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Review

Novel bioactive glycerol-based lysophospholipids: New data – New insight into their function

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ABSTRACT

Based on the results of research conducted over last two decades, lysophospholipids (LPLs) were observed to be not only structural components of cellular membranes but also biologically active molecules influencing a broad variety of processes such as carcinogenesis, neurogenesis, immunity, vascular development or regulation of metabolic diseases. With a growing interest in the involvement of extracellular lysophospholipids in both normal physiology and pathology, it has become evident that those small molecules may have therapeutic potential. While lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P) have been studied in detail, other LPLs such as lysophosphatidylglycerol (LPG), lysophosphatidylserine (LPS), lysophosphatidylinositol (LPI), lysophosphatidylethanolamine (LPE) or even lysophosphatidylcholine (LPC) have not been elucidated to such a high degree. Although information concerning the latter LPLs is sparse as compared to LPA and S1P, within the last couple of years much progress has been made. Recently published data suggest that these compounds may regulate fundamental cellular activities by modulating multiple molecular targets, e.g. by binding to specific receptors and/or altering the structure and fluidity of lipid rafts. Therefore, the present review is devoted to novel bioactive glycerol-based lysophospholipids and recent findings concerning their functions and possible signaling pathways regulating physiological and pathological processes.

1. Introduction

For many years lysophospholipids (LPLs) have shied away from the limelight. However, the rapidly expanding field of bioactive LPLs has recently shown that they are not only intermediates in the pathways for the synthesis of various phospholipids – the main constituents of biological membranes, but are also important signaling mediators in their own right, with wide-ranging biological effects. In particular, LPLs with glycerol (lysophosphatidic acid, LPA) or sphingoid (sphingosine-1-phosphate, S1P) backbones are attracting attention in this area. While LPA and S1P have been studied in detail, the actions of other LPLs such as lysophosphatidylglycerol (LPG), lysophosphatidylserine (LPS), lysophosphatidylinositol (LPI), lysophosphatidylethanolamine (LPE) or even lysophosphatidylcholine (LPC) have not been elucidated to such a high degree. Although very little is known about their endogenous receptors, recent *in vitro* studies suggest that they can induce various and unique cellular responses.

In spite of their simple structure, LPLs were found to be very important biologically active compounds. Glycerol derivatives of lysophospholipids share a few structural features: they possess a glycerol backbone, a phosphate head group at the *sn-3* position, a hydroxyl group at the *sn-2* (or *sn-1*) position and a single fatty acid chain at the *sn-1* (or *sn-2*) position (Fig. 1). There are no more properties that characterize the whole family, as the linkage between the phosphate head group and fatty acid tail, the level of unsaturation and substituents vary within different molecules. It is also well known that the acyl chain at the *sn-2* position of the 2-acyl-lysophospholipid has a tendency to migrate to the *sn-1* position, thus resulting in the creation of the 1-acyl-lysophospholipid [1].

The relative simplicity and diversity of lysophospholipid structures lead to interactions of those compounds with various biomolecular targets. The hydrophobic tail of fatty acid residue and the

Abbreviations: ALP, alkaline phosphatase; CMC, critical micelle concentration; FPRL1, formyl peptide receptor like-1; HODE, hydroxyoctadecadienoic acid; IAP, intestinal alkaline phosphatase; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; LPG, lysophosphatidylglycerol; LPI, lysophosphatidylinositol; LPL, lysophospholipid; LPS, lysophosphatidylserine; LPT, lysophosphatidylthreonine; OEA, oleoylethanolamide; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PL, phospholipid; PLC, phospholipase C; PS, phosphatidylserine; ROS, reactive oxygen species; S1P, sphingosine-1-phosphate; SPC, sphingosylphosphorylcholine; TRP, transient receptor potential.

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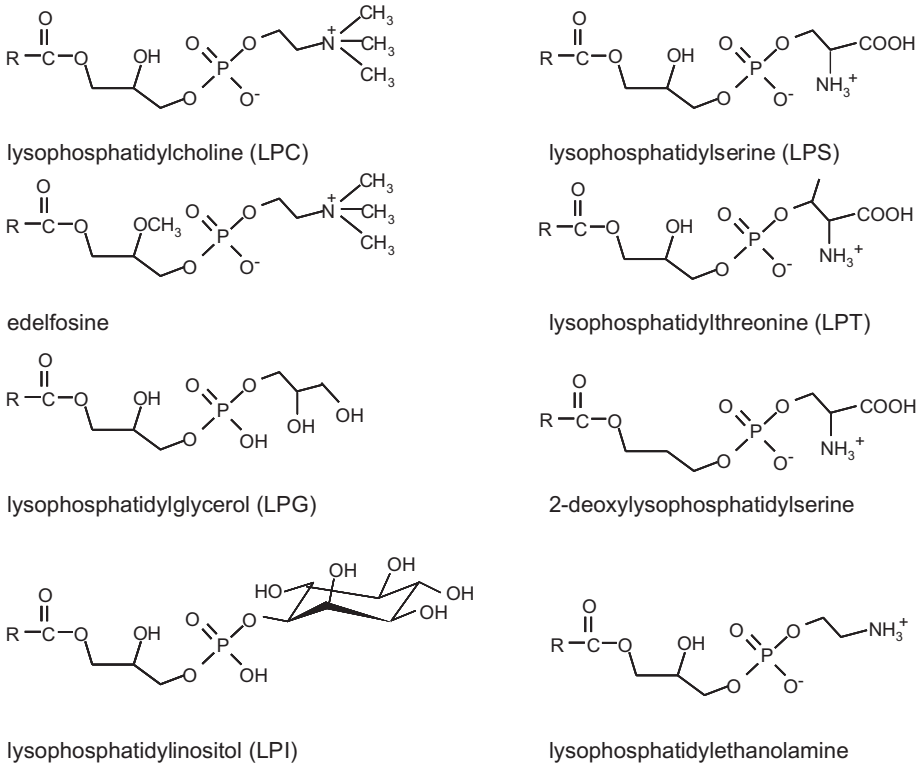

Fig. 1. Structures of glycerol-based lysophospholipids; R-fatty acyl chain.

hydrophilic head group determine the specific chemical construction of LPL molecules and consequently affect their unique biological activities: detergent-like action, an ability to alter mechanical properties of lipid membranes, and interaction with G-protein coupled receptors and ion channels. A broad range of LPL's biological properties has prompted many synthetic efforts to construct new lysophospholipid analogs. Special attention has been paid to a class of ether-linked LPL analogs (Fig. 1) due to their antitumor activities [2]. Another example comes from studies by Iwashita et al. who synthesized 2-deoxy derivatives of LPS and replaced its serine with threonine residue (Fig. 1) [3]. These modifications led to changes in activities of the new compounds both *in vitro* and *in vivo*.

Since biological activities of LPA and S1P have been amply reviewed elsewhere [4,5], this paper will focus on other aforementioned LPLs, and in particular glycerol-based lysophospholipids. Those molecules have been shown to be involved in such diseases as cancer, diabetes, obesity, atherosclerosis, and inflammation. Within the last couple of years much progress has been made in deorphanizing novel GPCRs for LPC, LPS, LPI, LPG and LPE as well as in identifying other targets responsible for their biological activity. Therefore, the present review is devoted to novel glycerol-based lysophospholipids and recent findings concerning their functions and possible signaling pathways regulating physiological and pathological processes.

2. *In vivo* distribution, biosynthesis, and activities of LPC, LPS, LPI, LPG, and LPE

LPLs have been observed to be produced by various pathways: by enzymes mediated *de novo* synthesis from glycerol-3-phosphate and fatty acyl-CoA, and through hydrolysis of one acyl group of phospholipids (PLs). In enzymatic biosynthesis of LPLs from PLs mainly phospholipases and acyltransferases are involved [1,6,7] (Table 1).

2.1. Lysophosphatidylcholine

LPC is the most abundant LPL with relatively high (around 150 μM) concentration in human blood [8]. However, the concentration of total LPC in mouse serum has been recently estimated as 66 μM [9]. Most of the circulating LPC molecules are associated with albumin. LPC is also a major phospholipid component of oxidized low-density lipoproteins [8]. Several types of LPC molecules with various acyl chains (16:0, 18:0, 18:1, 18:2, 20:4 and 22:6) have been found in human plasma [10].

LPC present in plasma is derived from phosphatidylcholine by lecithin:cholesterol acyltransferase (LCAT) catalyzing the transacylation of the *sn-2* fatty acid residue of lecithin to free cholesterol, resulting in the formation of cholesterol ester and LPC [7]. The rate of ester formation by LCAT depends on the nature of the headgroup, fatty acid residues, and the macromolecular properties of the lipid [6,11]. It is also generated by the action of phospholipases A_2 (PLA_2) and phospholipases A_1 (PLA_1), which are able to cleave the *sn-2* and *sn-1* ester bond, respectively [12,13] and which are subdivided into several classes [14–16]. Appreciable amounts of LPC are also formed in plasma by endothelial lipase [8] (Table 1).

LPC was recognized as carriers of fatty acids, phosphatidylglycerol and choline between tissues [17]. As a pro-inflammatory LPL, it is involved in modulation of T cell functions and immunity. In activated microglia (brain macrophages), LPC has been found to trigger IL-1β processing and release [18]. LPC has been reported to enhance the expression of cytokine-induced IFN-γ [19] and TGF-β1 [20]. Moreover, LPC-dependent NADPH oxidase stimulation and production of reactive oxygen species (ROS) has been demonstrated to activate caspase-1 that converts pro-cytokines to their mature, biologically active forms (IL-1β, IL-18 and IL-33) [21]. LPC is also involved in the production of prostacyclin PGI_2 *in vitro* in primary human aortic endothelial cells and *in vivo* in mice model. Among LPC species under studies, LPC 18:1 and 20:4 have been