# Neurobiology of Receptor-Mediated Lysophospholipid Signaling

## From the First Lysophospholipid Receptor to Roles in Nervous System Function and Development

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**ABSTRACT: Identification of the first lysophospholipid receptor, $LP_{A1}$/Vzg-1, cloned by way of neurobiological analyses on the embryonic cerebral cortex, has led to the realization and demonstration that there exist multiple, homologous LP receptors, including those encoded by a number of orphan receptor genes known as "Edg," all of which are members of the G-protein-coupled receptor (GPCR) superfamily. These receptors interact with apparent high affinity for lysophosphatidic acid (LPA) or sphingosine-1-phosphate (S1P or SPP), and are referred to based upon their functional identity as lysophospholipid receptors: $LP_A$ and $LP_B$ receptors, respectively, with the expectation that additional subgroups will be identified (i.e., $LP_C$, etc.). Here an update is provided on insights gained from analyses of these receptor genes as they relate to the nervous system, particularly the cerebral cortex, and myelinating cells (oligodendrocytes and Schwann cells).**

### INTRODUCTION

Lysophospholipids are known metabolites in the synthesis of membrane phospholipids. Additionally, these simple phospholipids have cell signaling properties, best documented for two forms in particular, lysophosphatidic acid (LPA or 1-acyl-*sn*-glycerol-3-phosphate) and sphingosine-1-phosphate (S1P or 1-phosphate-2-amino-4-*cis*-octadecene-1,3-diol). Numerous cell signaling features of these lipids have been documented, and many contributions in this volume provide clear examples of these effects. Perhaps the best studied lysophospholipid is LPA. As one examines the literature through the mid-1990s, it is striking how much variability exists in parameters used to assess the effects of LPA. These parameters include the concentrations used, ranging over at least 5 orders of magnitude (e.g., from 1 nM[1] to 100 μM[2]); mode of application, duration of application, which could range from minutes to days; employed cell lines, which range from fibroblasts to oocytes to peripheral nervous system neuroblastomas; the use of serum that itself contains

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**TABLE 1. Nomenclature for lysophospholipid receptors[a]**

| LP Receptor | High Affinity Ligand | Orphan Names |
|---|---|---|
| A1 | LPA | *Vzg-1*/*edg-2*/mrec1.3/GPCR 26 |
| A2 | LPA | *edg-4* |
| A3 | LPA | Bandoh *et al*. (Note Added in Proof) |
| A4 | LPA | unpublished |
| B1 | S1P | *edg-1* |
| B2 | S1P | AGR16/H2118 |
| B3 | S1P | *edg-3* |
| B4 | S1P | unpublished |
| C1 | ? | *edg-6* |

[a]Lysophospholipid receptors are designated by subtype, reflecting functional ligand interactions, genomic structures, and predicted amino-acid sequences. $LP_A$ receptors interact with lysophosphatidic acid, $LP_B$ receptors interact with sphingosine-1-phosphate, and $LP_C$ receptors have unknown ligand specificity. Unpublished receptors have appeared as ESTs in various databases.

LPA; and the assayed responses that varied from cell proliferation to ionic conductance changes to cytoskeletal reorganization. Because of the variability in the systems used to assay the effects of LPA (and other LPs), mechanistic explanations for these phenomena remained uncertain. Fundamentally complicating interpretations was the absence of a cloned LPA receptor—indeed, of any lysophospholipid (LP) receptor—that could allow a solid analytical foundation based on a defined receptor. If it existed, a receptor would be amenable to approaches from which the signaling properties of lysophospholipids and their receptors could be assessed using molecular genetic approaches. It should be noted that much evidence predicted the existence of specific G-protein-coupled receptors (GPCRs) for LPA (and S1P); however, a significant body of data supported nonreceptor mechanisms as well.[3–5] The absence of truly specific antagonists to block LP activities further frustrated classic approaches to possible receptor identification and pharmacological analyses.

The emergence of the first LPA receptor from basic analyses of the embryonic cerebral cortex was unexpected based on what was known about LPA responses, yet made strong biological sense in view of what LPA had been previously shown to do in at least some cell lines. In studies of the embryonic cerebral cortex,[1] a screen for new GPCRs with enriched cortical expression identified a gene that was named "ventricular zone gene-1" (*vzg-1*) because of its expression in the neuroproliferative zone of the cortex called the ventricular zone (VZ).[6] Overexpression of this gene within the cell lines from which it was derived—thus enabling it to interact with biologically relevant G-proteins and downstream signaling pathways—provided clear evidence that it encoded a high-affinity receptor for extracellular LPA (EC50 in the low nM range). This identity received support from additional overexpression studies,[7] and was confirmed by heterologous expression in mammals[8] as well as yeast.[9] In view of its clear functionality, *vzg-1* was renamed lysophospholipid receptor A1 ($LP_{A1}$).[8,10–12] A related orphan receptor gene (*edg-1*) was later shown to interact with the structurally similar LP, sphingosine-1-phosphate (S1P),[13,14] and thus constituted the first member of a family of high-affinity S1P receptors, the $LP_B$ subfamily;[12,15] TABLE 1 summarizes this nomenclature. Additional information on the

molecular biology of these receptors can be found elsewhere.[8,10,12,15] In addition to providing a biology leading to the first LP receptor, the nervous system appears to be a major site for LP receptor function. Here we review some recent data on our growing understanding of the neurobiological roles for LP signaling.[16]

## EXPRESSION PATTERNS OF *lp$_{A1}$* WITHIN THE EMBRYONIC NERVOUS SYSTEM

Normal expression of *lp$_{A1}$/vzg-1* was first observed within the developing brain,[1] where it was present from the middle trimester (the earliest point examined) through adulthood. A characteristic band by Northern blot of around of 3.8 kb was identified that could contain both the long form of the receptor and/or a truncated form.[10] The spatial localization of gene expression was determined by *in situ* hybridization that identified two cellular loci of gene expression that occurred at distinct phases of development. During prenatal life, most expression was observed among cortical neuroblasts of the neuroproliferative VZ, along with a secondary signal found near the pial surface of the cerebral wall; the cells expressing this gene are not known, but may be related to pial cells of neural-crest origin. In the mouse, neurons are born over a discrete period of embryonic life that starts around embryonic day 11 (E11) and ends around E18. The expression of *lp$_{A1}$* then became undetectable toward the end of cortical neurogenesis, and was absent by birth.

With further development during the postnatal period, another region of expression was identified that was distinct from the VZ. The hybridization pattern was obvious during the first postnatal week, and it was localized to cells within developing fiber tracts that suggested glial cells, most likely the cells of myelination within the central nervous system, the oligodendrocytes. By combining the use of *lp$_{A1}$* with the PLP gene (an oligodendrocyte marker), double-labeling *in situ* hybridization allowed identification of the cells as oligodendrocyte but not astrocytes.[11] This pattern of *lp$_{A1}$* expression generally correlates with the period during which oligodendrocytes are myelinating axons, and the high level of expression is maintained over the course of the first several postnatal weeks. Following this period, the expression decreases to low levels that are generally observed at older ages of adulthood. In addition, myelinating cells of the periphery, the Schwann cells, also express high levels of *lp$_{A1}$*, although this expression appears to remain at the same high levels throughout life, at least within the sciatic nerve where it has been studied most carefully. These expression patterns pointed to two major loci of possible LPA receptor function: cortical neuroblasts and myelinating glia.

## ANALYSES OF LP$_{A1}$/VZG-1 IN CORTICAL NEUROBLASTS AND MYELINATING GLIA

Of the growing family of LP receptors, by far the most neurobiological information comes from studies of the first LPA receptor LP$_{A1}$/Vzg-1. The identification of this receptor came from fundamental studies on the development of the embryonic cerebral cortex, but lessons learned from this system also apply to the second locus

of expression, the oligodendrocytes of the central nervous system, and Schwann cells of the peripheral nervous system.

### *LPA Effects on VZ Embryonic Neuroblasts from the Cerebral Cortex*

The original name of $lp_{A1}$ was *ventricular zone gene-1* or *vzg-1,* based on its remarkable pattern of expression within the cortical proliferative region. There is a sizable literature comprising studies of this small region of the developing brain, and some of the clear cell fates that have been established include cell proliferation,[6] cell differentiation,[21,22] and the onset of significant apoptosis.[23–28] Somehow these cell fates are related to a very characteristic and well-known movement of VZ neuroblasts: they change their morphology in a way that approximates points in the cell cycle. First, cells are bipolar or fusiform during the DNA synthesis phase. Sometime toward the end of the S-phase, the VZ cell begins to change shape by first retracting its basal process (pointing toward the pial surface). Once the retraction commences, the process continues until the VZ cell completely changes its cell shape and becomes spherical, or "rounds-up" at the apical surface of the cerebral wall, overlying the lateral ventricle. From this rounded shape, the cell then commences mitotsis, producing two daughter cells. The process can then repeat itself if the daughter cells remain blasts, returning back to a bioplar, fusiform shape followed by a repeat of the cell-cycle process. In contrast, if a VZ neuroblast has become postmitotic, it can instead migrate in a basal direction, out from the VZ to locate within the cortical plate, an anatomical compartment that contains the postmitotic neurons destined to be the gray matter of the cerebral cortex. Although this change in cell shape, called "interkinetic nuclear migration," was described more than 60 years ago,[29,30] neither the biological significance of it nor the involved cellular mechanisms controlling neuroblast shape is known.

This neurobiology of VZ cortical neuroblasts provides clues to what LPA and other lysophospholipids could be doing within the developing brain. Cell lines derived from the VZ showed a similar type of initial movement that was initiated by LPA, whereby cells changed their shape to resemble the rounded morphology seen in the VZ.[1] Modest mitogenic stimulation was also observed, based on BrdU incorporation,[8] although the extent of stimulation suggested that this was not a major mitogen in the VZ. An aspect of this signaling was that cell proliferation studies required extended periods of LPA exposure. If LPA signaling were indeed relevant to the VZ, changes should be seen on a shorter time scale, say, less than a minute.

The way to examine such responses was by using electrophysiology on primary cultures of VZ cells, and we thus pursued this line of study.[18] Primary cultures of VZ embryonic cortical cells, as well as the original cortical neuroblast cell lines from which $lp_{A1}$ was originally identified,[1,17] were examined using whole-cell patch-clamp techniques.[31] Clusters of cells were examined, as compared to known stimuli that affect the electrophysiology of VZ cells, as had previously been reported from cortical tissue slice studies.[32–34] Exogenous LPA was delivered in a targeted manner by use of a puffer pipette at nM concentrations. This resulted in two clear types of ionic change within VZ cells that were identified in up to 60% of cells recorded within clusters. These changes had latencies of approximately 30 s, and consisted of increased chloride and increased nonselective cation conductances. The two ionic changes appeared to be within distinct cell populations. Additionally, approximately

one-third of the cells did not respond with ionic changes. Of particular note, the ionic responses developmentally preceded or existed simultaneously with the previously identified GABA and/or L-glutamate ionotropic conductances,[33] and these responses appeared to result in a depolarization of the cells, based on the resting potential. What role these LPA-dependent ionic changes play remains unknown; however, they could influence parameters of DNA synthesis.[33] Regardless, LPA signaling currently represents the earliest extracellular stimulus of cortical VZ cells thus far described.[18]

Complementing these electrophysiological changes, clear morphological changes were also observed. LPA induces clear neuroblast cell rounding and process retraction, and changes the shapes of VZ neuroblasts (Fukushima, Weiner, and Chun, submitted). The signaling pathways activated in response to LPA for morphological phenomena appear to be similar to those documented in cell lines.[1,8] We currently believe that receptor-mediated LPA signaling is a signaling component of interkinetic nuclear migration[29,30] for VZ neuroblasts of the cerebral cortex. The true roles and fate outcomes should become clearer with future study.

## PERIPHERAL AND CENTRAL MYELINATING CELLS: OLIGODENDROCYTES AND SCHWANN CELLS

Postnatal studies of *lp$_{A1}$/vzg-1* receptor gene expression revealed, in both mice[20,35,37] and rats,[36] that LPA signaling was likely to affect the biology of these myelinating cells. Of particular note were these two observations: first, a mouse mutant with increased oligodendrocyte apoptosis, the *jimpy* mouse, also was found to have decreased expression of *lp$_{A1}$/vzg-1*;[11] and, second, a previously identified mutation known as *vacillens* maps to the same chromosomal location as *lp$_{A1}$*.[10,12] This now extinct mutation exhibited signs of peripheral neuropathy consistent with a defect in nerve function that can accompany demyelination. Altogether, these data suggested that LPs, and particularly LPA via its receptor LP$_{A1}$/Vzg-1, could influence the basic cell biology of myelinating cells.

We recently examined this possibility in Schwann cells in primary culture to identify a biologically relevant function of LP signaling.[20,35,37] Schwann cells in primary culture express at least two LP receptor genes, *lp$_{A1}$/vzg-1* and *lp$_{B3}$*, although the intact sciatic nerve also expresses the S1P receptors *lp$_{B1}$* and *lp$_{B2}$*. This profile of expressed receptors indicates a high-affinity stimulus by LPA that should be distinguishable from those effects mediated by similar affinity actions of S1P. Using primary cultures of Schwann cells, we determined that LPA, administered exogenously at concentrations of 10 nM or greater, is a potent survival factor, with efficacy that equals or even exceeds the known survival effects of neuregulins.[38,39] This observation is of note in that the survival activity is as efficacious as the peptideric mediator, neuregulin, whose effects are mediated by single membrane spanning receptor tyrosine kinases. In Schwann cells, LPA activates both insensitive pertussis toxin and sensitive heterotrimeric G-protein. The survival activity appears to be mediated by $G_i$, a well-defined pathway for LP$_{A1}$ based on previous work.[1,8] Also, this receptor-mediated LPA survival activity was demonstrated to involve activation of PI3 kinase, which is also used in neuregulin-mediated survival. Consistent with the

observed survival activity induced by LPA was the activation of the down-stream kinase Akt (also called PKB) by the previously defined step of phosphorylation of Ser473. These results implicated receptor-mediated actions of LPA as a new stimulus of the Akt survival pathway, which could mechanistically account for the effects of exogenously applied LPA on cultured Schwann cells.[20] These data are also of note in view of the lack of S1P survival effects despite the presence of $LP_B$ S1P receptors[15] or the reported actions of S1P as a second messenger in cell survival.[40] Application of S1P had no statistically significant influence on cell survival, which leads us to conclude that receptor-mediated survival cannot be compensated for by the other LP receptors, nor by S1P as a second messenger.

## FUTURE DIRECTIONS

The field of LP signaling is changing rapidly with the availability of cloned receptors. Since the first receptor identify was published in 1996, the categorization of homologous orphan receptors, most from ESTs, has provided a new focus for understanding the biology of these signaling lipids. The prominent expression of many of these receptors in the nervous system, and the demonstration of functionality for the first such receptor, $LP_{A1}$, makes it likely that this receptor-ligand system will influence numerous aspects of nervous system function, development, and pathology. A number of essential issues, amenable to careful experimentation, should become clearer in the near future. First, what are the essential biological roles for individual receptors? Which LP receptors are expressed on individual cells, and how do these receptors or receptor combinations affect these cells? Third, what controls receptor expression? Fourth, what is the source of signaling lysophospholipids? There is little doubt that the near future holds exciting answers to these questions.

NOTE ADDED IN PROOF: LPA3/EDG7 has now been published: K. Bandoh, J. Aoki, H. Hosono, *et al.*, Molecular cloning and characterization of a novel human G-protein-coupled receptor, EDG7, for lysophosphatidic acid, J. Biol. Chem., **274**(39)**:** 27776–27785, 1999.

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