Published in final edited form as:

Prostaglandins Other Lipid Mediat. 2010 April ; 91(3-4): 130–138. doi:10.1016/j.prostaglandins.2009.02.002.

Lysophosphatidic acid (LPA) receptors: signaling properties and disease relevance

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Abstract

Lysophosphatidic acid (LPA), a water-soluble phospholipid, has gained significant attention in recent years since the discovery that it acts as a potent signaling molecule with wide-ranging effects on many different target tissues. There are currently five identified G protein-coupled receptors for LPA and more are undergoing validation. The complexity of the expression pattern and signaling properties of LPA receptors results in multiple influences on developmental, physiological, and pathological processes. This review provides a summary of LPA receptor signaling and current views on the potential involvement of this pathway in human diseases that include cardiovascular, cancer, neuropathic pain, neuropsychiatric disorders, reproductive disorders, and fibrosis. The involvement of LPA signaling in these processes implicates multiple, potential drug targets including LPA receptor subtypes and LPA metabolizing enzymes. Modulation of LPA signaling may thus provide therapeutic inroads for the treatment of human disease.

Introduction

Lysophosphatidic acid (LPA), once thought to be an inert metabolite in the biosynthesis of membrane phospholipids, is now well-recognized as an important signaling molecule. Acting through G protein-coupled receptors (GPCRs), LPA alters many different cellular responses, such as proliferation, survival, cytoskeletal changes, calcium influx and much more [1,2]. The stimulating action of LPA was recognized by the 1960s for its ability to elicit calcium responses in smooth muscle cells [3]. In the ensuing decades, numerous studies indicated that LPA could serve as a signaling molecule. The primary molecular mechanism was reported in 1996 with the cloning of the first cognate receptor for LPA [4]. The receptor, now called LPA₁, is a GPCR that couples to heterotrimeric G proteins (G_i, G_q, G_{12/13} alpha subunits) and can elicit multiple cellular responses upon LPA stimulation [1,5]. Based on sequence similarity, two other LPA receptors were soon identified: LPA₂ and LPA₃ [6,7]. Recently, two more distantly related GPCRs have been shown to respond specifically to LPA, LPA₄/P2Y₉/GPR23 and LPA₅/GPR92 [8,9]. LPA₄ is more closely related to purinergic receptors while sharing only 20–24% amino acid identity with LPA_{1–3} [8]. LPA₅ was identified using reverse transfection screening and shares about 35% identity with LPA₄ [9,10]. These receptors are encoded by distinct genes that are referred to as *LPAR1-5* (in humans) and *Lpar1-5* (in mouse) [11,12]. Two additional receptors, GPR87 and P2Y₅, have been proposed to be new LPA receptors [13,14], however, further validation of these identities is required.

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This review will focus on the receptor-mediated signaling characteristics of LPA and its potential involvement in human diseases. We will discuss the effects of LPA in different cell types, their employed receptors, and current diseases models influenced by receptor-mediated LPA signaling. GPCRs as a group are a major target for many current medicines suggesting that LPA receptors may represent future drug targets.

LPA metabolism and signaling

LPA is present in all mammalian cells and tissues, including blood, where concentrations in plasma range from 0.1 to 1 μ M, while serum concentrations can exceed 10 μ M. Different detection methods are in current use, including enzymatic assays, TLC-gas chromatography and HPLC/tandem MS. A detailed comparison of the techniques used to measure LPA was recently reviewed [15]. Biologically relevant LPA levels (well above apparent K_d and/or EC50 values for the five known LPA receptors) implicate their importance in physiological function.

There are at least two major pathways of LPA production. The first one involves hydrolysis of phosphatidic acids (PAs) by phospholipase A1 and A2 (PLA₁ and PLA₂). This pathway is thought to be mainly intracellular or on the cell membrane since the substrate PAs are located in cell membranes [16]. The second pathway is via cleavage of lysophospholipids (LPLs), such as lysophosphatidylcholine (LPC) and lysophosphatidylserine (LPS), by lysophospholipase D/autotaxin (LysoPLD/ATX). There are at least two additional pathways that can produce LPA: acylation of glycerol 3-phosphate by glycerophosphate acyltransferase (GPAT) and phosphorylation of monoacylglycerol by monoacylglycerol kinase (MAG-kinase). However, LPA produced by these two pathways appears to serve as precursors for glycerolipid synthesis rather than a source of extracellular signaling molecules [17]. ATX was first identified as a cell motility-stimulating factor that possessed nucleotide phosphodiesterase activity [18], but was subsequently identified as a major enzyme producing LPA [16]. ATX activity is present in blood and strongly correlates with LPA concentration [19]. While homozygous ATX knockout mice die at mid-gestation (see below) heterozygotes have an LPA concentration in the blood that is roughly 50% of that in wild type mice. This suggests that ATX activity accounts for the majority of LPA production in blood [20]. The degradation of LPA involves several different categories of enzymes, including LPA-acyltransferase (LPAAT), lipid phosphate phosphatase (LPP), and lysophospholipase [17]. LPA may be converted back to PA by LPAAT, hydrolyzed by LPP-1, 2, and 3, or converted into glycerol-3-phosphate by lysophospholipases [17,21]. A subclass of the LPP family, lipid phosphatase-related proteins or plasticity related genes (LRPs/PRGs), was also shown to modulate LPA signaling. However, whether the LRPs/PRGs directly hydrolyze LPA remains to be determined [22].

The biological activity of LPA is mediated largely through the activation of the five receptors, LPA₁ to LPA₅. All are Type 1, rhodopsin-like GPCRs with seven-transmembrane alpha helices. Distinct associations with heterotrimeric G protein subtypes and different expression patterns allow LPA to produce various effects on different cellular and organ systems. LPA₁ to LPA₃ signaling pathways are extensively reviewed elsewhere and will not be addressed in detail here [1,2,23,24]. Recent studies have provided insights into the signaling characteristics of the newly identified LPA₄ and LPA₅, which will be focused upon next (Figure 1).

LPA₄ specifically binds to LPA with an apparent K_d value of 45 nM and activates a number of G proteins. Evidence for G_{q/11}-coupling was provided in experiments where LPA₄-mediated transient increases in calcium concentration were completely inhibited by YM-254890 [25]. G_{12/13}/Rho signaling was demonstrated through LPA₄-mediated cytoskeletal rearrangement (cell rounding) that was completely inhibited by Y-27632 [25,26]. Evidence for G_s-coupling was shown through activation of LPA₄ that resulted in an increase in cAMP concentration using transfected CHO and B103 cells [8,26]. Evidence for G_i-coupling is less clear [8,26].

Recently, LPA₄ was reported to be a negative regulator of fibroblast motility using knock out strategies [27]. LPA₄ is expressed at high levels in the ovary, while moderate expression is seen in the testis, thymus, pancreas, and small intestine [8], and may have broader expression during embryonic development, although the null mutant phenotype is grossly normal [27].

LPA₅ signaling is similar to LPA₄. It couples to G_q to increase intracellular calcium levels, and G_{12/13} to induce neurite retraction [9]. Activation of LPA₅ also induces cAMP accumulation and phosphoinositide hydrolysis. The G-proteins responsible for these latter effects remain unclear, however, the phosphoinositide hydrolysis was insensitive to pertussis toxin treatment, indicating that G_i is not involved [9,10].

Receptor mutagenesis

There are currently no crystal structures for any native LPA receptors. Mutagenesis studies combined with computational analysis identified several important residues in LPA₁₋₃, most of them located in transmembrane domains (Figure 2). R3.28 is important for efficacy and potency for all three receptors, while Q3.29 mutation decreases ligand-interaction and activation of LPA₁ and LPA₂ more than LPA₃ [28]. In contrast, W4.64A is important for LPA₃ activation, but not LPA₁ and LPA₂. The R5.38A mutant of LPA₂ and the R5.38N mutant of LPA₃ also show decreased activation by LPA. Mutation K7.36A decreased the potency in LPA₂ but increased E_{max} in LPA₁. Lastly, K7.35A increased LPA₃ EC₅₀ to LPA about 10-fold [28]. LPA₄ and LPA₅ share less amino acid identity with LPA₁₋₃, and detailed models of their interaction with LPA are not available. Most of the residues described above are not present in LPA₄ and LPA₅, suggesting that these receptors have different ligand binding characteristics. Further research is needed to identify the critical residues for these receptors, and all will need to be re-evaluated once crystal structure data become available.

LPA signaling in human disease

Cardiovascular disease

Heart failure is one of the leading causes of death in the western world. In myocardial infarction, ischemia and hypoxia are the major causes of damage to cardiac myocytes. LPA appears to play a protective role under ischemic conditions. LPA levels are elevated and have been shown to protect different cell types from hypoxia-induced apoptosis, including cardiac myocytes, mesenchymal stem cells and renal cells [29–31]. The protective effect requires the PI3K/Akt and Erk pathway activation downstream of G_i [30,32]. In response to cardiac damage, the heart often enlarges to compensate for reduced contractile force, in a process known as hypertrophy. Experiments both *in vivo* and *in vitro* showed that LPA₁ and LPA₃ contribute to the hypertrophic response through the activation of G_i and multiple downstream effectors, including Rho, PI3K/Akt, and NF- κ B [33,34].

In addition to their survival, myocyte contractility is also regulated by LPA [35]. LPA suppressed the cell shortening induced by isoprenaline through the activation of LPA₁ and/or LPA₃ in a PTX-sensitive manner. It was also shown that LPA increases lipoprotein lipase (LPL) activity in cardiac myocytes, augmenting the utilization and deposition of lipids, and might lead to contractility impairment [36].

Outside of the heart, LPA induces vascular smooth muscle cell (SMC) contraction [37] and elevates arterial blood pressure in rats [38]. LPA was reported to induce intimal hyperplasia, one of the steps leading to atherosclerosis, by the activation of membrane-bound GPCRs. With the use of LPA₁/LPA₂ double knock out mice, Panchatcharam et al. showed that these receptors are responsible for the growth of arterial walls following ligation-induced vascular injury. The *in vitro* proliferation and migration of smooth muscle cells (SMCs) were also attenuated in this

mouse, which might be the cause of the protective effect [39]. However, LPA₁ and LPA₂ are not required for LPA induced SMCs de-differentiation, an important step in neointima formation, which suggested the function of other LPA receptors in this model.

LPA not only participates in neointimal formation, but also in a number of other processes involved in arterial plaque formation, such as: endothelium dysfunction, monocyte attraction and adhesion, LDL uptake and pro-inflammatory cytokine release [40–46]. LPA increased the permeability of the endothelium via RhoA activation without altering the calcium concentration [40]. The increase of permeability may facilitate the entry of monocytes and LDL infiltration. Additionally, LPA recruits monocytes via inducing MCP-1 secretion in endothelial cells [42]. Monocytes differentiate into macrophages after invading the endothelium. Uptake of oxidized LDL may also be regulated by LPA through an LPA₃/G_i/class A scavenger receptor (SR-A) [45]. Furthermore, LPA also induces platelet activation. Since LPA is released by activated platelets, this forms a positive feedback loop *in situ*, thus underlying its role in clot formation [41,47].

Taken together, the data summarized here indicate that LPA is involved in many different aspects relevant to cardiovascular disorders. Depending on the expression of different receptors in various cell types, LPA may exert either a protective or destructive effect on the system.

Cancer

The progression of cancer involves the dysregulation of multiple cellular processes, including cell proliferation, growth, survival, migration, invasion, and promotion of angiogenesis. In both *in vivo* and *in vitro* systems, LPA has been shown to participate in each of these processes (see reviews [23,24,48,49]), underscoring the involvement of LPA and the potential therapeutic benefit of targeting LPA signaling.

LPA was first reported to induce *in vitro* tumor cell invasion in 1993 [50]. Thereafter, studies using many different tumor cell lines and samples from cancer patients showed that LPA was involved in cancer etiology. Pronounced LPA accumulation was identified in the ascites and blood of ovarian cancer patients [51,52]. LPA activates ovarian cancer cells and protects them from apoptosis [53,54]. It also increases the expression of urokinase plasminogen activator (uPA) and matrix metalloproteases (MMPs), which are important mediators of metastasis and invasion [55–57]. Through Rho/ROCK/actomyosin and Ras/MEKK1, LPA accelerates focal adhesion formation and enhances cancer cell migration [58,59]. Similar effects were also seen on other cancers including gastric, colon, prostate, pancreas, liver, and brain (glioma) [60–66]. The LPA effects described above are primarily mediated through LPA₂ and LPA₃, while LPA₄ was suggested to participate in the positive feedback of LPA production [67–71]. Interestingly, LPA₁ was recently reported to be a negative regulator in ovarian cancer [72]. Also, in two other reports, LPA₁ mutations were found in lung and liver tumors in rats [73, 74]. This suggests that LPA₁, unlike the other known LPA receptors, may act as a tumor suppressor gene.

These data suggested that LPA signaling may be important in influencing cancer, and may represent therapeutic targets for cancer treatment. Indeed, at least *in vitro*, inhibition of LPA generating enzymes (iPLA2 and ATX), introduction of LPA degrading enzyme (lipid phosphatase-3), and inhibition of LPA₂ all produced an attenuation of cancer cell activity [67,75–77].

During tumor growth, it is important to increase the supply of oxygen- and nutrient-rich blood through angiogenesis. Vascular endothelial growth factor (VEGF) is one of the factors produced by tumor cells to promote angiogenesis and its inhibition leads to tumor growth suppression [78,79]. Interestingly, LPA was shown to induce VEGF expression in ovarian

cancer cells via LPA₂ but not LPA₁ [80], an effect that requires the activation of hypoxia-inducible factor 1 alpha [81]. Additionally, evidence from knockout mouse phenotypes implicates the involvement of LPA in angiogenesis. *Lpar1*^{-/-} and *Lpar1*^{-/-}/*Lpar2*^{-/-} mice are born with frontal cranial hematomas (2.5% and 26% respectively) [82,83]; and ATX knockout mice die at embryonic day 9.5 (E9.5) with severe vascular defects [84]. Taken together, these results implicate LPA as a potential regulator of tumor angiogenesis.

LPA signaling clearly affects different aspects of tumor progression, and there are many different pharmacological targets that may be exploited, including specific receptor subtypes and enzymes involved in LPA production/degradation. Since the effect of LPA is generally pro-tumorigenic, yet might also be paradoxically tumor-suppressive (via activation of LPA₁), more studies on LPA's mechanism of action through different receptors and cell types will be needed to optimize a clinically beneficial approach.

Neuropathic pain

Neuropathic pain, or peripheral neuropathy, is a chronic pain caused by a primary trauma or inflammation in the nervous system. Approximately 7 to 8% of the populations of developed countries are affected by neuropathic pain, with 5% of these representing severe cases [85, 86]. Unfortunately, there is no effective therapeutic drug treatment for neuropathic pain. Treatment generally involves the use of analgesia or narcotic pain relievers, which often have limited efficacy. The cause of neuropathic pain is largely unknown; however, spontaneous signaling from nociceptive c-fibers or cross talk with low threshold A-delta sensory fibers may be contributing factors [87,88].

In mouse models of neuropathy, LPA has been shown to elicit pain while administered locally to the hind paw. This occurs through the activation of LPA₁ and subsequent release of the pro-nociceptive factor substance P [89,90]. The role of LPA in neuropathic pain was further demonstrated with the use of LPA₁ knockout mice. Intrathecal injection of LPA produced allodynia and hyperalgesia in wild type mice, which is seen commonly in neuropathic pain [91]. This effect is totally blocked by LPA₁ deletion or by inhibition of Rho signaling, thus demonstrating the involvement of LPA₁/Rho/ROCK pathways in the initiation of neuropathic pain [91]. Furthermore, *Lpar1*^{-/-} mice are also resistant to neuropathic pain induced by partial nerve ligation [91].

Recently, Inoue et al. published a series of papers providing evidence that autotaxin induces neuropathic pain through the conversion of LPC to LPA [92–94]. This is supported by the observation that heterozygous autotaxin knockout mice (ATX^{+/-}) are characterized by a 50% decrease in ATX activity and a 50% recovery from the neuropathic pain induced by partial sciatic nerve ligation (PSNL) [92]. All the data above implicate LPA signaling in the initiation of, and altering neuronal responses in, neuropathic pain.

In addition, another aspect of neuropathic pain, demyelination, is influenced by LPA signaling. The two axon-myelinating cell types, Schwann cells of the periphery and oligodendrocytes of the CNS, are responsive to LPA. It has been shown that LPA increases Schwann cell survival against serum withdraw through LPA₁/G_i/PI3K pathway [95]. LPA also causes Schwann cells to form wreath-like structures, cell-cell adhesions, and focal adhesion reassembly [96]. In addition, LPA₁ mRNA expression levels are increased after sciatic nerve transection [96]. Similarly, oligodendrocytes also responded to LPA exposure. Phospholipase C (PLC) activity, intracellular calcium levels, protein kinase C (PKC) activity, and mitogen-activated protein kinase (MAPK) activity were all activated through LPA signaling in oligodendrocytes [97, 98]. Recently, it was shown that LPA participates in oligodendrocyte maturation, since exogenous LPA administration leads to an increased oligodendrocyte protrusion network, an important step in maturation. Also, LPA stimulates myelin basic protein (MBP) mRNA

expression and the numbers of MBP positive oligodendrocytes [98]. This LPA effect requires ATX downregulation, while ATX also regulates focal adhesion formation in oligodendrocytes [98,99]. Combined with the previous observations that *Lpar1*^{-/-} mice are resistant to injury induced demyelination, and that LPA induces *ex vivo* DRG neuron demyelination [91,100], it has become clear that LPA signaling influences the histopathological events associated with demyelinating lesions. Further investigation is needed to characterize the relationship between LPA, myelination, and neuropathic pain.

Neuropsychiatric disorders

Many studies have suggested that there is a significant contribution of genetic/biological factors in psychiatric disorders. Developmental defects are thought to be involved in different conditions, such as schizophrenia and bipolar disorders [101,102]. LPA might contribute to the progression of these diseases in view of its potential to alter the physiology of neurons, glial cells, and their progenitors. Effects of LPA on these cell types include survival, proliferation, rounding, process retraction, growth cone collapse, migration and differentiation [2,103]. The measurement of LPA concentration also reveals a biologically significant amount of LPA in rat brain [104]. Moreover, in *ex vivo* cultures of mouse embryonic brain, LPA exposure induced cortical folding, thickening of the cortical wall, increased terminal mitosis/early differentiation in neural progenitor cells (NPCs), and increased survival for the proliferating cells of the ventricular zone (VZ) [105]. Neuronal plasticity comes from the rearrangement of synaptic connections, requiring such processes as neurite retraction and outgrowth, which are regulated by LPA signaling [106,107]. Cytoskeletal rearrangement is also a critical step in long-term memory formation: both processes involve the activation of the Rho-ROCK pathway, which is a major endpoint of receptor-mediated LPA signaling. This signaling pathway may account for reported LPA-related increases in long-term spatial memory [108].

LPA receptor knockout mice provide essential information on the potential role of LPA in CNS function. *Lpar1*^{-/-} mice are characterized by craniofacial dysmorphism, which is also seen in some cases of schizophrenia [83]. Additionally, a variant of this mouse line called the “Malaga variant” showed some additional phenotypes compared to the original null mutant for LPA₁ [83]. Specifically, neurogenesis, maturation, and proliferation of NPCs were decreased, implicating the interaction of a single receptor, LPA₁, with as yet unknown genetic modifiers that can influence cortical development [109,110]. Another LPA₁ knockout strain, independently produced by Harrison et al., showed a schizophrenia-like phenotype [111]. The LPA₁ knockout causes deficits in prepulse inhibition (PPI), a phenotype observed in schizophrenia [112]. Additionally, the 5-HT (serotonin) neurotransmitter system, which is the target of many antipsychotic and antidepressant drugs, is significantly affected through lowered 5-HT turnover in the brains of knockout mice [111]. In other studies, LPA-induced calcium responses were altered in B lymphoblast cell lines originating from bipolar disorder patients [113]. This elevated calcium concentration has been reported to be associated with bipolar 1 disorders [114]. LPA was also shown to interfere with the signaling of an atypical antipsychotic agent, Risperidone, on glial cells [115].

Taken together, evidence is emerging that supports a contribution by LPA signaling to psychiatric disorders. Understanding the complexity of this relationship will require more detailed investigation. The use of receptor subtype-specific agonists/antagonists combined with genetic and behavioral studies on wild type and receptor null-mice will provide more insights into the role of LPA signaling in neuropsychiatric disorders.

Reproductive disorders

LPA receptors are differentially expressed in both testis and ovary, along with other reproductive tissues [116]. In mouse tissues, LPA₁₋₃ are highly expressed in testis, while LPA₁, LPA₂, and LPA₄ are present in the ovary [116]. In humans, LPA₁₋₄ are also expressed in the ovary, and interestingly, LPA₄ expression is higher in the ovary than in any other tissue examined [8,116]. Also, the LPA generating enzymes, PLA1, PLA2, and autotaxin are seen in the testis, while other experiments showed increased autotaxin activity in ovaries of women who received hormonal stimulation [116]. These observations suggest that LPA plays a significant role in the function of the male and female reproductive systems.

The use of LPA₃ knockout mice provided key data demonstrating involvement of LPA signaling in reproductive processes. Timing and spacing of embryo implantation into the uterine wall are affected by the loss of LPA₃, leading to delayed implantation and complete loss of normal spacing of embryos in *Lpar3*^{-/-} dams [117]. The timing defect was caused by the disruption of prostaglandin signaling, since the exogenous administration of prostaglandins rescued the delayed implantation phenotype in LPA₃ knockout mice [118]. In contrast, embryo spacing was not mediated through prostaglandins, but appeared to be the result of uterine contraction induced by LPA₃ activation [119]. Recently, similar LPA/prostaglandin signaling was shown to be important in embryonic development and maintenance of pregnancy in sheep and pig, further confirming the role of LPA signaling in reproduction [120,121]. Other studies have also revealed a role for receptor-mediated LPA signaling in male reproduction. LPA_{1/2/3} triple knockout mice showed reduced sperm production and lowered mating activity, followed by age-related azoospermia (no sperm detected in semen) [122]. This phenotype was associated with increased apoptosis of germ cells in the testis, suggesting that LPA promotes cell survival in the male reproductive system.

Taken together, LPA showed significant involvement in both the male and female reproductive systems. This area requires further investigation and may result in novel therapeutics for assisted reproductive technologies and/or birth control in the future.

Fibrosis

Fibrosis, the formation of excess fibrous connective tissues, was found to be strongly influenced by receptor-mediated LPA in different organs. LPA effects were examined in an animal model of renal fibrosis: unilateral ureteral obstruction (UUO). UUO resulted in increased LPA₁ expression while LPA₃ expression was decreased. The levels of LPA in conditioned media from kidney explants also significantly increased [123]. LPA has been shown to induce connective tissue growth factor (CTGF) expression in renal fibroblast cell lines [124]. Not surprisingly, *Lpar1*^{-/-} mice showed attenuated renal fibrosis in this model; an observation that was further confirmed using Ki16425 and ROCK-inhibitors [124]. Similar effects were also seen in pulmonary fibrosis, however, through a slightly different mechanism. LPA was identified as a fibroblast chemoattractant in post-injury bronchoalveolar lavage (BAL). In a model using bleomycin to induce fibrosis in lung, *Lpar1*^{-/-} mice showed decreased fibroblasts and collagen deposition [125]. Also, the vascular leakage induced by bleomycin is also attenuated in these mice, demonstrating LPA involvement in pulmonary fibrosis. Furthermore, LPA was shown to induce stellate cell and hepatocyte proliferation, which are the main contributors to extracellular matrix (ECM) accumulation in liver [126,127], and the plasma levels of LPA and ATX also rise in hepatitis C induced liver fibrosis [19].

Other diseases

In addition to the major disease areas described above, associations between LPA and other disorders have been reported. A single nucleotide polymorphism (SNP) analysis on 368 individuals with osteoarthritis revealed a linkage between LPA₁ and this disease [128]. This

SNP (rs3739708) located in the promoter region of LPA₁, affects AP-1-mediated transcriptional activity and may increase the expression of LPA₁ [128]. Being the major receptor of LPA in the synovium, the increase of LPA₁ expression might contribute to disease progression, since LPA stimulation *in vitro* induces synovial cells to release inflammatory cytokines and MMPs [128].

Lastly, cholera toxin-induced secretory diarrhea seems to be inhibited by LPA. LPA₂ is expressed by intestinal epithelial cells and interacts with cystic fibrosis transmembrane conductance regulator (CFTR), leading to inhibition of CFTR-induced iodide efflux [129]. CFTR-dependent intestinal fluid secretion in mice was attenuated by LPA administration, suggesting a therapeutic potential of LPA in certain forms of diarrhea [129].

Concluding remarks

LPA signaling has received increasing attention for its involvement in various disease processes as well as normal physiological functions. Here we have tried to provide a brief summary of the mechanisms of LPA signaling and recent findings regarding its potential involvement in different human disease settings (Figure 3). LPA signaling participates in organismal development and maintains normal physiological functions through the orchestrated regulation of LPA production, degradation, receptor expression, and activity. Not surprisingly, LPA plays both positive and negative roles in disease processes. Key to both mechanistic and potential therapeutic approaches is the identification of specific LPA receptors and their involved functions. Further research will provide a foundation towards the development of clinically beneficial therapies based upon receptor-mediated LPA signaling.

Acknowledgments

We would like to thank Howard Tsai for graphical assistance. This work is supported by National Institutes of Health (NIH) grants MH051699, NS048478, and HD050685 awarded to J. C.

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Figure 1.
Summary of the downstream signaling pathways activated by known lysophosphatidic acid (LPA) receptors.

Figure 2.

Protein sequence alignment and phylogenetic tree of human lysophosphatidic acid receptors. (A) Multiple alignment of LPA₁ to LPA₅. The seven transmembrane domains of LPA₁ are shaded red, purple, blue, green, yellow, orange, and grey respectively. Critical residues for ligand interactions identified by mutagenesis studies are indicated with black arrows. (B) Phylogenetic tree of the five known LPA receptors (LPA₁₋₅), two possible LPA receptors (P2Y5 and GPR87), an S1P receptor (S1P₁), and Rhodopsin.

Figure 3.
Schematic summary of human diseases that are known or suspected to involve dysregulation of LPA signaling.