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Review

Lysophosphatidic Acid Signaling in the Nervous System

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The brain is composed of many lipids with varied forms that serve not only as structural components but also as essential signaling molecules. Lysophosphatidic acid (LPA) is an important bioactive lipid species that is part of the lysophospholipid (LP) family. LPA is primarily derived from membrane phospholipids and signals through six cognate G protein-coupled receptors (GPCRs), LPA_{1-6}. These receptors are expressed on most cell types within central and peripheral nervous tissues and have been functionally linked to many neural processes and pathways. This Review covers a current understanding of LPA signaling in the nervous system, with particular focus on the relevance of LPA to both physiological and diseased states.

Introduction

The human brain is composed of approximately 60%–70% lipids by dry weight (Svennerholm et al., 1994). These lipids can be divided into two major pools, structural and signaling, which include well-known families such as cholesterol, fatty acids, eicosanoids, endocannabinoids, and prostaglandins (Figure 1). Structural lipids classically comprise cell membranes and may be passively organized by protein factors (reviewed in Rossy et al., 2014), whereas signaling lipids function in a predominantly extracellular fashion through receptors to activate downstream pathways (reviewed in Bieberich, 2012). Lysophospholipids (LPs) are an important family of lipid signaling molecules, and lysophosphatidic acid (LPA) is a major member of this family, present in numerous tissues and fluids, notably within the developing and adult nervous system. LPA effects are now known to act through cognate, cell-surface GPCRs termed LPA receptors (LPARs, reviewed in Noguchi et al., 2009; Choi et al., 2010; Yung et al., 2014).

Since the discovery of the first LP receptor for LPA in the developing brain (Hecht et al., 1996), five other LPARs have been characterized and all are expressed in the nervous system (Figure 2). Many roles for LPA signaling have been elucidated, including effects on neuroprogenitor cell (NPC) function (Hecht et al., 1996; Yung et al., 2011), myelination (Weiner et al., 1998; Fukushima et al., 2002b; Anliker et al., 2013), synaptic transmission (Trimbuch et al., 2009), and brain immune responses (Möller et al., 2001; Schilling et al., 2004), which influence neural development, function, and behavior (Figure 3). Additionally, LPA signaling is important in endothelial cell and neurovascular function (Yukiura et al., 2011; and reviewed in Teo et al., 2009). LPAR discovery also led to the identification of another LP receptor subclass, sphingosine 1-phosphate (S1P) receptors, which bind this distinct LP (Kihara et al., 2014a). S1P and its five receptors also have important nervous system activities (Mizugishi et al., 2005; Meng et al., 2011; van Echten-Deckert et al., 2014), but they will not be covered here.

The ecosystem of neural LPA signaling has been considerably expanded with the characterization of both LPA precursors and LPA synthesis/degradative enzymes (reviewed in Sigal et al., 2005; Brindley and Pilquil, 2009; Perrakis and Moolenaar, 2014). In view of the broad neurobiological influences of LPA signaling, its dysregulation may lead to diverse neuropathologies (Bandoh et al., 2000; Houben and Moolenaar, 2011; Yung et al., 2011; Ueda et al., 2013). LPs and their relevance to non-nervous system tissues have been reviewed elsewhere (Choi et al., 2010; Mirendil et al., 2013).

LPA Metabolism and Distribution

LPA is a metabolite in the biosynthesis of membrane phospholipids and is ubiquitously present in all examined tissues. The generic term LPA (mono-acyl-*sn*-glycerol-3-phosphate) often refers to 18:1 oleoyl-LPA (1-acyl-2-hydroxy-*sn*-glycero-3-phosphate), reflecting its widespread laboratory use. However, many other chemical forms of LPA with different acyl chain lengths, saturation, and position also exist. The tissue distribution of LPA and its metabolites are relevant to both basic and medical applications (reviewed in Yung et al., 2014). LPA is prominently found in blood fractions, where it ranges from 0.1 μM in plasma to more than 10 μM in serum. These concentrations are significantly higher than the estimated nanomolar K_d values of LPA_{1-6} (Aoki et al., 2002; Hosogaya et al., 2008; Yanagida et al., 2009). Within the CNS, LPA is found in the embryonic brain, neural tube, choroid plexus, meninges, blood vessels, spinal cord, and cerebrospinal fluid (CSF) at low nanomolar to micromolar concentrations (reviewed in Yung et al., 2014). Total LPA can be measured via multiple assays (Hosogaya et al., 2008; Jesionowska et al., 2014), while individual chemical forms can be identified by chromatography coupled to mass spectrometry (Triebl et al., 2014). Such techniques are proving useful in analytical and diagnostic settings (Hosogaya et al., 2008; Okudaira et al., 2010; Yung et al., 2011).

LPA is generated through several different enzymatic pathways (Figure 1). A major pathway is through the enzymatic action of autotaxin (ATX) (Tanaka et al., 2006; van Meeteren et al., 2006). Constitutive removal of ATX (gene name: *Enpp2*) results

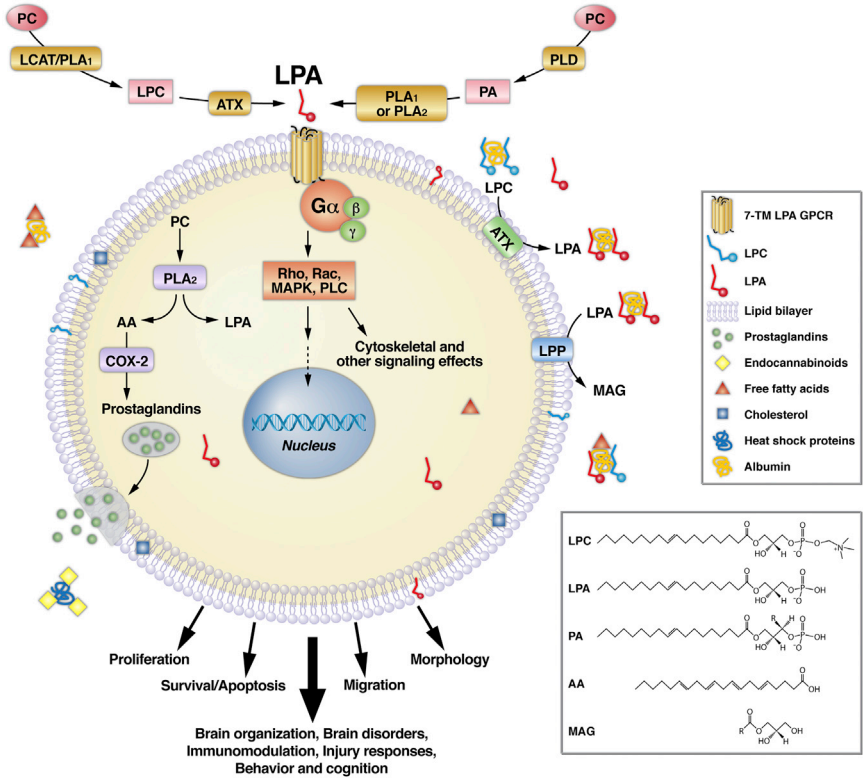

Figure 1. LPA Is a Bioactive Lipid that Signals through Defined GPCRs within the Nervous System

Lipids comprise a significant portion of the CNS and have differing structural, energetic, and bioactive signaling properties. Signaling lipids are often bound to carrier proteins such as albumin or heat shock proteins. LPA activates members of a family of G protein-coupled receptors (GPCRs) and influences multiple cellular processes including proliferation, survival, apoptosis, morphological change, and migration, as well as the production of other lipids such as prostaglandins through arachidonic acid (AA) conversion by cyclooxygenase-2 (COX-2). The synthetic pathways for LPA include conversion of phosphatidylcholine (PC) into lysophosphatidylcholine (LPC) by lecithin-cholesterol acyltransferase (LCAT) and phospholipase A (PLA) 1 enzymes, or by conversion of PC to phosphatidic acid (PA) by phospholipase D (PLD). LPC is then metabolized to produce lysophosphatidic acid (LPA) by the enzyme autotaxin (ATX). LPA can be broken down into monoacylglycerol (MAG) by a family of lipid phosphate phosphatases (LPPs). Chemical structures are shown to highlight acyl chain composition but do not reflect actual 3-D geometries. Other lipids in the CNS include the endocannabinoid family, fatty acids, cholesterol, and prostaglandins, which are beyond the scope of this Review.

in neural and vascular defects with death by embryonic day (E) 9.5 (Tanaka et al., 2006; van Meeteren et al., 2006). *Enpp2* heterozygous null mice have ~50% reduced LPA in plasma (van Meeteren et al., 2006; Fotopoulou et al., 2010). In addition, *Enpp2* conditional deletion from epiblasts mediated by Cre recombinase under the control of Sox-2 gene regulatory elements results in neural tube defects (Fotopoulou et al., 2010). ATX structure, splice variants, and functional domains are being actively examined (reviewed in Perrakis and Moolenaar, 2014). A second major pathway generates LPA from membrane phospholipids through the actions of phospholipases (Aoki et al., 2002). There are additional pathways for generating LPA, particularly involving acyltransferases (reviewed in Pagès et al., 2001).

The generated LPA forms reflect their precursor phospholipid structure (e.g., 18:1 lysophosphatidylcholine [LPC] produces 18:1 LPA) (Aoki, 2004). These pathways generate both intracellular and extracellular LPA (reviewed in Pagès et al., 2001). Extracellular LPA produces signaling through its receptors (reviewed in Choi et al., 2010; Yung et al., 2014 and noted below), while intracellular LPA serves as an intermediate for the de novo biosynthesis of complex glycerolipids (reviewed in Pagès et al., 2001). Additionally, these lipid pools can affect membrane vesicular curvature (McMahon and Gallop, 2005).

LPA can be degraded by liberation of the phosphate group to produce monoacylglycerol (MAG), mediated by several classes of enzymes, including lipid phosphate phosphatases (LPPs) (also called phosphohydrolases) (Brindley and Pilquil, 2009), LPA acyltransferase (LPAAT), lecithin-cholesterol acyltransferase (LCAT), and other lipid enzymes (reviewed in Pagès et al., 2001; Aoki et al., 2002; Aoki, 2004). Inhibition of LPP(1-3)-mediated degradation can elevate LPA levels in cerebral cortical tissue (Aaltonen et al., 2012). It has been difficult to spatiotemporally map LPA and related metabolites in specific cell types in the nervous system, particularly critical in light of the identified spatiotemporal distributions of LPARs. However, this is an area of active research that will benefit from emerging technologies.

LPARs

There are currently six LPARs: protein names LPA_1–LPA_6 with gene names *LPAR1-LPAR6* (human) and *Lpar1-Lpar6* (non-human) (reviewed in Chun et al., 2010; Kihara et al., 2014a; Yung et al., 2014). These 7-transmembrane GPCRs activate heterotrimeric G proteins defined in part by their G_α subunits ($G_{12/13}$, $G_{q/11}$, $G_{i/o}$, and G_s) to initiate various signaling cascades. During development, the cell types comprising the brain arise from distinct lineages and undergo cellular processes: these include proliferation, apoptosis, morphological changes, migration, and differentiation into cells with specialized functions underlying neural networks (Greig et al., 2013). LPARs are expressed in varying spatiotemporal patterns from fetal through mature life (Figure 2). LPA signaling drives diverse physiological and pathophysiological processes within the nervous system (Figure 3).

Fetal Cerebral Cortical Development

During cerebral cortical development, neuroepithelial cells proliferate to give rise to the ventricular zone (VZ), subventricular zone (SVZ), intermediate zone (IZ), cortical plate, and marginal zone (MZ) (Figure 2). NPCs that reside in the VZ undergo interkinetic nuclear migration (INM) and proliferate to generate distinct

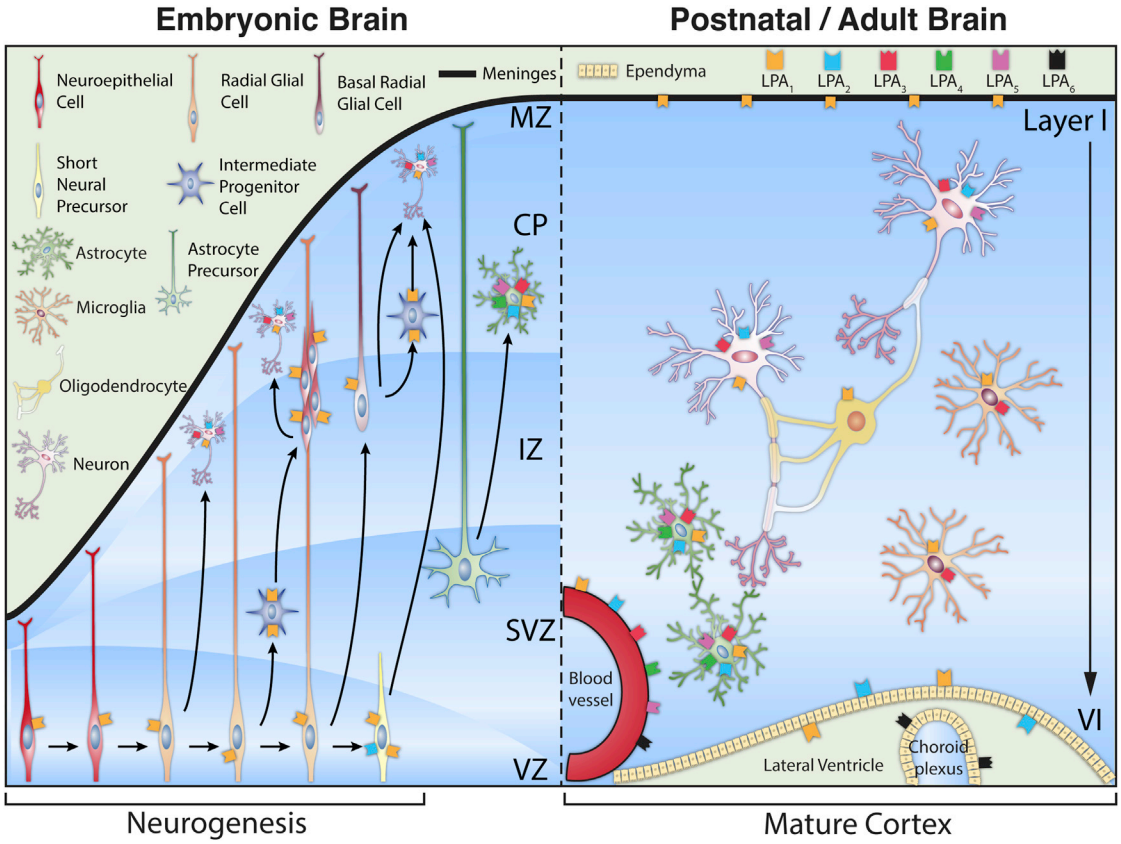

Figure 2. LPAR Subtypes in the Developing and Mature Cerebral Cortex

Reported LPAR subtype expression of the six LPA receptors, LPA_{1-6}, varies with developmental age and cell type. Left: LPARs are expressed in neural progenitor cells (NPCs) and other developing cortical cells. These expression patterns vary as the progenitors arise in the ventricular zone (VZ) and differentiate as they migrate through the subventricular zone (SVZ) and intermediate zone (IZ), to localize within the cortical plate (CP). In the embryonic brain, LPA-mediated processes include proliferation, interkinetic nuclear migration, neurite retraction, survival, morphological change, and cell migration. Right: most major cell types in the mature cortex express specific subtypes of LPARs. LPARs are also expressed in cells of the ependyma, blood-brain barrier, and meninges, which overlie the most superficial marginal zone (MZ). Postnatally, LPA signaling influences myelination, microglial and astrocytic responses, vascular stabilization, and higher cognitive processes.

progenitor pools, differentiate to generate nascent neurons, and migrate superficially to locate within cell layers and establish functional connections (reviewed in Taverna et al., 2014). Astrocytes and oligodendrocytes are generated during late embryonic and early postnatal periods, and together with neurons, comprise basic cellular elements of the cortex, complemented by other cell types such as endothelial cells, pericytes, ependymal cells, microglia, meninges, and cells of the choroid plexus (Figure 2).

Enrichment of *Lpar1* in the VZ and meninges of the developing cortex suggests roles for LPA signaling in cortical development, as reflected in its original name, ventricular zone gene-1 (VZG1) (Hecht et al., 1996). The characterization of LPAR null mice has critically helped to elucidate the LPAR dependency of diverse LPA-associated neural phenotypes. Constitutive deletion of *Lpar1* results in 50% perinatal lethality associated with olfactory and other nervous system defects (Contos et al., 2000; Harrison et al., 2003). Ex vivo whole cerebral cortical cultures treated with LPA form thicker cortices through decreased cell death within the VZ (rather than through increasing cell proliferation) and have an increased post-mitotic neuronal population (Kingsbury et al., 2003). Concomitant removal of *Lpar1* and *Lpar2* prevents these effects, demonstrating receptor dependency. Meninges at E13, as assessed by mouse embryonic meningeal fibroblasts (MEMFs), respond to the addition of LPA by the formation of actin-based stress fibers (Contos et al., 2002). Deletion of both, but not single, *Lpar1* and *Lpar2* prevents formation of LPA-induced MEMF stress fibers (Contos et al., 2002).

LPA has multiple effects on NPCs. Calcium conductance changes are mediated by LPA signaling and occur before ionic responsivity induced by neurotransmitters such as GABA and glutamate (Dubin et al., 1999, 2010). Electrical fluctuations based on calcium signaling are known to impact NPC proliferation, neuronal differentiation, chemotaxis, dendritic morphology, axon growth and guidance, and neurotransmitter phenotype (reviewed in Rosenberg and Spitzer, 2011), all of which can be influenced by LPA signaling.

INM is the to-and-fro movement of nuclei from apical to basal positions in the VZ during cell-cycle progression. Ex vivo and in vivo cortical exposure to LPA disturbs INM by increasing the

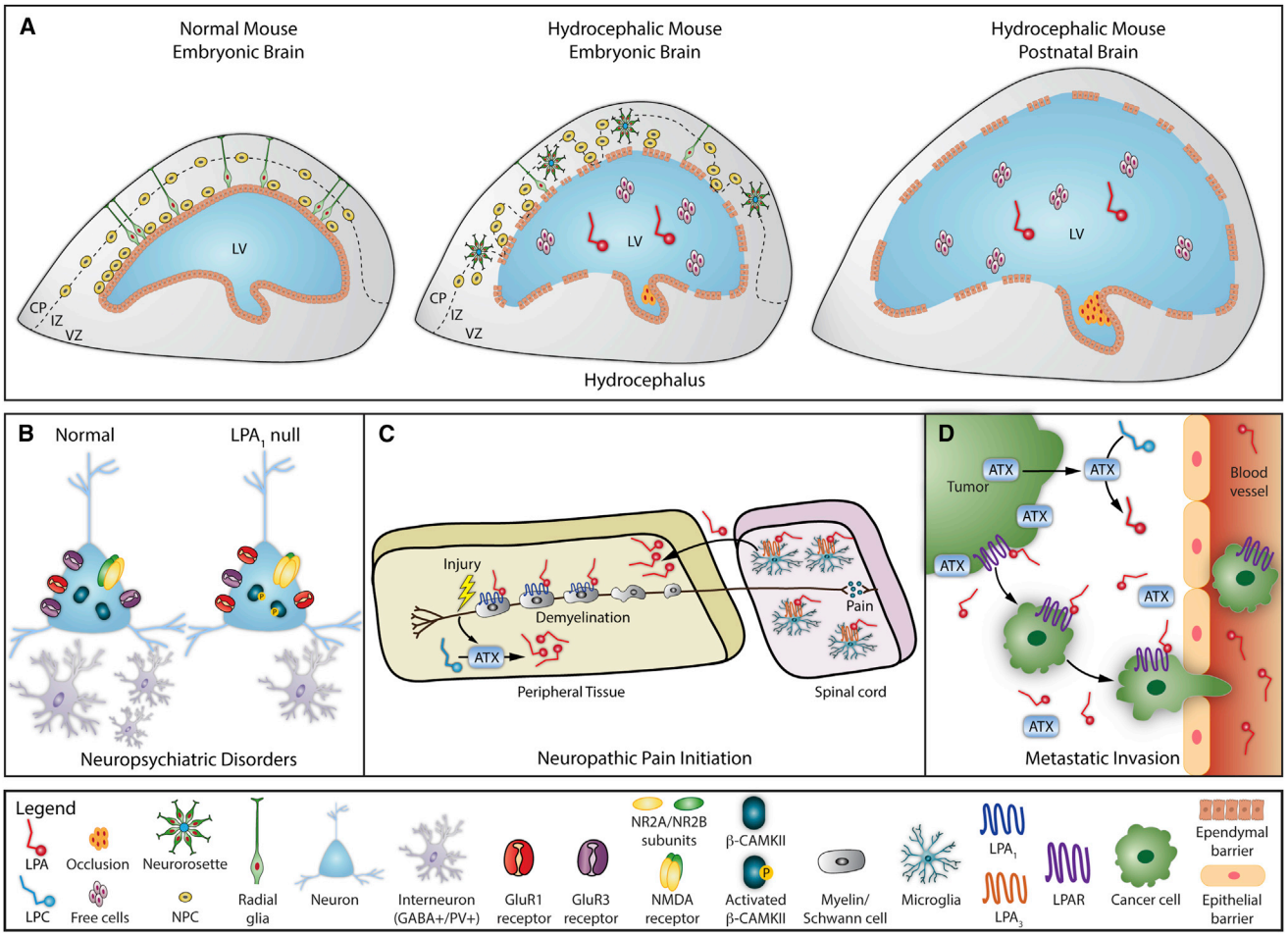

Figure 3. Dysregulated LPA Signaling May Lead to Nervous System Disorders

Aberrant LPA signaling, whether produced by overactivation, altered LPA production/degradation, or changes in receptor expression, can disrupt the nervous system to produce sequelae relevant to human brain disorders.

(A) LPA signaling has been linked to post-hemorrhagic hydrocephalus. A mouse model recapitulates multiple histological comorbidities seen in humans, including ventriculomegaly, thinning of the cortical plate (CP), formation of neurorosettes, disrupted NPCs within the ventricular zone (VZ) and intermediate zone (IZ), loss of cell adhesion that leads to the presence of free-floating cells in the CSF, compromised ependymal lining, and ventricular occlusions. Hydrocephalus is often chronic, with increased CSF pressure, ventriculomegaly, and decreased brain mass persisting throughout postnatal life.

(B) *Lpar1* null mice display dysregulated neural signaling, with disruption of glutamatergic (AMPA and NMDA receptor expression and composition) and GABAergic (GABA+/PV+ neuron decreases) function, leading to significant cognitive impairments in animal models.

(C) Nerve damage induces the production of LPA via ATX-mediated conversion of LPC. LPA stimulates LPA_3 on activated microglia, resulting in feedforward LPA release that, in turn, can activate LPA_1 on Schwann cells, leading to downregulation of myelin proteins, progressive demyelination, and initiation of neuropathic pain.

(D) Brain tumors often overexpress ATX and LPARs, leading to altered LPAR signaling. LPA_{1-3} stimulation by increased environmental LPA induces cell migration and promotes cancer cell metastasis.

percentage of mitotic cells found in the basal position, resulting in mitotic displacement (Kingsbury et al., 2003; Yung et al., 2011). Mitotic displacement also occurs in an *Lpar1*-dependent manner under hypoxic culture conditions (Herr et al., 2011). Future studies could refine the understanding of LPA signaling on specific progenitor populations in this context, such as apical, basal, or intermediate progenitors, or outer subventricular zone radial glia-like cells (Taverna et al., 2014).

A hallmark of cortical development is the migration of newly generated neurons to their final superficial location within the cortical plate. This migration is aided by leading processes that help sense the surrounding environment for signaling cues, such as growth factors, chemoattractants, and chemorepellents. In vitro studies utilizing the B103 cell line, wild-type E12 embryonic nestin-positive cortical progenitor cells, and E12 cortical explant cultures identified protruding lamellipodia and growth cones that rapidly retracted upon LPA exposure in a Rho-dependent manner, leaving fine F-actin retraction fibers. This supports LPA's role as an inhibitory cue during cell migration or process outgrowth (Fukushima et al., 2002b; Campbell and Holt, 2003).

During corticogenesis, programmed cell death can affect significant populations of developing cells (Blaschke et al., 1996, 1998; Yung et al., 2009). Culturing ex vivo cortices in LPA

reduces cell death in an *Lpar1*- and *Lpar2*-dependent manner (Kingsbury et al., 2003). LPA signaling activates cell survival pathways, including thymoma viral proto-oncogene (Akt) (Weiner and Chun, 1999) and β-catenin (Weiner et al., 2001). Moreover, β-catenin and T cell factor signaling can be activated by LPA and can contribute to the suppression of apoptosis in H197 cells (an embryonic hippocampal progenitor cell line) (Sun et al., 2013). LPA signaling has also been reported to influence neurosphere proliferation in culture (Svetlov et al., 2004). NPCs express multiple LPAR subtypes (Figure 2) and LPA signaling can influence their development and function.

Neurons

In mice, cortical neurogenesis extends from E10 to E18, during which NPCs divide to produce other progenitors and young postmitotic neurons. LPA promotes cortical NPCs to commit to the neuronal lineage via LPA_1 and the $G_{i/o}$ pathway (Kingsbury et al., 2003; Fukushima et al., 2007). Additionally, LPA can alter the actin cytoskeleton and promote microtubule rearrangement within neurons (Fukushima et al., 2002a; Fukushima and Morita, 2006) as well as influence the morphology and motility of young postmitotic neurons (Fukushima et al., 2002b). Neurite retraction (Hecht et al., 1996), an important response to chemical gradients, can be mediated by LPA via the ROCK pathway (Tigyi et al., 1996). More recently, transient receptor potential channel, subfamily M, member 2 (TRPM2) was reported to mediate LPA-induced neurite retraction in the developing brain (Jang et al., 2014). Finally, neurite branching, an important process for neuronal network formation, was induced through the introduction of LPA_3 and the addition of LPA into hippocampal cell cultures (Furuta et al., 2012). This physiological response was initiated through G_q and the Rho family GTPase 2 (Rnd2) (Furuta et al., 2012).

Maturing neurons establish polarity through the specification and development of neurites into axons and dendrites. In hippocampal neuronal cultures, axonal bases were predominantly found distal to an exogenous LPA source (Yamane et al., 2010). Localization of the Golgi apparatus and centromeres, which are associated with the establishment of neuronal polarity before axonogenesis (de Anda et al., 2005), were also positioned distal to the LPA source, suggesting that LPA signaling can influence the site of axonal sprouting (Yamane et al., 2010). *Lpar6*, the most recently characterized LPAR family member, is enriched in the neural plate of *Xenopus* neurulae. Deletion of *Lpar6* results in forebrain defects with concomitant reduction of telencephalic markers, as well as defects extending into the hindbrain (Geach et al., 2014). The roles of *Lpar6* in the development and function of the mammalian nervous system remain to be characterized, although human mutations of this receptor gene have most notably been associated with forms of hair loss (Pasternack et al., 2008).

Astrocytes

In vivo, astrocytes appear to express few LPA receptor subtypes aside from low levels of *Lpar1* (Tabuchi et al., 2000; Weiner et al., 2001; Cervera et al., 2002), whereas cultured astrocytes express *Lpar1-5* (Sorensen et al., 2003; Shano et al., 2008). Receptor subtype expression depends on age, species (Rao et al., 2003), and cell activation state. The expression of newly classified *Lpar6* in astrocytes remains to be examined.

During development, LPA has numerous effects on cultured astrocytes, including intracellular calcium mobilization (Tabuchi et al., 2000), generation of reactive oxygen species, and actin cytoskeletal rearrangement (Spohr et al., 2008). Most studies have shown LPA-mediated DNA synthesis and proliferation in astrocytes (Ramakers and Moolenaar, 1998; Sorensen et al., 2003; Shano et al., 2008), although some conflicting reports exist that may be a function of the employed LPA concentration (Fuentes et al., 1999; Shano et al., 2008), astrocyte origin, species, or cell selection in culture (Pébay et al., 1999; Furukawa et al., 2007). Additionally, LPA can induce astrocytes to express immediate-early genes through pertussis-toxin sensitive G proteins, as well as cytokine genes, including nerve growth factor (NGF), interleukin (IL)-1β, IL-3, and IL-6 (Tabuchi et al., 2000).

In culture, cross-talk between neurons and astrocytes through LPA signaling has been reported. For example, LPA-activated astrocytes can induce neuronal differentiation (Spohr et al., 2008) as well as axonal outgrowth of neurons via extracellular matrix proteins and the epidermal growth factor signaling pathway (Spohr et al., 2011). The production of NGF can also be enhanced by astrocytic exposure to LPA and other LPs (Furukawa et al., 2007). Astrocyte proliferation and astrogliosis appear to be influenced by LPA signaling, probably through *Lpar1-3* (Sorensen et al., 2003). Finally, stimulation of astrocytes by lipopolysaccharide (LPS) or IL-1β, induces LPA-responsive astrocyte migration (Sato et al., 2011). It is likely that other LPA-induced paracrine signals exist among cell types within the nervous system.

Oligodendrocytes

Oligodendrocytes are CNS myelinating glia that express *Lpar1* in a spatiotemporal manner that correlates with maturation and myelination, peaking between postnatal day (P) 15 and P21 in mice (Weiner et al., 1998). In vitro, LPA induces calcium mobilization, extracellular-regulated-kinase 1/2 (ERK1/2) phosphorylation, process retraction, and cell rounding in mature oligodendrocytes, but not in oligodendrocyte precursors (Möller et al., 1999). Early studies reported that *Lpar1* in oligodendrocytes did not promote myelination (Stankoff et al., 2002). However, a subsequent study supports a role for LPA signaling on the transition from process outgrowth to membrane sheath formation as oligodendrocytes switch from premyelinating to myelinating forms (Nogaroli et al., 2009). The maintenance of *Lpar1* in oligodendrocytes does not appear to require an axonal signal from neurons, suggesting that it is regulated by an intrinsic oligodendrocyte program (Stankoff et al., 2002). Finally, LPA stimulates process formation and increases the number of differentiating, but not mature, oligodendrocytes (Nogaroli et al., 2009).

Schwann Cells

Schwann cells (SCs) are peripheral myelinating glia that are also responsive to LPA signaling. At least three types of SCs exist. Myelinating SCs form the myelin sheath around axons and express *Lpar1* and possibly *Lpar2*. Perisynaptic SCs (also called terminal SCs) are present at the neuromuscular junction, express both *Lpar1* and *Lpar3* (Weiner et al., 2001; Kobashi et al., 2006),

and have known functions in synaptic transmission, synaptogenesis, and nerve regeneration (Armati and Mathey, 2013). The expression of LPARs in non-myelinating SCs, which ensheathe non-myelinated fibers, is currently unknown. LPA_1 signaling reduces SC death through G_i, phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), and Akt in vitro (Weiner and Chun, 1999), which is supported in vivo by observations that *Lpar1* null mice have increased apoptosis of SCs in sciatic nerves (Contos et al., 2000).

In addition to promoting SC survival, LPA also induces dynamic alterations to the actin cytoskeleton, with corresponding morphological and cell adhesion changes (Weiner and Chun, 1999; Weiner et al., 2001). In vitro, the effects of LPA on SCs include promoting wreath formation, activating N-cadherin-dependent cell aggregation, and enhancing focal adhesions. These responses are dramatically reduced in *Lpar1* null SCs (Weiner et al., 2001). P0 protein, a glycoprotein that is a major structural component of the myelin sheath, can be increased in SCs by LPA_2 signaling, which may contribute to SC differentiation (Li et al., 2003). Recently, it was shown that LPA via LPA_1 signaling coupled to G_i and Rac1 can promote embryonic SC migration, myelination, and cell-to-axon segregation. By contrast, *Lpar1* null mice showed delayed SC-to-axon segregation, abnormal polyaxonal myelination, and thinner myelin sheaths (Anliker et al., 2013).

In adult SCs isolated from axotomized sciatic nerve, *Lpar1* and *Lpar2* are coincidentally upregulated during post-axotomy SC proliferation, suggesting that LPA signaling promotes SC division in regenerating peripheral nerves (Weiner et al., 2001; Frohnert et al., 2003). In contrast, exogenous LPA induces demyelination of neurons in dorsal root ex vivo culture as well as in mice that have been intrathecally injected with LPA (Inoue et al., 2004).

Microglia

Microglia, derived from hematopoietic stem cells, are the resident macrophages of the CNS, showing multiple types and activation states including ramified (resting or quiescent) or activated. Activated microglia can scavenge, present antigens, phagocytose, and release inflammatory mediators during injury and neurodegeneration (Hu et al., 2014). Microglia from mouse or rat mainly express *Lpar1* and/or *Lpar3* (Möller et al., 2001; Tham et al., 2003), while human microglial cell lines express *LPAR1-3* (Möller et al., 2001; Bernhart et al., 2010). Receptor activation by LPA can induce intracellular calcium mobilization and potassium channel activation, as well as cell proliferation, cell morphology changes, upregulated chemokinesis, and membrane ruffling (Schilling et al., 2004; Fujita et al., 2008; Muessel et al., 2013). GPCR reciprocal modulation by both LPA and stromal cell-derived factor-1 (SDF-1) on their respective receptors produces microglial morphological changes through inward-rectifier potassium channel 2.1 (Kir2.1) modulation, although the specific LPAR subtype remains to be defined. As with other cell types in the brain, LPAR profiles and responses probably vary with microglia maturation, activation state, and species source. Recent distinctions between brain macrophage and microglia function (reviewed in Prinz and Priller, 2014) probably involve LPARs; further studies in this area are needed.

Choroid Plexus

The choroid plexus is the major site of CSF production. It consists of epithelial cells surrounding a central area with capillaries and is contiguous with the ependymal layer. Unlike the ependyma, the choroid plexus is structurally distinct with tight gap junctions that connect the apical surface of the epithelial cells (reviewed in Johansson, 2014). *Lpar5* appears in the fourth ventricular choroid plexus of the mouse embryo (Ohuchi et al., 2008). *LPAR6* is expressed in human lateral ventricular choroid plexus, and reduced expression is seen in major depressive disorder (Turner et al., 2014). Importantly, LPA-related metabolic enzymes such as ATX are highly expressed in the choroid plexus (Bächner et al., 1999; Savaskan et al., 2007). The presence of ATX in the choroid plexus, and the general proximity of the choroid plexus to neurogenic structures, may catalyze blood-derived LPC into bioactive LPA that can affect many aspects of neurodevelopment.

Brain Vasculature

Development of the nervous system occurs in tandem with establishment of the vascular network, which encompasses vasculogenesis, angiogenesis, vessel maturation and stability, as well as blood-brain barrier (BBB) formation (Greenberg and Jin, 2005; Eichmann and Thomas, 2013). Vascular factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and Notch have roles in CNS development (Eichmann and Thomas, 2013; Ruhrberg and Bautch, 2013). In parallel, LPARs and LPA signaling can also influence vascular biology (Teo et al., 2009). Notably, LPA and VEGF signaling are intertwined: LPA can induce VEGF expression via NF-κB signaling, and VEGF can induce ATX and *Lpar1* expression in endothelial cells (Lin et al., 2008; Ptaszynska et al., 2010; Dutta et al., 2011).

Studies linking LPA to vascular development demonstrated that ATX null mice die by E9.5 with vascular defects (Tanaka et al., 2006; van Meeteren et al., 2006). These defects are similar to those found in G_{13} null mice (Offermanns et al., 1997); LPA receptor subtypes are known upstream activators of $G_{12/13}$ (Yung et al., 2014). Indeed, *Lpar1*-null and *Lpar2* null mice have vascular defects, such as frontal cerebral hematomas (Contos et al., 2000, 2002). Additionally, *Lpar4* null mice have impaired pericyte recruitment related to dilated blood and lymphatic vessels (Sumida et al., 2010). Pericytes appear to mediate blood vessel stabilization by increasing the rate of LPA degradation, based upon an in vitro model of angiogenesis (Motiejūnaitė et al., 2014).

Cultured endothelial cells (ECs) have been shown to express *LPAR1-6* (Lin et al., 2007; Schleicher et al., 2011; Ren et al., 2013). LPA promotes the survival and proliferation of ECs from a variety of sources (English et al., 1999), including brain microvascular bEND.3 cells (Schleicher et al., 2011). LPA can also stimulate EC migration (English et al., 1999; Wu et al., 2005) and influence vascular tone. An early report, using a piglet model of intracranial hematoma demonstrated that LPA exposure produces dose-dependent vasoconstriction, which is reminiscent of that produced by hemorrhage (Tigyi et al., 1995). More recently, LPA has been found to mediate vasodilation via LPA_1, phospholipase C, and endothelial nitric oxide synthase (Ruisanchez et al.,

2014). LPA overexposure has been reported to increase BBB permeability (On et al., 2013; Yu et al., 2014), as may occur during pathological conditions like stroke.

Stressors and Neuropsychiatric Disorders

CNS Injury

Beyond development and normal function of the nervous system, LPAR signaling is also important during CNS stress or damage. During injury, LPA concentrations in brain and CSF are significantly elevated (Tigyi et al., 1995; Goldshmit et al., 2010) and can reach thousands of times the apparent K_d of LPA receptors (Yung et al., 2011). Traumatic injury can induce LPA_2 gene expression in human ependymal cells as well as mouse cortical and spinal cord astrocytes (Goldshmit et al., 2010; Frugier et al., 2011). *Lpar1* is also increased in reactive murine spinal cord astrocytes, while *Lpar3* expression is reportedly increased in cortical and spinal cord neurons (Goldshmit et al., 2010). Additionally, ATX levels in the human cerebral cortex are decreased after fatal closed head injury (Frugier et al., 2011). Whether this is due to negative feedback from injury-mediated LPA release (van Meeteren et al., 2005) or other factors remains to be determined. Conversely, ATX levels are dramatically increased in white matter adjacent to injury lesions in the rat cortex (Savaskan et al., 2007), suggesting possible overactive LPA signaling. Reported use of anti-LPA antibodies to improve CNS injury outcomes (Crack et al., 2014) are consistent with pathological roles of increased LPA signaling, although mechanistic validation of this approach awaits further study.

Hypoxia

Ischemia is a major cause of hypoxia, which results in decreased synaptic transmission, inflammation, and neural death (Corcoran and O'Connor, 2013). LPA_1 signaling has been tied to hypoxia through distinct mechanisms. For instance, hypoxia enhances LPA-induced hypoxia inducible factor-1 alpha (HIF-1α) expression in cancer cells and VEGF expression in the vasculature (Lee et al., 2006, 2013). Embryonic HIF-1α expression is also dependent on the presence of ATX and is rescued by LPA exposure in ATX null animals (Fotopoulou et al., 2010). Hypoxia can alter brain development and result in neurological disability or psychiatric disease; even short-term cortical exposure to low oxygen levels causes cellular abnormalities that include overactivation of LPA_1 and downregulation of G protein-coupled receptor kinase 2 (GRK2) (Herr et al., 2011). These abnormalities were previously seen upon stimulation of LPA_1 signaling in NPCs (Kingsbury et al., 2003) and could be reduced or prevented by an $LPA_{1/3}$ inhibitor, use of *Lpar1* null mice (Herr et al., 2011), or use of *Lpar1* and *Lpar2* double null mice (Kingsbury et al., 2003). Similar protection against mitotic displacement produced by hypoxia was seen with inhibition of Rac1, Rho-associated kinase (ROCK), and HIF-1α, indicating that these signaling molecules may be involved in this *Lpar1*-dependent pathway (Fotopoulou et al., 2010).

In postnatal brains, hypoxia can be caused by stroke or trauma (Corcoran and O'Connor, 2013). Increased LPA signaling promotes retinal cell survival under hypoxic conditions by upregulation of *Lpar1* and *Lpar2* expression in ganglion cells and the inner retinal layers (Savitz et al., 2006). However, retinopathy models of prematurity in rat neonates, produced by alternating cycles of hypoxia and hyperoxia, showed conflicting results (Yang et al., 2009): while *Lpar1* was upregulated in retinal tissue, LPA exposure or *Lpar1* overexpression decreased cell viability and LPA_1 inhibition or short hairpin RNA knockdown was protective to cell survival. LPAR signaling is clearly involved during hypoxia with ischemic insult, although continued investigation will be necessary to resolve LPA's role as a protective or harmful factor.

Hydrocephalus

Several neurological disorders are strongly correlated with a preceding hemorrhagic event during development, possibly resulting in enhanced LPA signaling through blood exposure. Fetal hydrocephalus, one of the most common neurological diseases of perinatal life, has been linked to overactivation of LPA signaling in an embryonic mouse model of disease (Yung et al., 2011) (Figure 3A). Hydrocephalus was induced by injecting LPA or blood components into the lateral ventricles, which resulted in up to 100% incidence of ventriculomegaly. Hydrocephalus was accompanied by related clinical characteristics, including neurorosette formation, displaced NPCs, cortical disruptions, and third ventricular and aqueductal occlusions (Fukumizu et al., 1995; Domínguez-Pinos et al., 2005). These phenotypes were reduced or prevented in an *Lpar1* and *Lpar2* double null mutant or by use of pharmacological $LPA_{1/3}$ antagonism. This and related disorders initiated by hemorrhage might be amenable to medical interventions involving LPAR signaling modulators.

Neuropsychiatric Models

Lpar1 null mice display a variety of negative behavioral signs and cognitive deficits, suggesting the importance of LPA_1 signaling in normal cognition. Neonatal *Lpar1* null mice display problems in olfaction related to suckling as well as pronounced craniofacial dysmorphism (Contos et al., 2000), a trait commonly seen in autism (Ploeger et al., 2010). ma*Lpar1* null mice, a spontaneous variant that arose during colony expansion of the *Lpar1* null line in Málaga, Spain, exhibit several negative behavioral signs, including generalized anhedonia (Santin et al., 2009), hypersensitivity to stress (Castilla-Ortega et al., 2011), and increased anxiety (Santin et al., 2009). *Lpar1* null mice also display deficits in prepulse inhibition (PPI) of the startle reflex (Harrison et al., 2003), a cognitive attention-related test that is significantly impaired in schizophrenia patients, as well as learning and memory deficiencies particularly related to spatial memory retention (Santin et al., 2009), consolidation, and working memory (Castilla-Ortega et al., 2011).

LPA signaling has additionally been linked to many of the underlying molecular and neurotransmitter pathways involved in both genetic and environmental risk factors for neuropsychiatric disorders. Glycogen synthase kinase-3 (GSK3)—a signaling network node associated with risk factors such as disrupted in schizophrenia 1 (Disc1), neuregulin 1 (Nrg1), Akt1, and reelin—is regulated by *Lpar1* (Lovestone et al., 2007; Mao et al., 2009). Additionally, glutamatergic signaling alterations are implicated in behavioral deficits associated with schizophrenia, autism, and other related neuropsychiatric disorders (Lin et al., 2012a; Hadley et al., 2014), and LPA is known to reduce glutamate uptake involving an LPA_1-independent mechanism (Shano et al., 2008). Modification of LPA_1 expression has been linked to altered miniature excitatory postsynaptic potential (mEPSP) kinetics and frequency, inhibitory postsynaptic potential (IPSP)

amplitude, and entorhinal cortex gamma oscillations (Cunningham et al., 2006; Trimbuch et al., 2009). *Lpar1* null mice also display alterations in serotonin (5-HT) neurotransmitter levels (Harrison et al., 2003), dysregulation of glutamatergic synapses particularly through regulation of the glutamate receptors GluR1, GluR3, and the NMDA receptor NR2A/B (Harrison et al., 2003; Roberts et al., 2005; Musazzi et al., 2011), increases in hippocampal CaMKII activity (Musazzi et al., 2011), and decreases in parvalbumin-positive neurons (Cunningham et al., 2006). These data present a compelling picture of LPA_1-initiated glutamatergic and GABAergic signaling dysregulation resulting in negative and cognitive behavioral deficits relevant to schizophrenia, depression, bipolar disorder, and anxiety disorders (Figure 3B).

The PLA_2 enzyme family, composed of at least 15 groups, is one of the main phospholipases responsible for LPA production. The activity of distinct forms of PLA_2, particularly cytosolic and intracellular forms, can be significantly increased in first-episode schizophrenia patients and is strongly associated with structural brain abnormalities (Smesny et al., 2010). In addition, rats with knocked-down PLA_2 expression show reductions in PPI (Lee et al., 2009). The removal of a lipid enzyme homolog associated with LPA degradation and uptake, plasticity-related gene 1 (PRG-1 or LPPR4: lipid phosphate phosphatase-related protein type 4, reviewed in Strauss and Bräuer, 2013), results in epilepsy in null mice (Trimbuch et al., 2009). Importantly, these seizures are prevented when LPA_2 signaling is also removed, suggesting a receptor-dependent pathology.

Many environmental risk factors for neuropsychiatric diseases, such as bleeding, infection, and hypoxia, are insults that overactivate LPA signaling (Eichholtz et al., 1993; Herr et al., 2011). Cortical LPA administration increased anxiety, anhedonia, and depression-associated immobility in adult mice (Castilla-Ortega et al., 2014). These behavioral deficits are similar to those seen in *Lpar1* null mice, suggesting that regulation of LPA signaling is critical for regulation of certain behaviors. Indeed, since cortical exposure to high concentrations of LPA during mid-neurogenesis also induces hydrocephalus, this suggests that either increased or decreased LPAR signaling could lead to a number of neurological and psychiatric disorders that might be considered "hypomorphs" of the severe changes seen in hydrocephalus. It is possible that the timing, severity, and duration of aberrant LPAR signaling contributes to specific pathologies, which requires further validation through clinical studies.

Alzheimer's Disease

One of the central pathologies in Alzheimer's disease (AD) is an abundance of senile plaques and tangles composed of beta-amyloid (Aβ) and tau aggregates. Increased ATX expression found in the frontal cortex of Alzheimer's patients (Umemura et al., 2006) suggests that altered LPAR signaling might contribute to the pathology of the disease. LPA enhances site-specific pathogenic tau phosphorylation, leading to GSK3-mediated growth cone collapse in neurons (Sayas et al., 1999). LPA also increases β-secretase activity, leading to elevated Aβ production (Shi et al., 2013). Gintonin, a bioactive fraction isolated from ginseng that has been reported to improve cognition in AD, is composed of protein-bound LPA that can activate LPA_{1-5}. Treatment of Aβ transgenic mouse AD models with gintonin has been reported to attenuate amyloid plaque deposition and prevent long-term memory impairment, resulting in cognitive dysfunction rescue (Hwang et al., 2012). It will be important to validate these reports, including determination of whether there are specific LPARs involved in Aβ plaque formation and cognitive deficits in AD.

Nerve Injury and Pain

LPA signaling is involved in nerve injury and pain responses through LPARs (reviewed in Ueda et al., 2013) (Figure 3C). Neuropathic pain, commonly caused by trauma or inflammation of the nervous system, is modeled using partial sciatic nerve ligation (PSNL), intrathecal LPA injection, UVB irradiation, or ischemia-induced pain. Intrathecal LPA injection initiates neuropathic pain in mice (Inoue et al., 2004; Ueda et al., 2013), while de novo synthesis of LPA through PLA_2 and ATX appears to mediate the initial phases of pain (Ma et al., 2010). Lysolecithin—also known as LPC—is a demyelinating agent (Hall, 1972) that induces neuropathic pain via ATX-mediated conversion into LPA (Inoue et al., 2008b). Notably, *Enpp2* heterozygous null mice that have a 50% decrease in plasma LPA also show a 50% recovery from PSNL-induced pain (Inoue et al., 2008a). Other types of pain may also be dependent on specific LPA forms (Ma et al., 2013).

Genetic removal of *Lpar1* blocks LPA-induced sequelae during PSNL injury, demonstrating receptor specificity (Inoue et al., 2004). Allodynia and demyelination are also reduced using Rho pathway inhibitors, implicating LPA_1-mediated Rho activation (Inoue et al., 2004). Furthermore, LPA_1 activation can induce a nociceptive response that mediates the release of substance P, a neuropeptide implicated in inflammation and pain (Renbäck et al., 1999). Intraperitoneal administration of Ki16425, an $LPA_{1/3}$ antagonist, can block LPA-induced nociception (Ma et al., 2013). PSNL-induced neuropathic pain can also be blocked in *Lpar5* null mice, resulting in decreased phosphorylated cAMP response element-binding protein (pCREB) expression in spinal cord dorsal horn neurons and distinct involvement of cAMP, independent of LPA_1 signaling but requiring LPA_5 (Lin et al., 2012b).

Lipids, including LPA, can indirectly activate or sensitize nociceptors by interacting with TRP or sodium channel families, or by recruiting immune cells to the site of inflammation. During UVB radiation-induced inflammatory hyperalgesia, LPA and other lipids are elevated in the skin, but not in dorsal root ganglia or dorsal horn (Sisignano et al., 2013). Sensitization of afferent Aβ and Aδ fibers are responsible for LPA-induced mechanical allodynia. Moreover, TRPV1 receptors in Aβ and Aδ fibers are thought to be involved in the maintenance of LPA-induced allodynia (Ohsawa et al., 2013).

Brain Cancer

LPA signaling may be relevant to cancer by promoting tumor growth, neovascularization, survival, and metastasis (reviewed in Tsujiuchi et al., 2014; Yung et al., 2014) (Figure 3D). Aberrant LPAR expression and signaling in CNS glioblastomas and neuroblastomas have been reported (Hoelzinger et al., 2008; Willier et al., 2013). *LPAR1* and *ENPP2* are overexpressed in highly malignant glioblastoma multiforme (GBM) (Kishi et al., 2006). Metabolism of LPC by ATX may provide a chemotactic source of LPA, since *ENPP2* knockdown in GBM reduces LPC-directed

migration, inhibits invasion, and enhances tumor radiosensitivity (Kishi et al., 2006; Hoelzinger et al., 2008; Schleicher et al., 2011). Induced LPA_1, LPA_2, or LPA_3 signaling stimulates increased cell motility (Van Leeuwen et al., 2003; Hama et al., 2004; Hayashi et al., 2012), while in contrast, LPA_4 expression in B103 cells may attenuate pro-migratory LPA_1 and LPA_2 responses (Lee et al., 2008).

Dysregulated Rho and Rac signaling appears to correlate with neural tumor proliferation and invasiveness (Khalil and El-Sibai, 2012), which can be altered by LPAR mechanisms. LPA_1 and LPA_2 signaling induces stress fiber formation, cytoskeletal rearrangement, and cell migration in GBM cells via downstream Rho/ROCK activation (Manning et al., 2000). ROCK inhibition in LPAR-expressing tumor cells decreases motility and invasion (Salhia et al., 2005; Hayashi et al., 2012). This pathway is balanced and antagonized by Rac1-mediated adhesion and PI3K signaling (Van Leeuwen et al., 2003; Seasholtz et al., 2004; Salhia et al., 2005). Other LPA-induced migration mechanisms may involve Ras-MAP kinase signaling and matrix metalloproteinases (Annabi et al., 2009; Kato et al., 2012).

Conclusion

Over the past two decades, the roles of LPA signaling have been progressively defined in the normal developing and adult nervous system, initiated by the identification of specific, cell-surface receptors. LPA signaling influences numerous developmental processes, including NPC proliferation, neural and glial development, proper cell migration, and cell survival. Environmental stressors such as hypoxia, inflammation, and hemorrhage that increase LPA signaling have links to multiple neuropathologies. Genuine therapeutics targeting LPARs are anticipated in the future, especially in view of the compound known as fingolimod, an FDA-approved medicine for treating multiple sclerosis, which modulates LP (S1P) receptors (Chun and Brinkmann, 2011; Groves et al., 2013), along with the entry of new chemical entities targeting LPARs into clinical trials for other indications (Kihara et al., 2014b; Yung et al., 2014). The prospects are increasingly bright for uncovering new mechanisms and medicines that impact the nervous system through LPA signaling.

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Note Added in Proof

After this Review was completed, Mirendil et al. (2015) was accepted for publication. This article demonstrates how in vivo exposure to LPA in the developing mouse brain, which mimics intracerebral bleeding, can produce postnatal schizophrenia-like changes:

Mirendil, H., Thomas, E.A., De Loera, C., Okada, K., Inomata, Y., and Chun, J. (2015). LPA signaling initiates schizophrenia-like brain and behavioral changes in a mouse model of prenatal hemorrhage. Transl. Psychiatry, in press.