

Review

Lysophospholipids and their receptors in the central nervous system[☆]Ji Woong Choi^{a,b}, Jerold Chun^{a,*}^a Department of Molecular Biology, Dorris Neuroscience Center, The Scripps Research Institute, La Jolla, CA 92037, USA^b Department of Pharmacology, College of Pharmacy, Gachon University, Incheon 406-799, Republic of Korea

ARTICLE INFO

Article history:

Received 13 June 2012

Received in revised form 17 July 2012

Accepted 18 July 2012

Available online 31 July 2012

Keywords:

Lysophosphatidic acid

Sphingosine 1-phosphate

G protein-coupled receptor

Central nervous system

CNS disease

ABSTRACT

Lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P), two of the best-studied lysophospholipids, are known to influence diverse biological events, including organismal development as well as function and pathogenesis within multiple organ systems. These functional roles are due to a family of at least 11 G protein-coupled receptors (GPCRs), named LPA_{1–6} and S1P_{1–5}, which are widely distributed throughout the body and that activate multiple effector pathways initiated by a range of heterotrimeric G proteins including G_{i/o}, G_{12/13}, G_q and G_s, with actual activation dependent on receptor subtypes. In the central nervous system (CNS), a major locus for these signaling pathways, LPA and S1P have been shown to influence myriad responses in neurons and glial cell types through their cognate receptors. These receptor-mediated activities can contribute to disease pathogenesis and have therapeutic relevance to human CNS disorders as demonstrated for multiple sclerosis (MS) and possibly others that include congenital hydrocephalus, ischemic stroke, neurotrauma, neuropsychiatric disorders, developmental disorders, seizures, hearing loss, and Sandhoff disease, based upon the experimental literature. In particular, FTY720 (fingolimod, Gilenya, Novartis Pharma, AG) that becomes an analog of S1P upon phosphorylation, was approved by the FDA in 2010 as a first oral treatment for MS, validating this class of receptors as medicinal targets. This review will provide an overview and update on the biological functions of LPA and S1P signaling in the CNS, with a focus on results from studies using genetic null mutants for LPA and S1P receptors. This article is part of a Special Issue entitled Advances in Lysophospholipid Research.

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1. Introduction

Lysophospholipids (LPs) are phospholipid derivatives originating from cell membranes and two of the best-studied LPs are lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P). These two LPs were previously known as biosynthetic metabolites of cell membrane phospholipids, but they are now regarded as important regulators for diverse biological functions through activation of their specific cognate receptors. At present, there is a family of 11 *bona fide* G protein-coupled receptors (LPA_{1–6}; S1P_{1–5}) that link into multiple downstream effector pathways (Fig. 1). LPA and S1P receptors are present in various organ systems, which accounts for their diverse biological roles [1–4]. Important LPA and S1P-mediated biological functions were discovered by studies utilizing genetic null mutants for LPA and S1P receptors [1,4,5]. Currently, there are 10 published receptor-null mice for the following LPA or S1P receptors: LPA₁, LPA₂, LPA₃, LPA₄, LPA₅, S1P₁,

S1P₂, S1P₃, S1P₄, and S1P₅, all of which have been used to uncover valuable receptor-mediated biological functions (summarized in Table 1).

The CNS is one of the biological systems markedly affected by LPA and S1P signaling. Many subtypes of LPA and S1P receptors are expressed in one or more CNS cell types, and their ligands are also enriched there [1,6,7]. Consequently, LPA and S1P signaling affects CNS cell types such as neuroblasts, neurons, astrocytes, and oligodendrocytes to influence cell survival, proliferation, migration, differentiation, and morphological changes (reviewed in [1,3,8–11]). To date, LPA and/or S1P receptors have been identified as important factors in CNS development, as well as having roles in diseases, including MS [12,13], fetal hypoxia and hydrocephalus [14–16], neuropathic pain [17–19], brain ischemic stroke [20,21], neurotrauma [22], developmental disorders like schizophrenia, as well as hearing loss [23–25], seizures [26–28], and Sandhoff disease [29].

In this review, we will focus on the biological roles of LPA and S1P receptors in different CNS cell types, including neurons, astrocytes, and oligodendrocytes, and discuss their involvement in CNS diseases. Specifically, we discuss *in vivo* and *in vitro* data that were obtained from studies using LPA or S1P receptor null mutants. Involved cell types affected in the CNS include not only CNS lineages but also non-CNS lineages such as resident cell types like microglia, which will also be considered.

[☆] This article is part of a Special Issue entitled Advances in Lysophospholipid Research.

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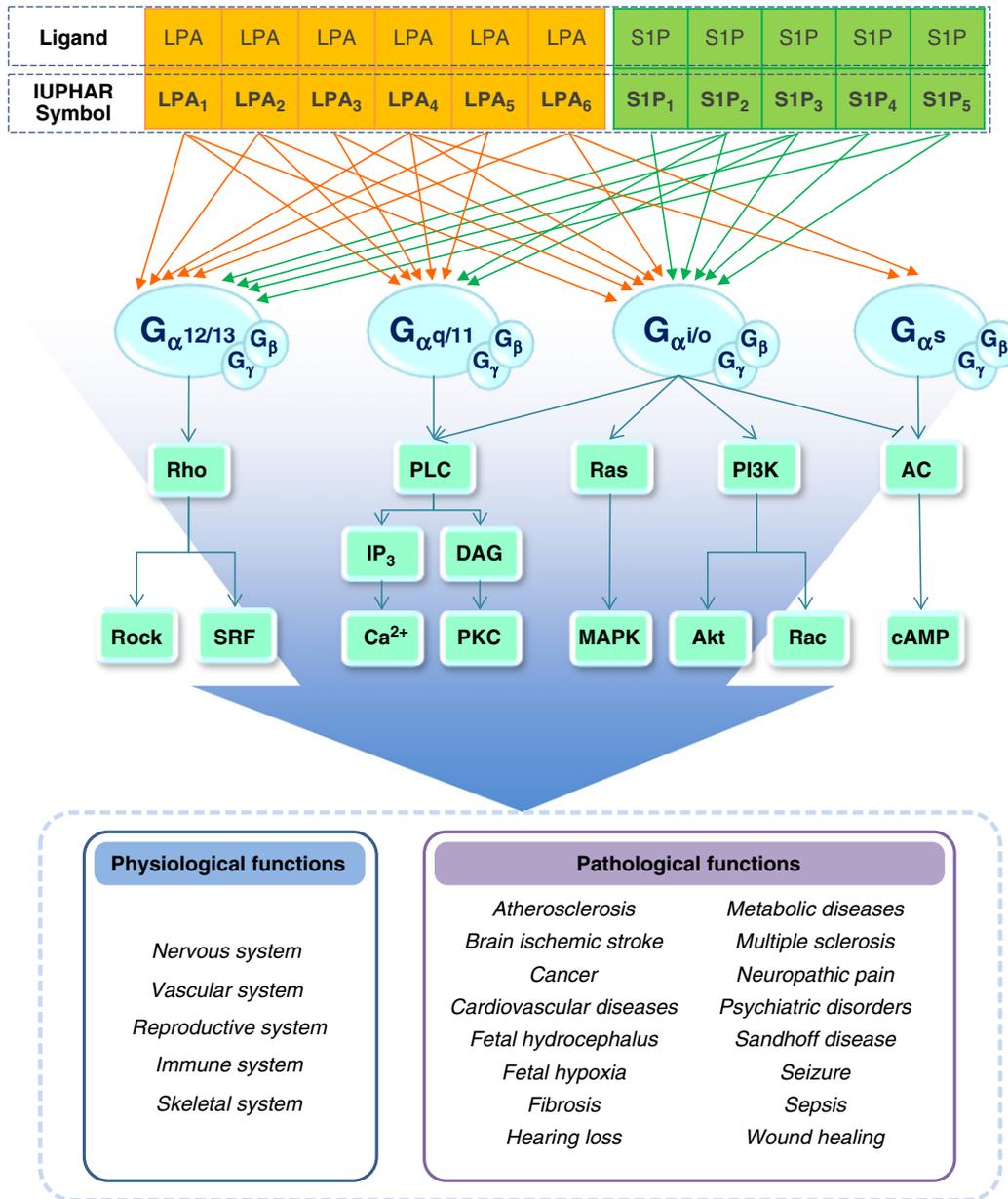


Fig. 1. LP receptors, effector pathways, and related biological functions. Note: Unlike other LPA receptors, 2-acyl-LPA is preferred for LPA₆ as a ligand rather than 1-acyl-LPA. Three more orphan GPCRs have been suggested as new LPA receptors, including GPR87, P2Y10, and GPR35, but more studies are needed to validate these suggested receptors. The effector pathways of LPA₆ have not been clearly identified.

2. LPA and S1P receptor expression in the CNS

In the past decades, the biological activities of LPA and S1P were mechanistically unclear, with explanations ranging from detergent-like membrane perturbation, second messenger activities, to possible receptors. In 1996, the first LP receptor, LPA₁, was identified in the ventricular zone of the embryonic brain [30,31] with subsequent deorphanization based on sequence homology of both new LPA and S1P receptors [7,32–41]. Now, there is a family of 11 LP receptors that are composed of 6 LPA receptors (LPA_{1–6}) and 5 S1P receptors (S1P_{1–5}) (Fig. 1) [2]. In the CNS, many LPA and S1P receptors are present and show varied expression patterns depending on cell type, neuroanatomical location and developmental stage (reviewed in [1,3,7]). This section will focus on the expression of LPA and S1P receptors in the CNS at tissue and cellular levels.

2.1. LPA receptors: brain and spinal cord

LPA_{1–6} are expressed at varying levels in the CNS during development and/or postnatal life [1,11,41,42]. The temporal changes in expression levels for LPA receptors were characterized in mouse brain using Northern blot and real-time PCR analysis. LPA₁, LPA₂, and LPA₄ are expressed in the developing brain [30,36,43,44], whereas LPA₃ is expressed in the postnatal brain [44,45]. LPA₁ shows high gene expression in the embryonic ventricular zone (VZ), a major site for neuroprogenitor cell proliferation during prenatal developmental stages, after which it diminishes with the transient VZ, reappearing during postnatal life within oligodendrocytes that may influence myelination [30,43,46], indicating roles for LPA signaling in cortical development. Pathological stimuli can increase expression levels of LPA receptors [22,47,48] (detailed in the “CNS diseases” section).

Table 1
Biological functions identified thru studies utilizing LPA or S1P receptor null mutants.

Receptor	Validated biological functions
LPA ₁	<ul style="list-style-type: none"> – Perinatal viability [63] – Body size, brain mass, suckling behavior, and craniofacial defects [63,72] – Pulmonary, renal, and dermal fibrosis [151–155] – MEF migration [156] – Adipogenic activity [157] – Vascular injury [158] – Bone development [159] – Hypoxia-induced pulmonary remodeling^a [160] – NPC signaling [50] – Schwann cell biology [63,161]
LPA ₂	<ul style="list-style-type: none"> – MEF and NPC signaling [50,68] – Tumor formation [162,163] – Indirect effect on neuronal differentiation [99]
LPA ₃	<ul style="list-style-type: none"> – Timing and spacing of implantation [165–167] – Spermatogenesis and germ cell survival [168]^b – Protease functioning in uterus [169] – Prostaglandin signaling [166]
LPA ₄	<ul style="list-style-type: none"> – Embryonic viability [62,172]^c – Vascular development [172]
LPA ₅	<ul style="list-style-type: none"> – Neuropathic pain [42]
S1P ₁	<ul style="list-style-type: none"> – Vascular development [173,174] – PDGF-induced MEF motility [175] – Pulmonary fibrosis [176] – Cortical neurogenesis and cell survival [78] – T or B cell trafficking [141,177,178]
S1P ₂	<ul style="list-style-type: none"> – Reduced litter size [179] – Vascular dysfunction [180,181] – Vasoconstriction [182] – Wound healing in injured liver [183,184] – MEF or hepatic myofibroblast biology [179,184,185]
S1P ₃	<ul style="list-style-type: none"> – Reduced litter size [179] – Alveolar epithelial barrier function [188] – MEF signaling [189,190] – Responses in splenic marginal sinus [191] – Myofibroblast differentiation [192] – Crosstalk with CXCR4 signaling in bone marrow cells [193]
S1P ₄	<ul style="list-style-type: none"> – Megakaryocyte differentiation [203]
S1P ₅	<ul style="list-style-type: none"> – NK cells trafficking [204–206]
	<ul style="list-style-type: none"> – Neuropathic pain [17,18,137–140] – Schizophrenia [14,96,97,142] – Cortical development [65,66,72] – Adult hippocampal neurogenesis [70,73] – Synaptic functions [14,96,97] – Astrocyte proliferation [101] – Indirect regulation of neuronal differentiation [99] – Anxiety, motor alteration, and memory impairments [69–71,73,74] – Fetal hypoxia [15] – Fetal hydrocephalus [16] – Synaptic function and neuronal hyperexcitability [27] – Vascular injury [158] – Allergic airway inflammation [164] – Chemotaxis of immature dendritic cells [170] – Neuropathic pain [139] – Leukocyte infiltration [171] – MEF migration [62] – Myelination-related protein expression [114] – EAE [81] – FTY720 efficacy on EAE [81] – Cuprizone-induced demyelination [114] – Angiogenesis in hypoxia [186] – Hearing loss and vestibular defects in nulls [23–25] – Seizure and offspring death in seizure-prone nulls [26,28]^c – Streptozotocin-induced diabetes [187] – Vasodilation by HDL or FTY720 [194–196] – Vascular tone regulation [197] – Cardiac fibrosis [198] – Cardioprotective effect of HDL, S1P, or SPC in ischemic injury [199–201]^d – PAR-1-mediated sepsis [202] – Sandhoff disease [29]

MEF: mouse embryonic fibroblasts and NPC: neural progenitor cells.

^a Negative regulation on remodeling in double nulls for LPA₁/LPA₂.

^b Related defects are observed in triple nulls for LPA₁/LPA₂/LPA₃.

^c Dependent on genetic background.

^d Another report indicates that both S1P₂ and S1P₃ are required for the cardioprotection.

LPA receptors are involved in a variety of cell biological processes, including proliferation, differentiation, morphological changes, migration, survival/apoptosis, as well as molecular physiological responses that include calcium signaling and electrophysiological changes [1,11,49,50]. In neuroprogenitor cells, a functional locus for LPA signaling, LPA₁, LPA₂, LPA₃, and LPA₄ are expressed [50]. In neurons, LPA₁ and LPA₂ are expressed, but the latter is more abundantly expressed [11,51]. A recent study identified LPA₅ expression on sensory and motor neurons in the spinal cord and linked its functional role to pain processing, whereby LPA₅ nulls showed a reduced pain phenotype accompanied by downregulation of phosphorylated cAMP response element binding protein (pCREB) signaling in the spinal cord [42]. This unique expression pattern may also involve astrocytes which express LPA₁ to LPA₅ [11]. Interestingly, LPA₁ and LPA₂ are upregulated in activated astrocytes following spinal cord injury [47], suggesting that these two receptor subtypes play possible roles in astrogliosis-related pathologies. In microglia, another important glial cell type for CNS pathogenesis, LPA₁ and LPA₃ are expressed, and the latter is upregulated following the administration of a neuroinflammation-inducing agent [52,53]. In oligodendrocytes, LPA₁ and LPA₃ are expressed and specifically, the LPA₁ expression pattern is correlated with oligodendrocyte differentiation [46,54–56].

2.2. S1P receptors: brain and spinal cord

The CNS is also a major locus for S1P receptors, in which 4 of the 5 S1P receptors are expressed, including S1P₁, S1P₂, S1P₃, and S1P₅ [3,4,6]. Among these, S1P₁ to S1P₃ are widely expressed throughout the body, while S1P₅ is expressed at relatively high levels in the CNS [3,6,57,58]. Like the LPA receptors, S1P₁ to S1P₃ are expressed in the developing brain [3], suggesting a possible role of these receptors in cortical development.

At a cellular level in the CNS, S1P receptors are also involved in a variety of biological processes. All four S1P receptors that are present in the CNS are expressed in neurons, astrocytes, microglia, and oligodendrocytes with varying expression patterns [6]. In astrocytes, 4 S1P receptors can be expressed at varying levels, depending on growth conditions (S1P₃>S1P₁>S1P₂>S1P₅) [6]. The astrocyte expression level of S1P₅ is very low, but its expression is upregulated upon exposure to growth factors [59]. When activated by pathological stimuli, S1P₁ and S1P₃ are upregulated in activated astrocytes [60], indicating that these receptor subtypes may be important for pathogenesis. In microglia, the expression level for S1P receptors is dynamically changed upon activation: in activated microglia, S1P₁ and S1P₃ are downregulated, but S1P₂ is upregulated [53]. In oligodendrocytes,

the expression pattern of S1P receptors depends on cell maturation [57]. S1P₅ is more highly expressed in mature oligodendrocytes than other S1P receptors, but, in contrast, its expression levels are relatively similar to other expressed S1P receptors before maturation.

3. Biological functions of LPA and S1P receptors in CNS cell types

The discovery of the first LPA receptor, LPA₁, and the role it plays in nervous system development, has served as a template for LP research in the CNS as well as other tissues. Since then, a variety of specific responses at cellular and tissue levels have been identified, including proliferation, morphological changes, cell migration, differentiation, and survival. This section will discuss biological functions of LPA and S1P receptors in CNS cell types, such as neuroblasts, neurons, astrocytes, and oligodendrocytes, and also in a non-CNS-resident cell type, the microglia.

3.1. Functions in neural progenitor cells (NPCs)

Neural progenitor cells (NPCs) are responsible for neurogenesis, which involves proliferation, morphogenesis, migration, apoptosis and differentiation. LPA and S1P signaling influence a range of neurogenesis-related functions of NPCs. Both signaling lipids are involved in development, but to date, more studies have identified roles for LPA receptors influencing neurogenesis, with comparatively fewer studies also identifying similar S1P receptor effects.

LPA signaling regulates biological responses of NPCs by at least 3 subtypes of LPA receptors, LPA₁, LPA₂, and LPA₄ ([50]; LPA₆ expression has not yet been established). As previously noted, the possible role of LPA receptors in CNS development was indicated by a restricted expression pattern of LPA₁ in the cortical VZ. Later, LPA₂ expression was identified in postmitotic neurons of the embryonic cortex [51,61] and LPA₄ in developing brain [38,62]. Neurogenesis-related biological responses relevant to NPCs have been revealed by heterologous expression studies utilizing cell lines where single or multiple LPA receptors (LPA₁–LPA₅) are expressed (reviewed in [7,11]). Subsequent studies using primary NPCs, neurospheres, and *ex vivo* cultures have shown that LPA controls cell proliferation and/or differentiation through at least, LPA₁ [63–67]. It has become clear that LPA₁ acts as an important modulator of cortical development through studies using LPA₁-deficient NPCs or whole cortical cultures [63,65,66]. In NPCs from LPA₁ nulls, the ability of LPA to induce normal neurogenesis-related responses like migration, morphological changes, proliferation, and differentiation is lost [63,65], strongly suggesting that LPA₁ acts as a modulator of neurogenesis. Studies using an organotypic whole cortex, *ex vivo* culture system, revealed that LPA₁ is a crucial factor in LPA-induced survival and differentiation of NPCs (LPA₂ was also revealed to be involved in this process) [66]. In addition, LPA has been identified as one of the earliest of neurotransmitter-like stimuli of ionic conductance changes in NPCs, further implicating LPA as a physiological component in cortical development [49,50]. These influences were associated with relatively minor anatomical defects in overall brain development, complicated by differential effects of background strain. LPA₁ nulls showed a smaller brain with reduced cortical width and cerebral wall thickness associated with 50% perinatal lethality [63] that limits *in vivo* examinations to studies of survivors; no obvious neuroanatomical differences were observed in null mutants for LPA₂ or LPA₄ [62,63,68]. The relatively mild phenotypes may reflect LPA receptor subtype rescue, or, in the case of LPA₁ nulls, strain-dependent effects were demonstrated by more pronounced developmental defects in a stable variant of LPA₁ null mutants, called the Málaga variant or malLPA₁ [69–74]. These null mutants showed increased survival to normal levels compared to the perinatal lethality previously reported for LPA₁ null mutants [72]. These malLPA₁ null mutants continued to display defective features in cortical development such as reduced cell proliferation and increased apoptosis and also defects in adult neurogenesis including within hippocampal regions [72,73].

With the current data demonstrating the importance of LPA signaling in neurogenesis, more research needs to be done to determine the mechanisms and possible roles of other LPA receptors. In fact, other LPA receptor subtypes, LPA₃ and LPA₅, are not expressed in NPCs, but they are expressed in postnatal brains and embryonic brains, respectively [37,39,43], and moreover, LPA₃ overexpression resulted in morphological changes in NPC cell lines [75].

All five known S1P receptors are expressed in NPCs [76] and S1P₁–S1P₃ are expressed in the developing brain [61]. In particular, S1P₁ is also highly expressed in the VZ, like LPA₁ [61]. S1P signaling related to neurogenesis has been demonstrated using cell lines such as PC12 cells, and S1P signaling influences cell proliferation and differentiation (reviewed in [8]). In primary cultures of rat hippocampal NPCs, S1P induced cell proliferation and morphological changes [77]. To date, only the S1P₁ null mutants show defects in neurogenesis [78], where cell death was increased and cell proliferation and mitotic cell numbers were reduced in embryos [78]. It may be worth determining how S1P₁ regulates neurogenesis by using an *ex vivo* system like the one used for LPA_{1/2} [66,79]. Recently, S1P signaling was reported in the migration of transplanted NPCs towards lesion sites of an ischemic brain and injured spinal cord where S1P₂ and S1P₁ play crucial roles, respectively [76,80] (see “CNS diseases”).

Numerous *in vitro* and *in vivo* studies have identified roles for LPA and S1P receptors in CNS development with particular effects on NPCs, particularly in various CNS disorders. Consistent with this view, LPA and S1P ligand levels are increased in several CNS diseases [20,29,76,80–82]. Studies on whether LPA and S1P signaling may be involved in adult neurogenesis after insults will be of interest.

3.2. Functions in neurons

Effects of LPA and S1P signaling have been evaluated *in vitro* using primary neurons and neuronal cell lines. The effects are largely related to morphological changes involving growth cone collapse and neurite retraction [3]. In addition, both LPA and S1P signaling regulate other neuronal functions involving migration, cell death/survival, synapse formation, and synaptic transmission, as reviewed elsewhere [1,8,9,11]. Here, we will discuss studies using LP receptor-null mutants.

In postmitotic neurons, LPA-induced morphological changes cannot be completely explained by LPA₁, LPA₂, and LPA₃ [51,83]. LPA-induced neurite retraction is accompanied by the formation of F-actin filament retraction fiber caps in postmitotic cortical neurons where two LPA receptors, LPA₁ and LPA₂, are expressed [51]. The effects were preserved even in LPA₁-deficient cortical neurons [51]. Recently, another report showed that LPA₁, LPA₂, and LPA₃ do not appear required to induce morphological changes in retinal neurons in response to LPA [83]. LPA induces neurite retraction and growth cone collapse in retinal neurons, which is preserved in cells lacking LPA₁, LPA₂, and LPA₃ [83]. Therefore, LPA's effects on morphological changes may be mediated by other LPA receptor subtypes, both known and unknown.

S1P acting through S1P₁ likely has similar effects on NPCs based on analyses of receptor and kinase mutants [78] and on studies using systems of gene upregulation by overexpression or gene downregulation by antisense have identified the possible involvement of S1P receptors in neuronal morphological changes [84,85]. Nerve growth factor (NGF) was reported to transactivate S1P receptors, activated *via* sphingosine kinase 1 (SPHK1), resulting in neurite extension, in which S1P₁ overexpression promotes and S1P₂ or S1P₅ overexpression inhibits [85]. When cellular S1P receptors were downregulated by applying specific antisense probes, similar results were obtained. S1P₁ downregulation reversed NGF-S1P-induced neurite extension [85], but S1P₂ downregulation enhanced the extension [84]. Roles for other receptor subtypes are still unknown, however the effects of sphingosine kinase mutants that disrupt normal ligand concentrations suggest that other relevant neuronal abnormalities may exist in S1P receptor genetic null mice that have not yet been fully assessed.

Another function modulated by LP receptors is the regulation of synaptic activity [27,86–88]. Regulation of synaptic activity, along with neuronal survival/death and neurogenesis, is likely an important issue related to memory impairments and psychiatric dysfunctions. Both LPA and S1P signaling are implicated as novel factors that regulate these responses. Regarding neuronal survival/death, both signaling pathways also seem to exert dual actions – neurotoxic and neuroprotective – depending on the applied concentrations or experimental conditions (reviewed in [8,9]). However, it is clear that LPA₁ is normally a survival factor for neurons because apoptotic cell death occurs in embryonic and postnatal LPA₁-null mouse brains [72]. In addition to neuronal survival/death, LPA and/or S1P signaling are linked to neuronal excitability [26,89–93], synapse formation [86,87], and synaptic transmission [14,94–96]. To date, a few pieces of this puzzle have been directly verified, but as yet unidentified receptor subtypes may mediate these responses. For example, some functional defects have been reported using genetic null mutants: in neurons lacking LPA₁, synaptic dysregulation occurs [97] along with a decreased release of neurotransmitters [14,96]; in neurons lacking LPA₂, LPA failed to evoke hyperexcitability [27], and moreover, LPA₂ deletion normalized seizure-like overexcitability by genetic deletion of plasticity related gene-1 [27]; and in cells lacking S1P₂, abnormal hyperexcitability with age-dependent seizures can also occur [26].

3.3. Functions in astrocytes

Astrocytes, the most abundant glial cell type in the CNS, regulate many biological as well as pathological processes that are epitomized by astrogliosis. Many *in vitro* effects of LPA and S1P signaling have been related to astrogliosis to affect proliferation, migration, morphological changes, and activation of related intracellular signaling [1,9,10,98–100]. So far, at least, 3 receptor subtypes, LPA₁, S1P₁, and S1P₃, have been shown to influence astrogliosis, however other receptor subtypes expressed by astrocytes need to be functionally examined. The cell proliferative effect of LPA was absent in astrocytes lacking LPA₁ [101]. S1P₁ and S1P₃ have been shown to be involved in astrogliosis in different disease models: S1P₁ plays a role in astrogliosis in multiple sclerosis animal models [81], while S1P₃ has roles in a Sandhoff disease model [29] or lysolecithin-induced demyelination [102]. Interestingly, functional discrepancy was observed in comparing astrogliosis that was associated with demyelination and CNS damage in an MS model vs. enhanced remyelination in a lysolecithin-induced demyelination model [81,103], suggesting the existence of contextual variables that dictate whether astrogliosis is associated with damage or repair. Similarly, in chronic disease conditions, S1P-mediated astrogliosis seems to be linked to neurotoxicity as in the above disease conditions [29,81], while in acute conditions, it seems to provide neuroprotective effects [102]. In addition to astrogliosis regulation, S1P₁ in this cell type is also important for FTY720 activity: FTY720 (fingolimod) is a new oral medication for MS, which may act through both immunological and non-immunological mechanisms [12,13,81,104–107].

Neuronal differentiation is another prominent function of astrocytes related to LPA signaling. LPA-primed astrocytes secrete soluble factors to increase neuronal differentiation [99,100]. To date, we do not know what soluble factors are released from LPA-primed astrocytes to induce the differentiation, but growth may be involved in this response. In fact, this neuronal differentiation was reversed by blocking the epidermal growth factor receptor [100] and LPA was reported to produce growth factor expression in astrocytes [108]. S1P is also known to produce growth factor expression in astrocytes [109–111]. In this regard, whether S1P-primed astrocytes exert a similar effect on neuronal differentiation remains to be determined. Astrocyte–neuron communication is important for CNS development and post-disease regeneration. Therefore, it is possible that LPA and S1P receptors in astrocytes are novel factors

that indirectly regulate regeneration through aspects of neuronal differentiation.

3.4. Functions in oligodendrocytes

Oligodendrocytes, another type of glia in the CNS, play a major role in myelination. Their functions are also important for CNS development as well as repair after injuries, particularly remyelination that is composed of a series of events like proliferation, migration, and differentiation of oligodendrocyte progenitor cells. Possible roles for LPA and S1P signaling were suggested by the restricted expression pattern of LPA and S1P receptors in oligodendrocytes. LPA₁ expression changes with oligodendrocyte maturation [46,54,55] while S1P₅ expression is highest in oligodendrocytes [6,57,58]. Many *in vitro* studies have reported that LPA or S1P influences cellular responses that are also varied, depending on oligodendrocyte maturation (reviewed in [8,9,11]). Notably, a study using primary oligodendrocytes cultured from S1P₅ nulls clearly showed the importance of this receptor subtype as a survival factor in mature cells [112]. However, there is no obvious myelination defect in LPA₁ nulls [63] or S1P₅ nulls [112], which may reflect functional redundancy between LPA₁ and S1P₅ signaling and/or possible involvement of other receptor subtypes considering that many LPA and S1P signaling pathways share downstream effector pathways [4,113]. In fact, S1P₁ conditional nulls that lack S1P₁ in oligodendrocytic cell lineages have a subtle decrease in expression of myelination-related proteins and subtly thinner myelin in the corpus callosum of nulls [114]. These conditional nulls were more susceptible to cuprizone, a reagent used in a CNS demyelination model [114], indicating that oligodendrocytic S1P₁ is a possible factor in myelination.

Effects of S1P signaling on myelination in oligodendrocytes have been assessed in view of studies using FTY720 that also targets S1P₅, a major S1P receptor subtype in oligodendrocytes. Although there is no direct *in vivo* evidence that the therapeutic effect of FTY720 on MS is via S1P₅, many *in vitro* studies have revealed that FTY720 influences remyelination-relevant biological responses of oligodendrocyte cell lineages, including survival, proliferation, migration, and differentiation (reviewed in [10]). Of note, a study using organotypic cultures identified that demyelinated slice cultures produced by lysolecithin exposure showed improved remyelination with FTY720 exposure [102]. FTY720 reduces clinical symptoms in an animal model of MS accompanied by enhanced remyelination [81] or reduced demyelination [115]. In the cuprizone model, FTY720 reduces demyelination via an unidentified receptor subtype [114]. To evaluate the direct action of FTY720 on remyelination in disease models, S1P receptor conditional nulls targeting implicated S1P receptor subtypes in oligodendrocyte and related cell lineages would be of interest.

3.5. Functions in microglia

Microglia are categorized as a non-neural cell type, but are CNS resident cells. Upon activation, microglia respond to mediate neuroinflammatory processes. Microglia can express a range of LP receptors including LPA₁, LPA₂, LPA₃, S1P₁, S1P₂, S1P₃, and S1P₅ [52,53,116–118]. LPA signaling was reported to regulate proliferation, membrane ruffling and hyperpolarization, metabolic changes, migration, chemokinesis, and growth factor upregulation [52,116,117,119,120]. S1P or its biosynthetic enzymes were reported to regulate membrane hyperpolarization and production of neurotoxic molecules such as tumor necrosis factor- α , interleukin-1 β , and nitric oxide [53,116,121,122]. LPA₃ is upregulated in immunostimulated microglia [53], while *de novo* synthesis of LPA in activated microglia could be one of the factors for the pathogenesis of neuropathic pain [123], and demyelinating agent-induced microglial activation was attenuated by antagonizing S1P₁ and S1P₅ [102]. Furthermore, increased microglial activation in EAE spinal cords was reduced by FTY720 and S1P₁ deletion in CNS cell lineages [81]. The latter indicates that indirect modulation of

S1P₁ can control microglial activation. The precise roles of these receptors in microglial activities remain to be determined.

4. LPA and S1P receptors as promising therapeutic targets in CNS diseases

The biological functions of LPA and S1P signaling on CNS cell types have led to translational research to identify medically relevant roles for LP receptors. Genetic nulls, combined with pharmacological LP receptor modulators, have been utilized to validate therapeutic functions in CNS diseases. The clearest success of this research is FTY720, an S1P receptor modulator approved by the FDA in 2010 as a first oral MS therapy [12,13]. This success has provided proof-of-concept for other therapeutic agents targeting LP receptors in CNS diseases that include ischemic stroke, neurotrauma, psychiatric diseases, seizures, hearing loss, and Sandhoff disease, and for the treatment of developmental disorders including fetal hypoxia and hydrocephalus that can also contribute to psychiatric disorders. In particular, recent data implicating LPA signaling in fetal (congenital) hydrocephalus suggests a novel, medicinal therapy through targeting LPA receptors (discussed below). This section will discuss CNS diseases that may be mechanistically and/or therapeutically accessed through LPA and S1P signaling (summarized in Table 2).

4.1. Multiple sclerosis (MS)

MS is an autoimmune and neurodegenerative disorder of the CNS, representing the most common demyelinating disease of young adults and which includes pathological hallmarks of immune cell infiltration into the CNS, astrogliosis, axonal damage, and demyelination [124,125]. While the underlying cause of MS is still unclear, both immunological and CNS components are essential to MS pathogenesis and progression.

The link between MS and LP receptors came through the discovery of FTY720 (fingolimod) that is a non-selective S1P receptor modulator that binds to 4 of the 5 S1P receptor subtypes (S1P_{1,3,4,5}) [126,127]. Fingolimod (Gilenya) is currently approved to treat relapsing forms of MS in the United States, Europe, United Kingdom, Russia, Mexico, Brazil, Japan and Australia, as well as other markets [12]. It is believed that this drug exerts its therapeutic effect *via* targeting S1P₁ in T-lymphocytes, resulting in the redistribution of lymphocytes to secondary lymphoid organs and a concomitant reduction of lymphocytes in peripheral blood to reduce entry of pathogenic T-cells into the CNS (reviewed in [13,107,128]). However, recent work in animal models of MS (using experimental autoimmune encephalomyelitis: EAE) revealed that FTY720's mechanism of action also involves direct CNS actions wherein it targets S1P₁ in astrocytes [81]. Disease symptoms in conditional nulls lacking S1P₁ in CNS cell lineages and particularly astrocyte lineages were not reduced by FTY720 administration despite the maintenance of its effects on the reduction of peripheral lymphocyte levels. This result indicates that the CNS, particularly astrocytes, may be a new locus of FTY720 efficacy in MS [81]. In addition, disease signs were lower in astrocyte conditional nulls than wild type mice challenged with EAE, indicating that the S1P₁ in the CNS, and more specifically the astrocyte population, may be an important factor for in MS [81]. It is of note that neuronal S1P₁ was not involved in either MS pathogenesis or FTY720 efficacy [81].

What we now know is probably just the tip of the iceberg and many questions remain to be answered regarding S1P₁ loss from oligodendrocytes, microglia, and/or other LP receptors which may reduce MS signs and symptoms and alter FTY720 efficacy. In oligodendrocytes, an important cell type for myelination, two important targets of FTY720, S1P₁ and S1P₅, are quantitatively highly expressed, so S1P signaling may be involved in demyelination as well as remyelination, all of which could be related to MS pathogenesis and FTY720 efficacy. In fact, S1P₅ may be important for FTY720-enhanced remyelination in lysolecithin-induced demyelination [102]. To verify these possibilities,

studies need to be pursued using conditional nulls for S1P₁ in oligodendrocytes, S1P₅ nulls, or combined null mutants. In microglia, the other important cell type for neuroinflammation, S1P₁ could be a possible target for assessment. During EAE, microglia are activated, which is histologically reduced by genetic deletion of S1P₁ in the CNS or by FTY720 exposure [81], suggesting that microglial S1P₁ is involved in MS pathogenesis and FTY720 activity. It cannot be excluded that other LP receptors may also be involved in MS or FTY720 efficacy because some of the reported LP receptors regulate biological events that are related to MS pathogenesis or recovery. Considering that FTY720 targets other S1P receptors – S1P₃, S1P₄, and S1P₅ – it would not be surprising to uncover other receptor-mediated activities relevant to MS, including effects on the endothelium and blood–brain barrier. Moreover, it has been shown that expression levels of each S1P receptor are altered during MS and by FTY720 exposure. In human MS brain lesion sites, S1P₁ and S1P₃ are upregulated in reactive astrocytes [60]. In rat EAE spinal cords, S1P₁ and S1P₅ are downregulated while S1P₃ and S1P₄ are upregulated, and FTY720 administration restores these changes [129]. While some reports provide conflicting results, these studies nonetheless implicate other S1P receptors as possible targets for FTY720. The precise *in vivo* mechanisms of FTY720 efficacy need to be clarified, especially regarding aspects of inflammation, regeneration, and remyelination, all of which are influenced by FTY720 administration in EAE [81]. FTY720 did not prevent neuronal death in a model of optic neuritis as compared to protection seen in EAE models, suggesting response variability as a function of model and possibly neuronal subtypes [115]. In addition, S1P levels are elevated during MS, and can be reduced by S1P₁ deletion in CNS cell lineages, suggesting other levels of control that may be accessed through S1P receptor modulation [81].

4.2. Ischemic stroke

Ischemic stroke is caused by interruption of the blood supply to the brain that results in damage through excitotoxicity and neuroinflammation; both LPA and S1P levels are increased in ischemic stroke, showing elevated LPA levels in plasma and local S1P levels in the infarct area [20,76,82]. Along with elevated ligand levels, SPHK2, an enzyme that produces S1P, is upregulated in ischemic brains [130,131]. However, another study showed no changes in SPHK1/2 in transient ischemic stroke, but instead revealed SPHK2 as a protective factor, through the use of genetic null mutants [132]. In addition to the elevated LP ligand levels, it has been reported that two LPA receptor subtypes, LPA₁ and LPA₂, are also upregulated during retinal ischemia–reperfusion injury [48]. Among these, one study suggested the importance of LPA₁ in a similar system where the blockade of LPA₁ functions by shRNA expression reduced hypoxia-induced retinal ganglion cell death [133]. Distinct mechanisms involving LPA₁ potentiation that promotes fetal CNS damage have also been reported [15]. Combined, these results implicate the involvement of LP signaling in brain ischemic injury, with responses that appear to be neurotoxic or neuroprotective. FTY720 exposure has been reported to reduce brain damage in model systems, such as infarct size, neurological score, and neuronal death, which is induced by transient and permanent ischemic injury [21,118,132,134]. The efficacy may come from an indirect action through reduced inflammatory reactions as well as direct CNS effects. FTY720 administration reduces T cell or neutrophil infiltration into the CNS and microglial activation [21,118,134]. S1P₂, which is not a target of FTY720, has also been associated with brain ischemic injury through a different mechanism – the blockade of S1P₂ by an antagonist or shRNA expression enhanced migration of transplanted neural stem/progenitor cells into the lesion sites where S1P levels are elevated [76]. Considering that LP signaling induces neuroinflammatory responses like astrogliosis, which as noted previously can have opposing roles, the contradictory LP associations observed in stroke likely reflect combinations of altered ligand levels and/or receptor-based changes that, combined with cellular effects of astrogliosis or microglia, produce a

Table 2
Identified functions of LPA or S1P receptors in CNS diseases.

Disease	Receptor	Validated functions	
Multiple sclerosis	S1P ₁	– Attenuation of EAE development and pathogenesis like astrogliosis in nulls [81]	
	S1P ₁	– Loss of FTY720 efficacy in nulls [81]	
	S1P ₁	– Blockade of the increase in S1P levels in EAE spinal cord in nulls [81]	
	S1P ₁	– Upregulation of S1P ₁ and S1P ₃ on reactive astrocytes of MS patients [60]	
	S1P ₁	– Upregulation of S1P ₃ and S1P ₄ and downregulation of S1P ₁ and S1P ₅ in EAE, and reversal of these changes by FTY720 [129]	
Neuropathic pain	S1P ₁	– Downregulation of myelination-related proteins expression in nulls [114]	
	S1P ₅	– FTY720-enhanced remyelination [102]	
	S1P ₁	– Increased susceptibility to cuprizone-induced demyelination in nulls [114]	
	LPA ₁	– Reduced responses to pain <i>via</i> a likely peripheral mechanism [1,17,18,137,138,140]	
Ischemic stroke	LPA ₃	– Reduced LPA levels relevant to pain [139]	
	LPA ₅	– Reduced responses to pain through a distinct, CNS mechanism [19]	
	LPA ₁	– Increased LPA or S1P levels in patients or animal models [20,76,82]	
Neurotrauma	S1P ₂	– Upregulation or no changes of S1P producing protein in the ischemic brains [130–132]	
		– Upregulation of LPA ₁ and LPA ₂ by retinal ischemic injury [48]	
		– Decreased retinal ganglion cell death by hypoxia [133]	
		– Protective effect of FTY720 against transient or permanent ischemic injury [21,118,132,134]	
	S1P ₂	– Enhanced NPC migration into ischemic lesion sites by blocking S1P ₂ [76]	
Traumatic brain injury	S1P ₁	– Upregulation of LPA ₂ and appearance of LPA ₁ on reactive astrocytes of patients [22]	
		– Upregulation of LPA ₂ or LPA ₃ on reactive astrocytes or neurons after the injury [47]	
Spinal cord injury	S1P ₁	– Upregulation of LPA ₁ and LPA ₂ on reactive astrocytes and LPA ₃ on neurons after the injury [47]	
		– Increased S1P levels in injured spinal cords [80]	
Neuropsychiatric diseases	S1P ₁	– NPC migration into lesion sites of spinal cord injury <i>via</i> S1P ₁ [80]	
Schizophrenia	LPA ₁	– Prepulse inhibition, 5-HT synthesis alteration, and craniofacial dysmorphism in nulls [14]	
	LPA ₁	– Schizophrenia-related neurochemical and biochemical changes in nulls [96,97,142]	
Behavioral dysfunctions	LPA ₁	– LPA ₁ downregulation in patients [143]	
	LPA ₁	– Anxiety, motor alterations, and memory impairments in nulls [71,73,74,144]	
	S1P ₂	– Anxiety and spatial memory impairments in seizure-prone nulls [28]	
Alzheimer's disease	LPA ₁	– Attenuation of cocaine-induced locomotor activity in nulls [69]	
	LPA ₁	– Enhanced defects of hippocampal neurogenesis in nulls under chronic stress conditions [70]	
	LPA ₁	– Upregulation of LPA or S1P producing proteins in patients [145,146]	
	LPA ₁	– Direct or indirect S1P exposure reduces BACE1 activity [145,147]	
	LPA ₁	– Decreased S1P levels in patients [148]	
Developmental disorders	LPA ₁	– Interconnection between A β and S1P producing protein [149]	
		– LPA reduces neuronal death by A β [150]	
		– Attenuation of hypoxia-induced cortical disorganization in nulls [15]	
		– Development of fetal hydrocephalus model by injecting LPA into embryo [16]	
		– Attenuation of LPA-induced fetal hydrocephalus features in nulls [16]	
Fetal hypoxia	LPA ₁		
Fetal hydrocephalus	LPA ₁		
Others	S1P ₂	– Neurodegenerative hearing loss and vestibular defects in nulls [23–25]	
		– Seizure-like behaviors and hyperexcitability in nulls [26]	
		– Offspring death in nulls along with astrogliosis in the hippocampus and neighboring cortex, anxiety, and spatial memory impairments [28]	
		– LPA- or S1P-evoked neuronal hyperexcitability [26,27,89–93]	
		– Attenuation of PRG-1 deficiency-mediated seizure-like symptoms in nulls [27]	
Sandhoff disease	S1P ₂	– Increased S1P levels and upregulation of S1P ₂ and S1P ₃ [29]	
		S1P ₃	– Delayed disease progression in nulls for S1P ₃ or S1P producing protein [29]
		S1P ₃	– Reduced astrogliosis in nulls [29]

more complex picture of LP signaling that is nonetheless of increasing relevance to stroke.

4.3. Neurotrauma

Neurotrauma is used here to refer to traumatic brain injury and spinal cord injury where both neurons and glia play key roles in pathogenesis as well as recovery. LPA and S1P signaling have recently become possible targets to manage traumatic injuries. Temporal changes of LPA receptor expression following neurotrauma in rodents, as well as humans has been reported [22,47]. In human postmortem trauma brain tissues, LPA₂ is upregulated compared to normal brains and has been reported to be expressed in ependymal cells lining cerebral ventricles around the corpus callosum, while expression levels of the other receptors examined (LPA₁ and LPA₃) are not changed [22]. LPA₁ is expressed in injured tissues and possibly in reactive astrocytes in lesion

sites [22]. In rodents, temporal expression changes for 3 LPA receptor subtypes (LPA₁–LPA₃) have been reported in two different injury models, traumatic brain injury and spinal cord injury [47]. In both injury models, LPA₂ and LPA₃ expression is upregulated in reactive astrocytes and motor neurons, respectively, but LPA₁ upregulation is only observed in reactive astrocytes following spinal cord injury. These observations may be relevant to the pathogenesis of neuropathic pain that can involve activation of astrocytes in the spinal cord [135,136]. More importantly, a series of studies have identified LPA₁ signaling as an initiator of neuropathic pain in a pain model (partial sciatic nerve ligation (PSNL)) [17,18,88,137–140]. Direct linkage between LPA₁ in spinal cord astrocytes and induction of neuropathic pain remains to be explored. LP signaling pathways in spinal cord and the pathogenesis of neuropathic pain have received further recent support [42]. LPA₅ null mutants were protected from neuropathic pain, which is associated with the downregulation of phosphorylated cAMP response element binding

proteins in dorsal horn neurons where LPA₅ expression is prominent [42].

An experimental therapeutic approach to neurotrauma is transplanting neural stem/progenitor cells. S1P signaling in this context may promote migration to the injury site. Since S1P is locally produced in injury sites, transplanted cells could migrate to the injury site through an S1P gradient mechanism as observed with S1P₁-mediated lymphocyte trafficking [80,141], while S1P₂ may have an inhibitory effect on migration based on studies of stroke models [76] (see “Ischemic stroke”). These results implicate S1P signaling as a possible therapeutic avenue in neurotrauma.

4.4. Neuropsychiatric diseases including Alzheimer's disease (AD)

Neurobiological functions of LPA and S1P signaling related to cell survival, neurogenesis, differentiation and synaptic activities may be relevant to neuropsychiatric disorders, particularly those associated with developmental defects, CNS injuries, and inflammation. To date, *in vivo* and *in vitro* studies have indicated that LPA and S1P signaling can play multiple roles in relevant to CNS disorders, based upon analyses of model systems for psychiatric disorders that include schizophrenia, anxiety, memory impairment, and neurological disorders like Alzheimer's disease (AD). In particular, LPA₁ has been associated with these disorders, while other LPA and S1P receptor subtypes may also have disease relevance.

LPA₁ null mutants were reported to exhibit schizophrenia-like defects involving deficits in pre-pulse inhibition, 5-HT synthesis alterations, and craniofacial dysmorphism [14]. Additional studies have reported that LPA₁ null mutants share phenotypes consistent with schizophrenia including neurochemical [96,142] and biochemical changes [97]. Tracking with these observations, a microarray study, along with real-time PCR analysis, revealed that the *LPAR1* gene is downregulated in blood lymphocytes of schizophrenia patients [143]. LPA₁ and other aspects of LPA signaling may therefore provide new insights into this complex disorder.

Behavioral studies have indicated that LPA₁ deficiency is also linked to anxiety, memory impairment, and motor abnormalities [70,71,73,74]. A recent report also showed that cocaine-induced conditioned locomotor response is attenuated in malLPA₁, a variant derived from the original LPA₁-null mice [69]. LPA infusion into the hippocampus improves spatial memory [144], which seems to be mainly mediated by LPA₁ [70,71,74], and LPA signaling influences neurogenesis in the hippocampus *via* LPA₁ [70,73]. The malLPA₁ nulls show defects in a series of neurogenic events in newborn hippocampal neurons under normal conditions, as well as after enrichment and exercise [73]. Further studies indicate that growth factors such as brain-derived neurotrophic factors and insulin growth factor 1 may represent some of the downstream effectors induced after initiating LPA₁ signaling during neurogenesis [73]. Under chronic stress conditions, defects in hippocampal neurogenesis are much higher in malLPA₁ than wild type mice [70]. Consistent with these defects in hippocampal neurogenesis, memory impairment occurs in mice lacking LPA₁ [70,71,73]. Contrasting with LPA, little is known about the regulatory function of S1P signaling on the alterations that are seen in LPA₁ nulls, even though S1P signaling is involved in neurogenesis and hyperexcitability *via*, at least, S1P₁ and S1P₂ [26,77,78]. One recent study showed anxiety and spatial memory impairments in seizure-prone S1P₂ null mutants [28], a phenotype that shows background strain dependence. Overall, these results support roles for LP signaling in neuropsychiatric disorders.

There is no direct evidence of LPA or S1P signaling involvement in the pathogenesis of AD. However, a variety of correlative signals have been observed in AD patients and relevant cellular systems. For example, two enzymes partially responsible for LPA or S1P production, autotaxin or SPHK2, respectively, have been reported to be upregulated in AD brain samples [145,146], while S1P exposure reduces the activity of the β -site APP cleaving enzyme-1 (BACE1) that causes abnormal

amyloid β (A β) accumulation, a characteristic feature of AD [145,147]. It has also been reported that S1P levels are reduced in AD patients [148] and that A β downregulates another S1P synthetic enzyme, SPHK1, while overexpression of SPHK1 reduces A β -induced death [149]. In addition, it was also reported that LPA promotes neuronal survival upon A β exposure [150]. To clarify the neuroprotective or neurotoxic effects of LPA and S1P signaling in AD, additional studies are needed. Clarifying the role of LP signaling in AD could extend these signaling mechanisms to other aspects of CNS dysfunction.

4.5. Developmental disorders

Hypoxic/ischemic injury is common in preterm infants where the resulting neurological defects can manifest as neurological and psychiatric disorders. A recent study identified LPA signaling as a requisite element in a variety of sequelae induced by fetal hypoxia within the developing CNS. *Ex vivo* and *in vivo* results showed that fetal hypoxia causes cortical disorganization amongst NPCs through N-cadherin disruption, displacement of mitotic NPCs, and impairment of neuronal migration, in which LPA₁ has a pivotal role along with its effector pathways, G_i and Ras [15]. These data also implicate LPA₁ as a possible therapeutic target for ischemic stroke, so it will be interesting to determine whether brain damage by ischemic stroke is reduced by either pharmacological or genetic inhibition of LPA₁ signaling.

Another recent study also identified new aspects of LPA₁ signaling in fetal hydrocephalus [16] that has been epidemiologically associated with psychiatric diseases, such as schizophrenia and autism. Fetal hydrocephalus is the most common neurological disorder of newborns and young children. It is characterized by abnormal accumulation of cerebrospinal fluid in the cortex, an enlarged head, and neurological dysfunction where prenatal bleeding was thought to be a responsible factor, and currently lack medical therapies. This study generated a new animal model of hydrocephalus that is achieved by injecting blood components or LPA into the fetal brain of embryos to over-activate LPA receptors, followed by birth and postnatal development. Data in this study showed that blood-borne LPA induces fetal hydrocephalus *via* LPA₁, a result that ties post-hemorrhagic clinical events previously associated with fetal hydrocephalus to LPA receptor activities and raising the possibility of medically relevant therapies that target LPA receptors towards the prevention and amelioration of fetal hydrocephalus [16]. This study underscores not only the elucidation of a new role for LPA₁ signaling, but also the development of new animal model to study fetal hydrocephalus.

4.6. Others

LPA and S1P signaling have also been identified as regulators of pathogenesis for other CNS disorders associated with hearing loss, seizures, and Sandhoff disease. Three independent groups have reported hearing loss in S1P₂ null mutants [23–25]. This defect results from degeneration of vestibular and cochlear hair cells in the absence of S1P₂ signaling. Further studies are needed to clarify the precise mechanisms, but this functional role may be useful to manage degenerative hearing loss. S1P₂ null mutants backcrossed onto C57BL/6 background were reported to have seizure-like behaviors and hyperexcitability [26,28]. S1P₂ null mutants this pure background can experience episodic running, freezing, and tonic-chronic convulsion, with almost half of the null mutants die from the seizure [28]. Interestingly, postnatal lethality is markedly increased in pups from S1P₂ null mutant dams probably due to impaired maternal nurturing [28]. Therefore, it would be interesting to establish links between psychiatric dysfunction and impaired maternal nurturing. The possible involvement of LPA₂ signaling has also been implicated based on its role in hyperexcitability [27], however there is currently no direct evidence linking LPA₂ or other LPA receptors to seizures.

Sandhoff disease is a genetic lipid storage disorder where lysosomal β -hexosaminidase A is deficient, thereby blocking ganglioside degradation, resulting in an accumulation of abnormal lipid metabolites. This accumulation occurs in neurons, which triggers neurodegeneration and astrogliosis. Sandhoff disease is clinically similar to Tay–Sachs disease, another genetic lipid storage disorder where lysosomal β -hexosaminidase A malfunctions. In a study using a mouse model of Sandhoff disease, *Hexb* nulls, S1P signaling was revealed to be important in the pathogenesis of this disease, especially at terminal stages [29] when S1P levels and relevant receptors, S1P₂ and S1P₃, are increased, and genetic deletion of S1P₃ or SPHK1 slows the progress of the disease by inhibiting astrogliosis [29]. Thus, both S1P₁, as identified in studies of MS, and S1P₃, appear to contribute to distinct initiating stimuli that promote astrogliosis, raising the possibility of more general effects of S1P-mediated astrogliosis in the pathology of other CNS disorders.

5. Conclusions

Since the discovery of the first LP receptor, LPA₁, 11 receptors are now included in this family of 6 LPA and 5 S1P receptors. These *bona fide* GPCRs are widely and diversely expressed throughout the body and during development, to influence myriad biological as well as pathological processes. A growing number of studies using genetic null mutants for these LP receptor subtypes (LPA₁, LPA₂, LPA₃, LPA₄, LPA₅, S1P₁, S1P₂, S1P₃, S1P₄, and S1P₅) have clarified specific functions mediated by each, singly and in combination with other receptor subtypes. Recent data also indicate that LPA and S1P receptors are regulators of diverse biological functions in the CNS, a major locus for LPA and S1P receptors. We now know that LPA and S1P receptors are tractable therapeutic targets for the development of small molecule agents in human CNS diseases, through the success of fingolimod as an oral treatment for MS. However, work to reveal the functions of LPA and S1P signaling in the CNS is still in its nascent stage. Using genetic and pharmacological approaches, more functions await discovery, towards a better understanding of the mechanistic and therapeutic roles of LP signaling in CNS disorders.

Acknowledgements

We thank Danielle Letourneau for editorial assistance and Sook-Hyun Yoon for figure editing. We apologize for any oversights. This work was supported by the National Institutes of Health (NS048478 and DA019674) to JC, and the Korean National Research Foundation (2010-0003058) and a Novartis Postdoctoral Fellowship (Novartis Pharma, AG) to JWC.

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