and IL-33 production, while an LPAR2 antagonist controls IL-33 production. According to the conclusion of M. Kondo et al., blockade of LPAR2 may be an effective therapeutic strategy for bronchial asthma [5]. N.G. Jendzjowsky et al. demonstrated that administration of an LPA receptor antagonist (BrP-LPA) effectively blocks bronchoconstriction experimentally [3].

Drugs that inhibit synthesis or enhancing the degradation of LPA.

There are currently many therapeutic drugs that inhibit LPA synthesis

influencing a decrease in autotoxin activity or an increase in LPA degradation. Today, there is enough evidence confirming that the ATX-LPA axis is involved in the processes of initiation and metastasis of cancer, 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. Some researchers continue to support and develop the idea that this axis plays an important role in the development of airway inflammation [21], in particular in bronchial asthma. For example, the role of the ATX-LPA axis in lung development, normal functioning and pathology is brilliantly summarized in the recent work of S. Zulfikar et al.

One possible method of influencing the LPA signaling pathway is ATX inhibition. ATX inhibitors may be effective in treating chronic inflammation. New proimidazo[1,2-a]pyridine derivatives are considered to be powerful allosteric inhibitors of ATX. Their promising antifibrotic efficacy was demonstrated in a mouse lung model. J.W. Cuozzo et al. In experimental conditions, inhibition of LPA production through the interaction of compound 1 (X-165) with autotaxin was established. The compound also demonstrated efficacy in a mouse model of fibrosis. It can be assumed that ATX is a relatively safe therapeutic target, however,

Today there is not enough information about its safety for humans. Currently, there are no ATX inhibitors approved by the US Food and Drug Administration, with only two drugs in clinical trials - BBT-877 and BLD-0409. Researchers of ATX inhibitors agree that optimization of their kinetic properties is necessary, as well as the development of inhibitors with multiple targets. For example, in LPA-mediated diseases, ATX, PLA, and PPAR may be targets.

TRPV receptor antagonists.

As mentioned above, LPA is able to activate TRP channels (TRPA1, TRPM2 and TRPV1), some of which are involved in the pathogenesis of bronchial obstruction. These experimental data demonstrate the ability of allergens to sensitize carotid bodies and activate the LPAR1 – PKCε – TRPV1 pathway, which plays an important role in the pathogenesis of asthmatic reactions. Considering that the administration of a TRPV1 receptor antagonist (AMG9810) blocks the development of bronchial obstruction, vannilloid receptors may be an important target for the treatment of bronchial asthma. Thus, there are currently a number of LPAR antagonists, LPA synthesis inhibitors and drugs that enhance LPA degradation that are effective in bronchial asthma. In addition, data have emerged indicating the promise of using TRPV1 receptor antagonists to relieve bronchial obstruction.

CONCLUSION.

LPA controls many physiological processes in the cell and is one of the mediators whose expression increases during inflammation localized in the bronchopulmonary system. It has been established that LPA receptors are activated by a number of downstream signaling pathways through interaction with LPARs, nuclear receptors and TRP channels. Despite the fact that LPARs are powerful activators of signaling pathways, the study of TRP channels also deserves close attention, since they are involved in the pathogenesis of bronchial obstruction. As can be seen from the presented literature data, some ATX and LPA antagonists reduce inflammation and hyperresponsiveness of the airways, which underlie the pathogenesis of bronchial asthma. A number of studies also indicate the promise of developing receptor antagonists.

dat LPA (in particular LPAR2) for the treatment of bronchial asthma. In addition, evidence has emerged indicating that TRPV1 receptor antagonists are promising for treating

bronchial obstruction. Recent research findings also indicate that LPA is involved in the pathogenesis of bronchial obstruction through interaction with LPAR and TRPV1, which opens interesting prospects for the development of inhibitors with multiple targets. Indeed, a number of researchers emphasize the need

the need not only to optimize the kinetic properties of ATX inhibitors, but also to develop inhibitors with multiple targets of their action. For example, in LPA-mediated diseases, ATX, PLA, and PPAR may be multiple targets. Based on the literature sources we analyzed, it can also be assumed that LPAR and TRP channels can serve as such multiple targets for the development of LPA inhibitors, which will make it possible to effectively influence the main links in the pathogenesis of bronchial obstruction. The purpose of this review was to attract research attention to this area, which undoubtedly requires further study.

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