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REVIEW

Lysophosphatidic Acid Is a Lipid Mediator with Wide Range of Biological Activities. Biosynthetic Pathways and Mechanism of Action

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Abstract—Lysophosphatidic acid (LPA) is a lipid mediator required for maintaining homeostasis of numerous physiological functions and also involved in development of some pathological processes through interactions with G protein-coupled receptors. Recently many data have appeared about the role of this phospholipid in humans, but pathways of LPA biosynthesis and mechanisms of its action remain unclear. This review presents modern concepts about biosynthesis, reception, and biological activity of LPA in humans. Natural and synthetic LPA analogs are considered in the view of their possible use in pharmacology as agonists and/or antagonists of G protein-coupled receptors of LPA.

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Key words: lysophosphatidic acid, LPA analogs, autotaxin, G protein-coupled receptors, expression of human phospholipase genes

Lysophosphatidic acid (LPA) is a simple phospholipid containing 1 mol fatty acid per mol lipid. *In vivo* determination shows that LPA is a mixture of different fatty acids. Different LPAs containing both saturated (16:0, 18:0) and unsaturated fatty acid residues (16:1, 18:1, 18:2, 20:4) are found in various biological specimens: serum [1, 2], plasma [3], activated platelets [4, 5], and saliva [6]. The activity of LPA forms depends on the position of the fatty acid residue (sn1 or sn2) relatively to the glycerol moiety, its length, and the number of double bonds [7-11]. Serum LPA is active only when bound with albumin or some other blood proteins [12]. Note that LPA species display different biological activities due to selective activation of LPA receptors [10, 13-15].

Abbreviations: ATX, autotaxin; DAG, diacylglycerol; GPC-receptors (GPCR), G protein-coupled receptors; LPA, lysophosphatidic acid; lysoPLD, lysophospholipase D; MAPK, mitogen-activated protein kinase; NPP, nucleotide phosphatase/phosphodiesterase; PA, phosphatidic acid; PLA_1, phospholipase A_1; PLA_2, phospholipase A_2; PLC, phospholipase C; VEGF, vascular endothelial growth factor.

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BIOSYNTHESIS OF LPA

LPA is produced as a result of hydrolysis of membrane phospholipids by different phospholipases, such as phospholipase C (PLC), phospholipases A_1 (PLA_1) and A_2 (PLA_2), and lysophospholipase D (lysoPLD). Although the metabolic pathway of LPA synthesis is studied insufficiently, at least two pathways of LPA biosynthesis are described [16].

The first pathway is specific for blood serum and plasma where LPA is produced mainly from lysophospholipids [17]. In fat tissue cells, adipocytes, LPA is synthesized similarly [18]. In this pathway of LPA biosynthesis the key role belongs to lysoPLD, which cleaves lysophosphatides with production of LPA. LysoPLD is similar to autotaxin (ATX, NPP2), which is an extranuclear nucleotide phosphatase/phosphodiesterase (NPP) [19, 20].

The domain structure of ATX is similar to that of other NPPs (NPP1 and NPP3) and consists of two N-terminal somatomedin B-like domains, the central catalytic phosphodiesterase domain, and the C-terminal nuclease domain [20]. Just the nuclease domain is necessary for the

correct folding, intracellular localization, and secretion of the enzyme. ATX is synthesized as an immature precursor protein with a signal peptide consisting of 27 amino acid residues (aa). The secretion of the enzyme is preceded by proteolytic processing with detachment of the signal peptide. Mature ATX is an active glycopeptide glycosylated at three sites (N52, N410, and T524), and glycosylation at the third position is necessary for its activity.

The gene *ENPP2* encoding human ATX consists of 27 exons. Three isoforms are produced as a result of alternative splicing [21]. The most widely distributed and shortest form (ATX^{ter}) consisting of 863 aa has been cloned from teratocarcinoma line cells and is identical to plasma lysoPLD. The second isoform (ATX^{mel}, 915 aa), cloned from melanoma cells contains a 52-aa insertion in the region of the catalytic domain. The least frequent third isoform (PD-1α) is mainly expressed in brain oligodendrocytes and contains a 24-aa insertion near the nuclease domain.

ENPP2 expression is found in various cells and tissues, and the highest level of mRNA is observed in brain, ovaries, lungs, intestine, and kidneys. ATX is accumulated in plasma and cerebral fluid. An increased expression of *ENPP2* is also observed in cells of various malignancies [22-24]. A high expression of the *ENPP2* gene is found in synoviocytes of patients with rheumatoid arthritis [25] and also in the frontal cortex cells of patients with Alzheimer's disease [26]. An increased content of the ATX protein is also found in the cerebrospinal fluid of patients with multiple sclerosis [27].

The other pathway of biosynthesis is specific for active platelets and some cancer cells, where LPA is mainly synthesized from phosphatidic acid [16] under the influence of PLA_1 and PLA_2. Nine types of A_1 phospholipases are now known – six extracellular and three intracellular [28]. They have no significant homology and probably perform different functions. Extracellular phospholipases form a family of pancreatic lipases with wide substrate specificity and are capable of hydrolyzing phospholipids, triacylglycerols, and galactolipids.

Three other phospholipases – phosphatidylserine-specific phospholipase A_1 (PS-PLA_1), membrane-associated phosphatidic acid (PA)-specific phospholipase $A_1\alpha$ (mPA-$PLA_1\alpha$/LIPH, $PLA_1\alpha$, phospholipase H), and membrane-associated PA-specific phospholipase $A_1\beta$ (mPA-$PLA_1\beta$/LIPI, $PLA_1\beta$, phospholipase I) – have a strict substrate specificity. PS-PLA_1 specifically acts on phosphatidylserine with production of the signaling lipid lysophosphatidylserine, whereas two other pancreatic lipases (LIPH and LIPI) are involved in LPA synthesis from PA [29].

According to crystallographic data, pancreatic lipases consist of two domains, and of these the N-terminal domain has catalytic activity. A catalytic triad conservative over the whole family is formed by amino acids Ser154, Asp178, and His248. The region of cysteine residues, which form intramolecular disulfide bonds, is also very conservative. Human PLA_1 have three surface loops called the lid, the β5 loop, and the β9 loop that cover the active site and determine the substrate specificity of the phospholipases [30]. Note that in insects all lipase-like molecules have only the N-domain [31] that also indicates its catalytic activity.

The function of the C-domain remains unclear, but it might be involved in regulation of the catalytic activity of the enzyme. This domain is also supposed to be involved in the interaction with lipids. Moreover, it seems that the C-terminus can interact with the N-terminal domain and thus contribute to formation of dimers, as has been shown for some lipases [32, 33].

Phospholipase H is especially interesting. LIPH is supposed to be the main enzyme controlling LPA generation in different domains of hair follicles and skin cells and be able to play the key role in the cyclic process of cell, tissue, and organ regeneration through regulation of stem cells [34].

The *LIPH* gene encoding human phospholipase H is localized on the third chromosome in the region 3q27 and contains 10 exons (Fig. 1a). The *LIPH* gene is strongly expressed in intestine, skin, hair, prostate, testes, liver, kidneys, lungs, pancreas, and fibroblasts [34-37]. Lower expression is reported in tissues of brain, heart, and spleen (Fig. 1b).

Maximal expression is characteristic for anagen bulbs (Fig. 1b). Studies on different structural domains of hair follicles and skin cells have revealed that the *LIPH* gene is mainly expressed in a specific morphologic domain, bulge, which is a reservoir of stem cells (Fig. 1b) [34]. Note that the physiological role of the *LIPH* gene is insufficiently studied. Nevertheless, a deletion in the fourth exon of the *LIPH* gene is shown to result in the loss of the functional activity of the protein product of this gene, phospholipase H, in hair follicles, this affecting LPA production and leading to development of hypotrichosis [34]. Thus, phospholipase H seems to be a promising target for elaboration of drugs for treatment of such diseases as hypotrichosis.

LPA RECEPTORS

Although LPA is a simple phospholipid, this signaling molecule is involved in various cell processes because it interacts with G protein-coupled receptors (GPCR). At least seven GPC receptors of LPA are now known; they can be subdivided into two groups depending on their primary structure. The first group includes three receptors: LPA1/EDG2 [38], LPA2/EDG4 [39], and LPA3/EDG7 [40]. These receptors are 50% homologous on the level of amino acids and are encoded by the family of endothelial differentiation genes (EDG) [41]. The other group

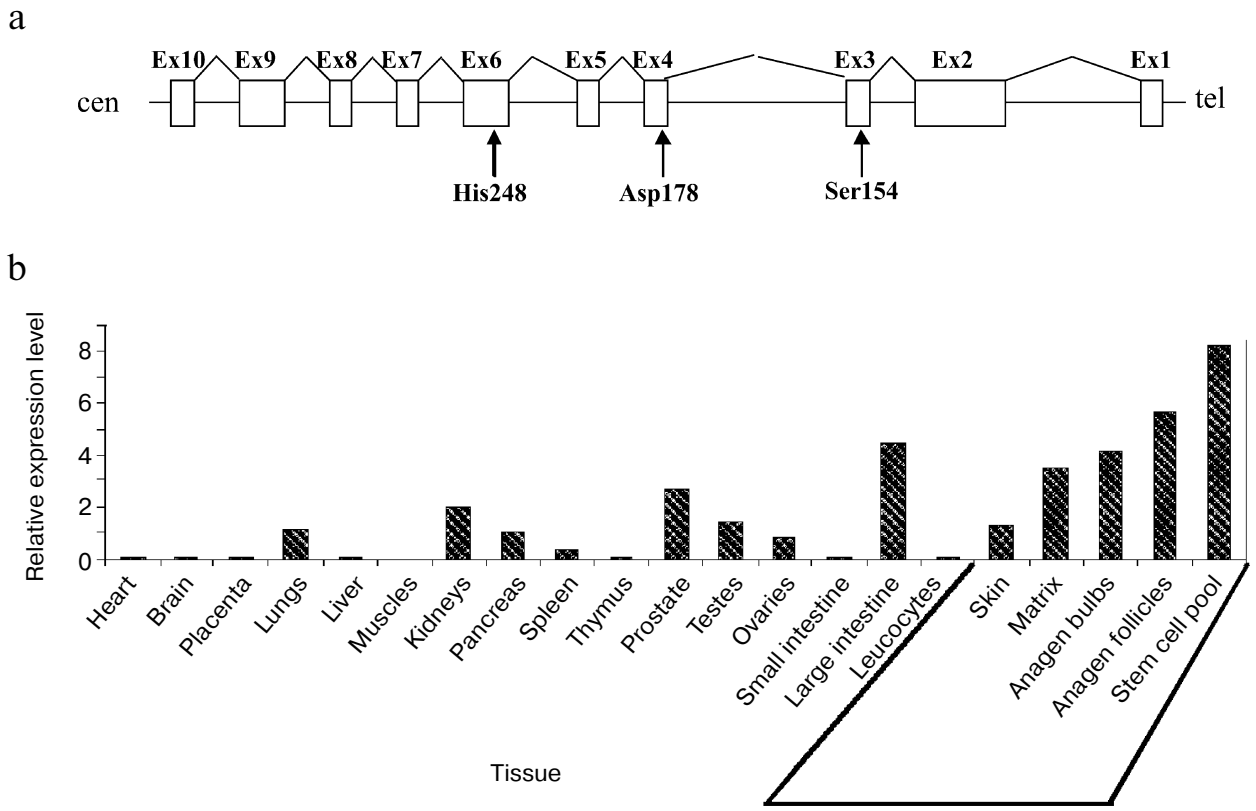


Fig. 1. a) Scheme of intron–exon structure of the *LIPH* gene with indicated positions of the supposed catalytic amino acid residues. b) Spectrum of *LIPH* gene expression [34].

includes four recently found receptors (table): LPA4/GPR23/p2y9 [42], LPA5/GPR92 [43], GPR87/LPA6 [44], and P2Y5/LPA7 [45]; they are ~35% homologous on the level of amino acids (Fig. 2). These receptors are supposed to belong to the group of purinergic receptors (P2Y), but their role is not quite clear. Because the receptors GPR87 and P2Y5 are not formally renamed as LPA receptors, in the table they are presented with a question mark.

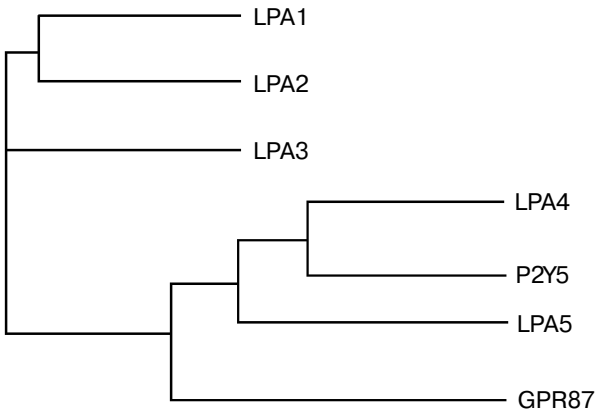


Fig. 2. Phylogenetic tree of human LPA receptors (Clustal W algorithm) [45].

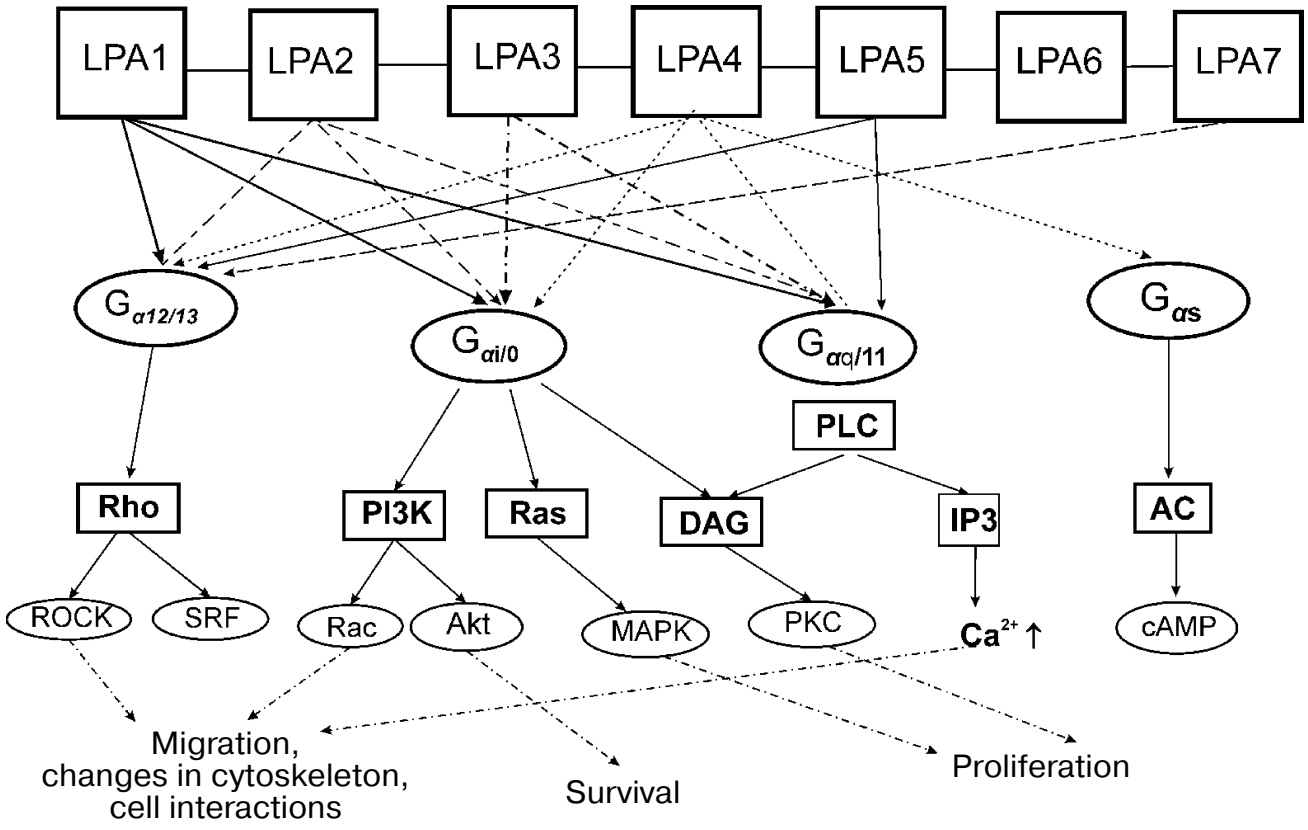
The most widely distributed receptor is LPA1, the expression of which is strongest in placenta, brain, and heart (table) [41]. The expression of LPA2 and LPA3 receptors is tissue-specific. Thus, LPA2 is mainly expressed in thymus and spleen [39], whereas LPA3 is mainly expressed in pancreas, heart, testes, and prostate (table) [40, 46]. The expression of LPA4 in human tissues is rather low (being maximal in ovaries) [42]. The receptor LPA5 is expressed in small intestine, spleen, and embryonic stem cells [47]. An increased level of GPR87 mRNA is found in cells of differently localized squamous cell carcinomas, in particular, in cells of squamous cell carcinoma of the lung [48], and also in their metastases in lymph nodes [49]. Data on P2Y5/LPA7 receptor expression have accumulated recently (table) [50], and the specific expression of P2Y5 in hair follicles seems to be the most interesting [45] because it can play a key role in hair growth due to induction of LPA. LPA receptors are analyzed in some earlier published reviews [51-53], including one in Russian [54].

LPA can also have other targets in cells. In particular, LPA can act as an endogenous ligand for the hormonal receptor PRAPγ [55]. Moreover, recent studies have shown that, along with the signaling lipid sphingo-

Transmembrane G protein-coupled receptors of LPA

LPA receptor	Synonyms	Chromosomal localization (human)	Expression specificity in the adult organism	Signaling pathways		Cellular effects	References
				family of G-proteins	effector		
LPA1	EDG2	9q32	majority of tissues; dominates in placenta, brain, and heart	$G_{\alpha i/o}$, $G_{\alpha q/11}$, $G_{\alpha 12/13}$	AC↓, ERK↑, Akt↑, Rho↑, Rac↑, PLC↑, $[Ca^{2+}]_i$↑	involved in the development of brain, neuropathy pain, kidney and lung fibrosis; responsible for LPA-induced migration of tumor cells determining their invasiveness and ability to metastasize	[41, 46, 51-53, 56-59]
LPA2	EDG4	19p12	majority of tissues; dominates in thymus and spleen	$G_{\alpha i/o}$, $G_{\alpha q/11}$, $G_{\alpha 12/13}$	AC↓, ERK↑, Akt↑, Rho↑, PLC↑, $[Ca^{2+}]_i$↑	influences cell proliferation and survival (protection of epithelial cells during irradiation and chemotherapy)	[39, 41, 46, 51-53, 61, 62]
LPA3	EDG7	1p22.3-p31.1	majority of tissues; dominates in pancreas, heart, testes, and prostate	$G_{\alpha i/o}$, $G_{\alpha q/11}$	AC↑↓, ERK↑, PLC↑, $[Ca^{2+}]_i$↑	plays key role in embryo implantation in pregnancy (shown in mice)	[40, 41, 46, 51-53, 63]
LPA4	GPR23/ P2Y9	Xq13-q21.1	rather low in majority of tissues; maximal in ovaries	$G_{\alpha q/11}$, $G_{\alpha 12/13}$, $G_{\alpha s}$	AC↑, $[Ca^{2+}]_i$↑	influences actin stress fiber formation; inhibits growth of neurons and their morphological differentiation; prevents LPA-dependent migration and invasiveness of tumor cells	[42]
LPA5	GPR92	12p 13.31	low in majority of tissues, high in small intestine, spleen, embryonic stem cells, and dorsal root ganglion cells	$G_{\alpha q/11}$, $G_{\alpha 12/13}$	AC↑, $[Ca^{2+}]_i$↑	influences actin stress fiber formation	[43, 47]
LPA6 (?)	GPR87	3q25	high in placenta and prostate; low in thymus; increased in cells of squamous cell carcinoma of the lung			determines proliferation and survival of cells of planocellular carcinomas	[44]
LPA7 (?)	P2Y5	13q14	high in stomach, bone marrow, nerve terminals, skin, hair follicles; moderate in placenta, kidneys, gall bladder	$G_{\alpha i/o}$, $G_{\alpha 12/13}$	ERK↑, $[Ca^{2+}]_i$↑	decreases adhesion of intestinal cells and plays key role in hair growth	[45, 50]

Note: AC, adenylate cyclase; ERK, extracellular signal-regulated kinase; Akt, protein kinase B; Rho and Rac, GTP-binding proteins; $[Ca^{2+}]_i$, intracellular free calcium concentration.



Pathways of signaling transduction with involvement of LPA receptors. Designations: Rho, Ras, Rac) GTP-binding proteins; PI3K) phosphoinositol-3 kinase; DAG) diacylglycerol; IP3) inositol-3-phosphate; AC) adenylate cyclase; ROCK) Rho kinase; SRF) serum response factor; Akt) protein kinase B; PKC) protein kinase C; cAMP) cyclic adenosine-3′:5′-monophosphate; $Ca^{2+}\uparrow$) increase in intracellular concentration of free calcium

sine-1-phosphate, LPA can activate the orphan receptor P2Y10 [56].

Studies on mice with knockout of genes encoding LPA receptors, as well as studies on some familial diseases in humans, have shown that LPA receptors are involved in various physiological and pathological processes. Thus, the receptor LPA1 is involved in brain development [57], in neuropathy pain [58], and in development of kidney fibrosis [59] and of lung fibrosis [60]. Moreover, LPA1 is responsible for the LPA-induced migration of tumor cells, which determines their invasiveness and ability to metastasize [61]. LPA2 is involved in protection of the intestinal epithelium cells against damage caused by irradiation and chemotherapy [62, 63]. LPA3 plays a key role in the embryo implantation in pregnancy [64]. The receptor GPR87 is probably involved in the regulation of survival and proliferation of human tumor cell lines [49]. It is shown that GPR87 is necessary for the p53-dependent cell survival in response to damage of DNA and can be considered as a promising target for therapy and prevention of cancer [65].

As mentioned, the receptor P2Y5 is directly involved in hair growth, and mutations in the gene encoding P2Y5 are shown to be related with development of autosomal-recessive hypotrichosis [34, 66].

Despite the variety of cellular receptors of LPA, there are some common elements in the regulatory pathways controlled by them [54]. This concerns the receptor interaction with G protein. GTP-binding proteins (Ras and Rho) are involved in mechanisms of the signal conversion from LPA (Scheme). These proteins stimulate the cell proliferation and the initial stage of transformations of cytoskeleton proteins. They are all coupled with G protein in transmitting the signal through mitogen-activated kinase (MAPK), phospholipase C, and some protein tyrosine kinases. Thus, the signal arising as a result of binding of GPC receptors with LPA is transmitted through the G protein chain and induces proliferation by triggering intermediate transcription factors SRF and TCF (Scheme). For functioning, they require inclusion of the Ras- and Rho-pathways. These transcription factors, in turn, bind to certain regions of DNA and initiate cell responses such as proliferation, migration, or cell interactions [67].

As mentioned, depending on the structure (number of double bonds and sn1- or sn2-position of fatty acid in

the molecule) LPA can selectively activate GPC receptors [40]. Thus, the receptor LPA3 displays rather high affinity for LPAs with unsaturated fatty acids. This seems to be an explanation for selective cell response induced by unsaturated LPAs, exemplified, in particular, by calcium mobilization in human A431 cells and proliferation and differentiation of smooth muscle cells [10, 13].

It is not yet clear what type of receptor is involved in various effects of LPA, in particular because of insufficiency of data on agonists and antagonists of LPA receptors. Note that knowledge about mechanism(s) of LPA receptor action will be valuable for chemical genomics and will promote searches for drugs to modify LPA responses.

NATURAL AND SYNTHETIC ANALOGS OF LPA

Cyclic phosphatidic acids are natural analogs of LPA (Fig. 3). A cyclic phosphatidic acid called PHYLPA was first isolated from the plasmodium *Physarum polycephalum* [68]. PHYLPA was shown to reversibly inhibit the activity of eukaryotic DNA polymerases of the α-family [68], as well as cell division [69]. Cyclic PAs were found in human blood serum [70], but until recently it was unclear what enzyme could be involved in their generation. Tsuda et al. have shown that cyclic PAs in mammalian serum are generated under the influence of ATX, which catalyzes intramolecular transphosphatidylation of lysophospholipid molecules [71].

Despite the chemical structure similar to that of LPA, cyclic PAs display an opposite biological activity: while LPA activates cell proliferation, cyclic PAs suppress proliferation [68]. As discriminated from LPA, cyclic PAs inhibit the invasiveness of tumor cells and their ability to metastasize [72]. Natural cyclic PAs, along with their synthetic analogs, are weak activators of LPA1-, LPA2-, LPA3-, and LPA4-receptors of LPA [73]. However, they

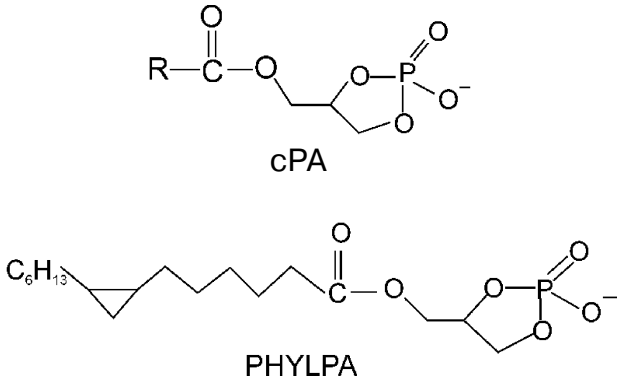


Fig. 3. Structural formulas of natural analogs of LPA – cyclic phosphatidic acid (cPA) and PHYLPA.

are potential inhibitors of ATX activity and thus suppress synthesis of LPA inhibiting the *in vitro* invasiveness of tumor cells and their *in vivo* ability to metastasize [73, 74].

Thus, cyclic analogs of LPA seem promising for antitumor therapy. Nevertheless, there are some limitations. First, one must not forget that hydrolytic cleavage of the cyclic phosphate ring will result in production of LPA, which is involved in the activation of tumor tissue proliferation. Second, cleavage of fatty acid residues by phospholipases can decrease the half-life of cyclic forms of PAs. Therefore, some attempts were made to synthesize different derivatives of cyclic PAs. Carbacyclic PA (ccPA) derivatives of cyclic PAs with the phosphate group oxygen substituted by methylene group in sn2- or sn3-position were more efficient in inhibiting the migration of tumor cells *in vitro* and their ability to metastasize *in vivo* [74].

It would be interesting to create different LPA derivatives chemically modified for decreasing their sensitivity to phospholipases and phosphatases but manifesting the same activity as long-living specific agonists and antagonists of LPA receptors or as inhibitors of the lysophospholipid activity of ATX [75, 76]. Such compounds might be useful in fundamental studies on the role of different LPA-specific receptors *in vitro* and *in vivo*, and are also promising for the treatment of various human diseases.

PHYSIOLOGICAL FUNCTIONS OF LPA

LPA stimulates the growth and differentiation of various types of cells, influences their survival, and also determines changes in cell morphology and mobility. LPA is necessary for maintaining homeostasis of many physiological processes including the development of brain and vascular system, the functioning of the nervous system, and reproduction [77]. However, this lipid mediator can also contribute to development of some pathologic processes, including progress of cancer [24, 78]. Some examples of the biological activity of LPA are presented further.

Data suggesting the role of LPA in pathophysiology of the cardiovascular system have recently accumulated. The LPA level in blood serum increases due to its release from platelets in response to damage and thrombosis [79] and also in myocardial infarction [80]. Some data indicate that LPA can be involved in the development of atherosclerosis and in the regulation of vascular tonus [15]. LPA increases expression of genes regulating angiogenesis, including vascular endothelial growth factor (VEGF) [81] and interleukin IL-8 [82]. A direct involvement of LPA in angiogenesis is shown on a chicken chorioallantoic membrane system (CAM) [83].

In mouse experimental models, ATX also displayed angiogenic properties *in vivo* and was necessary for development of blood vessels [84, 85].

LPA plays an important role in recovery processes and it stimulates proliferation and migration of endothelial cells [86], smooth myocytes [87], and also of fibroblasts [88]. LPA can display a vasoconstrictive effect and increase synthesis of cell matrix metalloproteinases involved in recovery of tissues [89]. Local application of LPA promotes healing of skin wounds [90], and injected rectally it stimulates recovery of intestinal epithelium cells in rats [91].

LPA in physiological concentrations is present in saliva and seems to contribute to recovery of damage in the upper region of the digestive tract. LPA significantly increases the *in vitro* growth of cell cultures from esophagus, pharynx, and tongue [6].

LPA receptors act differently on nervous system cells activating different signaling pathways. Thus, the LPA1 receptor contributes to development of neuropathy by transmitting a signal through the Rho/Rho-kinase pathway [58]. In mice with knockout of the *lpa1* gene, LPA was shown to play an essential role in processes responsible for demyelinization. Moreover, LPA can inhibit the growth of neurons and morphological differentiation of some neuronal cell lines due to activation of the receptor LPA4 [92, 93].

Recent data suggest that LPA together with sphyngosine-1-phosphate is involved in regulation of immune response [94]. LPA can influence migration, adhesion, or activation of different cells of the immune system – T- and B-lymphocytes [95, 96], monocytes [97], and mast cells [98, 99]. LPA is involved in development of inflammation in such diseases as asthma and allergy, acting as a proinflammatory factor.

LPA and its receptors play an important role in development of different malignancies such as cancer of breast, ovaries, prostate, brain, and thyroid [24]. The role of LPA is best studied in ovarian cancer, where this lipid mediator promotes the growth, development, and metastasis of tumor cells [100, 101]. This is associated with a significant increase in LPA concentration in serum and ascitic fluid of patients with verified ovarian and cervical cancer – the LPA concentration can reach 80 μM [102], whereas its normal physiological concentration in blood serum is 1-5 μM. LPA seems to be involved in development of ovarian cancer from the earliest stages because a significant increase in its concentration is recorded in 90% of patients with stage I of this cancer. Consequently, LPA concentration in plasma can be used as a marker in oncogynecology.

In cell lines of ovarian cancer LPA manifests various biological activities: adhesion/interaction, synthesis of angiogenic factors such as VEGF [81], IL-6 [103], and IL-8 [82]; it increases expression of urokinase plasminogen activator (uPA) [104] and of cyclin D1 enhancing cell proliferation [105]; it prevents apoptosis of tumor cells [106]. As an inducer of IL-6 and IL-8, LPA promotes the metastasis of tumor cells into bone tissue during progression of breast and ovarian cancer [107, 108].

The expression of LPA receptors is increased in different tumors – of LPA2 in colorectal and thyroid gland carcinoma [109, 110], of LPA2 and LPA3 in ovarian cancer [108], of LPA1, LPA2, and LPA3 in cell lines of breast cancer [111]. It is supposed that the mitogenic activity of LPA is mediated through LPA2 and LPA3 receptors and that the migration of cancer cells is regulated through LPA1 [109]. The increased expression of LPA1 correlates with metastasis into lymph nodes in thyroid gland cancer [110]. However, LPA1 also regulates cell proliferation during development of tumors of breast and of prostate [107, 112]. Just this receptor is used as a therapeutic target, especially for prevention of tumor metastasis into bone tissue [113].

Recently accumulated data indicate that both LPA and ATX are involved in tumor growth [24]. An increased expression of ATX is observed in cells of various malignancies including glioblastoma [22], mammary gland carcinoma [114], renal cell carcinoma [23, 24], neuroblastoma [24], thyroid gland cancer [24], and Hodgkin's lymphoma [115].

The available data suggest that lysophosphatidic acid, G protein-coupled receptors, and enzymes involved in LPA metabolism are promising targets for development of drugs for treatment of various pathological conditions.

Interest in studies on LPA is now increasing first of all due to the broad spectrum of its biological activities. We have attempted to generalize the available data on metabolism, reception, and physiological role of LPA in the human organism. It should be noted that despite certain progress in understanding mechanisms of signal transduction with involvement of G protein-coupled receptors, LPA-related metabolism remains unclear.

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