Review

Role of Lysophosphatidic Acid in Neurological Diseases: From Pathophysiology to Therapeutic Implications

Simona Dedoni[1],*[ID], Valeria Avdoshina[2][ID], Maria C. Olianas[3][ID], Pierluigi Onali[3][ID]

[1]Department of Biomedical Sciences, Division of Neuroscience and Clinical Pharmacology, University of Cagliari, 09142 Cagliari, Italy
[2]Department of Neuroscience, Georgetown University Medical Center, Washington, DC 20057, USA
[3]ExplorePharma s.r.l., Parco Scientifico e Tecnologico della Sardegna, Località Piscinamanna, 09010 Cagliari, Italy
*Correspondence: dedoni@unica.it (Simona Dedoni)
Academic Editor: Hongquan Wang

Abstract

Lysophosphatidic acid (LPA), a bioactive lipid molecule, has been identified as a critical regulator of several cellular processes in the central nervous system, with significant impacts on neuronal function, synaptic plasticity, and neuroinflammatory responses. While Alzheimer's disease, Multiple Sclerosis, and Parkinson's disease have garnered considerable attention due to their incidence and socioeconomic significance, many additional neurological illnesses remain unclear in terms of underlying pathophysiology and prospective treatment targets. This review synthesizes evidence linking LPA's function in neurological diseases such as traumatic brain injury, spinal cord injury, cerebellar ataxia, cerebral ischemia, seizures, Huntington's disease, amyotrophic lateral sclerosis, Hutchinson-Gilford progeria syndrome, autism, migraine, and human immunodeficiency virus (HIV)-associated complications Despite recent advances, the specific mechanisms underlying LPA's actions in various neurological disorders remain unknown, and further research is needed to understand the distinct roles of LPA across multiple disease conditions, as well as to investigate the therapeutic potential of targeting LPA receptors in these pathologies. The purpose of this review is to highlight the multiple functions of LPA in the aforementioned neurological diseases, which frequently share the same poor prognosis due to a scarcity of truly effective therapies, while also evaluating the role of LPA, its receptors, and signaling as promising actors for the development of alternative therapeutic strategies to those proposed today.

Keywords: neurological diseases; lysophosphatidic acid; traumatic brain injury; spinal cord injury; cerebral ischemia; seizures; Huntington's disease; autism; amyotrophic lateral sclerosis; HIV

1. Introduction

Neurological diseases encompass a broad spectrum of disorders affecting the central and peripheral nervous systems, leading to significant morbidity and mortality worldwide. According to the World Health Organization (WHO), neurological disorders are estimated to affect over a billion individuals globally, with an increasing burden due to aging populations and environmental conditions [1]. Various factors, including genetic predisposition, pollution, radiation exposure, antioxidants, and dietary habits, contribute to the rising incidence of neurological pathologies across different age groups [2–4]. The role of diet and lipid metabolism in neurological health has garnered increasing attention in recent years. Lipids, essential components of cell membranes and signaling molecules, play crucial roles in maintaining neuronal structure and function [5]. Dysregulation of lipid metabolism has been implicated in various neurological disorders, including Alzheimer's disease (AD), multiple sclerosis (MS), epilepsy, and many more [6–8]. Of particular interest is lysophosphatidic acid (LPA), a bioactive lipid with diverse physiological functions in the nervous system. LPA exerts its effects through interaction with specific G protein-coupled receptors, including LPA receptors 1–6 [9,10]. Specifically, lysophosphatidic acid receptor (LPAR)1 is key in neuropathic pain, alveolar development, intestinal epithelial cell proliferation, bone mineralization, and vascular remodeling [11–16]. LPAR2 plays protective roles in intestinal health, stroke recovery, and immune cell migration while regulating exploratory behaviors post-fasting [17–20]. LPAR3 contributes to reproduction and neuropathic pain [21,22], and LPAR4 and LPAR6 are critical for vascular development and metabolic regulation [23–25]. LPAR5 is involved in T-cell inhibition and gut homeostasis and LPAR6 influences oligodendrocyte development [26–28]. These findings highlight LPA's extensive impact on physiological and pathological processes, with potential therapeutic implications. For instance, LPA's promotion of cortical neuronal progenitor commitment through LPAR1 during cortical neurogenesis highlights its critical developmental functions [29]. Additionally, LPA influences cytoskeletal dynamics and neurite retraction, which is essential for neuronal morphology and motility [30,31]. Beyond neurons, LPA modulates astrocyte proliferation, cytokine expression, and neuroinflammation, facilitating neuron-astrocyte crosstalk and impacting processes like axonal growth and differentiation [32]. Similarly, microglia respond to LPA through receptor-mediated calcium signaling, chemokinesis, and morphological changes, underscoring its broader influence in central nervous system (CNS) cell interactions [31] (Fig. 1).
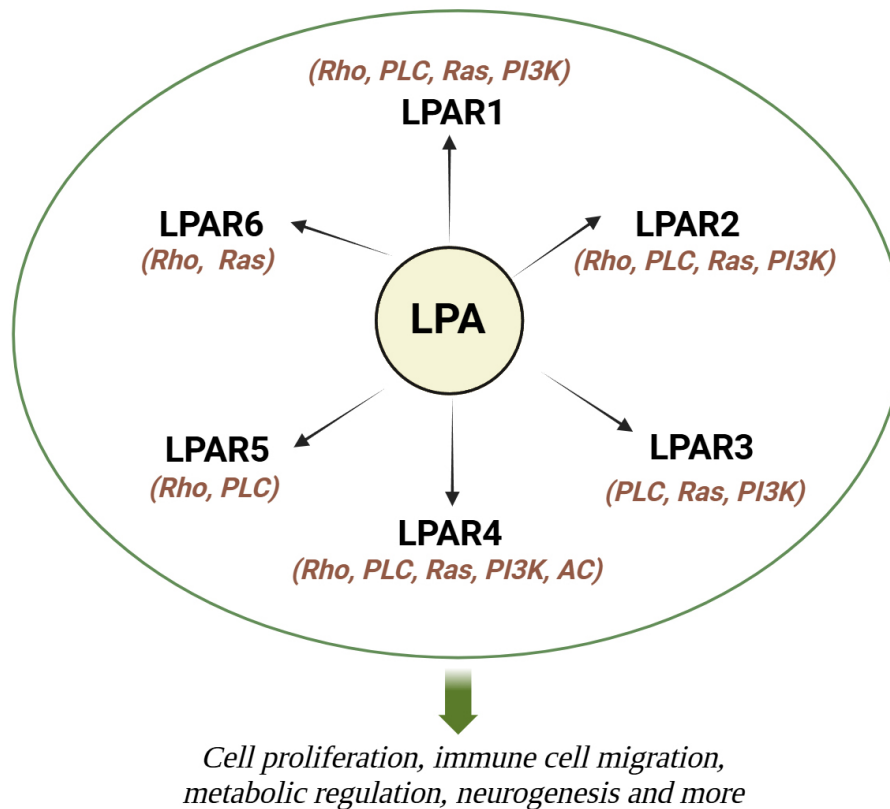
Fig. 1. Summary of cellular and molecular mechanisms of LPA. LPA works by activating 6 transmembrane G-coupled protein receptors (LPAR1-6), which in turn trigger many signaling pathways by activating various G proteins. LPA, lysophosphatidic acid; LPAR, lysophosphatidic acid receptor; Rho, Rho-kinase; PLC, phospholipase C; Ras, Ras kinase; PI3K, phosphoinositide 3-kinase; AC, adenylyl cyclase. Created with Biorender.com.

Merging evidence suggests that dysregulation of LPA signaling contributes to the pathogenesis of neurological diseases by modulating neuroinflammatory responses, neuronal survival, and synaptic plasticity [8,33–35]. This review intends to illustrate the implication of LPA in the pathogenesis of various neurological diseases, such as traumatic brain injury (TBI), spinal cord injury (SCI), cerebellar ataxia (CA), cerebral ischemia, seizures, Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), Hutchinson-Gilford progeria syndrome (HGPS), autism spectrum disorders (ASD), migraine and in human immunodeficiency virus (HIV)-associated neurocognitive disorders, which frequently share the same poor prognosis and a lack of effective treatment options, while additionally assessing the role of LPA, its receptors, and signaling as potential actors for the establishment of alternative therapeutic strategies to those proposed today (Fig. 2).

2. Role of LPA in Different Neurological Conditions

2.1 LPA in Neurological Injuries

2.1.1 Traumatic Brain Injury

TBI is a major public health problem worldwide, with millions of cases recorded each year. It is frequently caused by a variety of circumstances, such as falls, car accidents, sports injuries, violence, and many more, where the collision to the head causes a variety of deficits, depending on the location and degree of the lesion. TBIs are classified according to their severity as mild, moderate, or severe. Children, teenagers, and the elderly are more prone to TBIs [36]. It was estimated that roughly 2.87 million TBI-related emergencies occurred in 2012 each year in the United States [33,36]. The probability of survival after TBI ranges according to the extent of the patient's age, the damage, and the timing of medical care. While moderate TBIs have an improved outcome, severe TBIs increase the chance of death and long-term impairment. Based on recent data, around 69,000 TBI-related fatalities occurred in the United States in 2021 [37].

LPA has recently been discovered as a possible mediator of subsequent brain damage after TBI. Elevated levels of LPA in the brain were identified following TBI, contributing to neuronal injury, neuroinflammation, and blood-brain barrier (BBB) disruption [38]. LPA signaling has also been linked to the control of synaptic plasticity and neurodegeneration, indicating its potential relevance in the rehabilitation phase post-TBI [39]. It was shown that LPA levels raised considerably in cerebral spinal fluid (CSF)
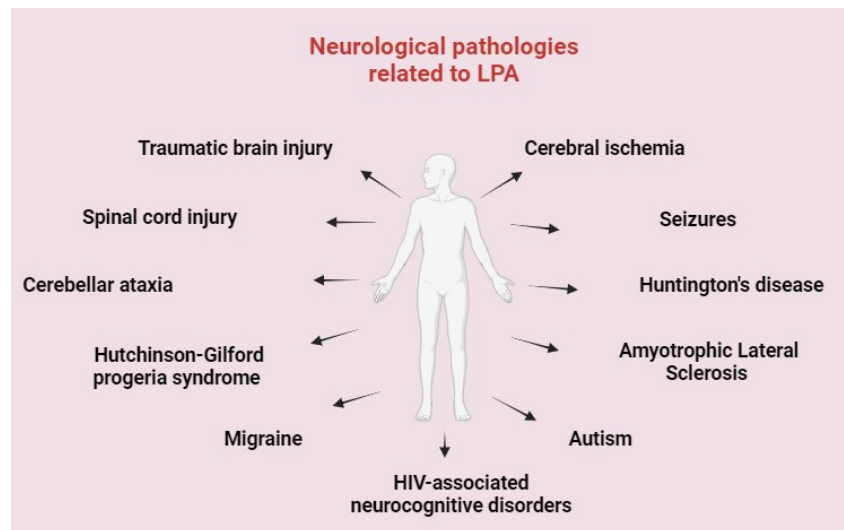
Fig. 2. General overview of LPA-related neurological disorders. HIV, human immunodeficiency virus. Created with Biorender.com.

from TBI individuals and mice exposed to control cortical impact (CCI) injuries. These high levels promoted secondary injury processes such as neural inflammation and cell death determining BBB disruption that all participated in aggravating the damage produced by the initial trauma [38]. Moreover, brain tissue samples showed reduced levels of markers of inflammation and cytokines, with consequent lower neuroinflammatory response, and tissue damage following TBI [38].

LPAs were also investigated as biomarkers for blast-induced traumatic brain injury (bTBI). Samples of CSF were obtained from rats exposed to single or repeated blasts and analyzed for various LPA species using mass spectrometry, revealing significantly higher levels of LPAs in the CSF. LPA levels in the CSF, but not the plasma, were shown to be correlated with the extent of injury and neurological impairments in rats, related to greater damage and poor clinical outcomes, indicating that LPAs might be useful as predictive indicators in bTBI. Longitudinal studies demonstrated variable differences in LPA levels after bTBI. The highest LPA levels were detected immediately after injury, followed by a slow fall during the next few days to weeks. This time course showed that in CSF the LPA levels might represent the acute and subacute stages of bTBI pathophysiology, and LPA levels might be good indicators of the severity of the injury [40] (Table 1, Ref. [38,40–53]).

Other studies examined the changes in LPA distribution following TBI utilizing matrix-assisted laser desorption ionization (MALDI) methods in brain samples of rats with TBI. MALDI mapping indicated substantial alterations in the spatial distribution of LPAs in the brain after TBI. Specifically, at 3 hours after damage, increased intracellular LPA expression was related to neuronal degeneration; hence, alterations in LPA signaling after TBI outside of hemorrhagic zones may also contribute to neuronal death. MALDI examination of the thalamus revealed a con-

siderable rise in the distribution of the intracellular precursor of LPA, phosphatidic acid (PA) 18:0/18:1, one hour after damage. This was followed by an increase in neuronal degeneration 3 hours following the damage. The current investigation found that bioactive LPA isoforms 18:1 and 20:1 were more efficiently metabolized in damaged cortical gray matter, but saturated species levels remained constant. The increased expression of unsaturated LPA is most likely due to blood coagulation near the damaged epicenter. The corpus callosum analysis revealed that, while there were no general white matter differences in LPA levels, there was a positive connection between LPA 20:1 and axonal injury sites, indicating that LPA may be an indication of damage to axonal cells post-TBI. These findings support LPA as an initial signaling component responsible for contributing to the pathophysiology of TBI, not just in hemorrhagic areas, but throughout the brain, particularly in white matter areas [41] (Table 1).

Several studies have investigated numerous tactics for modulating LPA transmission in TBI, such as the use of pharmaceutical agents that target LPA receptors and enzymes that participate in LPA synthesis and metabolism [38,54,55]. These investigations have demonstrated encouraging results in reducing neuroinflammation, maintaining neuronal integrity, and enhancing performance in animal models of TBI [38]. The use of anti-LPA antibodies has shown tremendous efficiency towards TBI-related damage. In fact, inhibiting LPA with the murine anti-LPA mAb, B3, improved brain function in CCI mice providing the first indication that therapeutic anti-LPA antibodies could be effective in treating TBI-associated secondary damage [38]. Indeed, the animals treated with anti-LPA antibodies increased their cognitive performance compared to the control-treated mice and behavioral assessments suggested greater recovery. In addition, anti-LPA antibody therapy maintained the health of neurons and decreased neuronal

Table 1. LPA system alterations in neurological disorders.

Disorder	LPA system alterations	References
Traumatic brain injury	↑ LPA in CSF of TBI patients and mice with CCI	[38]
	↑ LPA in CSF of rats after bTBI	[40]
	↑ LPA species in injured areas and white matter in rats with TBI	[41]
Spinal cord injury	↑ LPA levels and LPAR1/3 activation	[42,44]
	↑ LPAR2 expression in the spinal cord and microglia in mice after SCI	[43]
Cerebral ischemia	↑ LPAR5 expression in ischemic areas and microglia in tMCAO mice	[45]
	↑ LPA levels in MCAO mice	[46]
Seizures	↑ LPAR1 expression in NCSs in mice	[52]
Amyotrophic Lateral Sclerosis	↑ LPA-LPAR1 signaling	[47,48]
	↑ LPAR2 expression in the spinal cord	
Hutchinson-Gilford progeria syndrome	↑ LPAR3 activation	[50,51]
Autism	↓ LPA 18:2 serum levels	[49]
HIV	↑ LPA levels and plasma levels	[53]

CSF, cerebral spinal fluid; CCI, control cortical impact; TBI, traumatic brain injury; bTBI, blast-induced traumatic brain injury; SCI, spinal cord injury; tMCAO, transient middle cerebral artery occlusion. ↑, Increased; ↓, Altered.

damage in the interested areas. This shows that anti-LPA antibodies protect neurons from injury and death. Immuno-histochemical investigations revealed that mice treated with anti-LPA antibodies had higher levels of indicators linked with neurodegeneration and synaptic plasticity. This shows that anti-LPA antibodies may play a role in aiding healing and rehabilitation after TBI. These experimental results provide strong proof for anti-LPA antibodies' beneficial effects for enhancing endpoints after a traumatic brain injury. Anti-LPA antibodies, which target LPA signaling pathways, offer a potential method to reduce secondary damage mechanisms while promoting neural protection and recovery in TBI [38]. The effectiveness of these antibodies was further investigated in relieving post-TBI neuropathic pain using Sprague-Dawley rats that had undergone controlled cortical impact damage to generate TBI. Upon damage induction, animals were monitored for the onset of neuropathic pain responses such as mechanical allodynia and temperature hyperalgesia. Rats were then given either anti-LPA antibodies or a control therapy. Animals treated with anti-LPA antibodies demonstrated a substantial decrease in neuropathic pain behaviors when compared to control animals, with mechanical allodynia alleviated in the treated group and thermal withdrawal latencies significantly prolonged [54]. Another study revealed that the treatment with the anti-LPA antibody B3/Lpathomab successfully reduced the production of pro-inflammatory cytokines (tumor necrosis factor (TNF)-α and interleukin (IL)-1β), together with the lesion volumes and neuronal damage in a mouse model of TBI, which led to a significant improvement in clinical outcomes. This data provides strong evidence for the potential anti-LPA antibodies' therapeutic value in the management of neuronal damage after TBI [55].

2.1.2 Spinal Cord Injury

SCI is a severe medical disorder caused by trauma or damage to the spinal cord, resulting in variable degrees of mainly motor and sensory impairment. The spinal cord, a critical component of the CNS, acts as a route for neural impulses throughout the brain and every part of the body, allowing movement, sensation, and coordination. When the spinal cord is injured, changes in these neuronal pathways can result in severe and sometimes permanent deficits in motor function, sensation, and physiological functions below the level of damage.

In the last few years, LPA has emerged as an important component in the pathogenesis of spinal SCI. Elevated levels of LPA after SCI correspond with the severity of the damage, indicating its participation in pathological processes. The major player involved seems to be the LPAR1 which has a variety of negative consequences in SCI [42] (Table 1). LPAR1 activation exacerbates neuroinflammation by increasing the production of inflammatory cytokines and chemokines [56]. Furthermore, LPAR1 activation has been linked to neuronal death and inhibits axonal regeneration, limiting functional recovery after SCI [57]. It was discovered that LPA levels rise following a SCI, and this rise is related to the severity of the lesion. The LPAR1 is hypothesized to trigger a range of physiological reactions, including not only the stated inflammation, but also promotes glial scar formation, neuronal death, and slows axonal regeneration, all of which are critical in SCI, limiting functional recovery (Table 1). LPAR1 activation is implicated in promoting neuronal apoptosis [58] and inhibiting axonal regeneration [59] crucial processes for functional recovery following SCI.

Besides LPAR1, LPAR2 was also shown to contribute to myelin loss and secondary damage following SCI. A

study conducted in mice revealed that the expression and activation of LPAR2 is increased following contusion damage, at least partially via microglia. Furthermore, the demyelinated lesion caused by an intraspinal injection of LPA into the undamaged spinal cord was decreased in the absence of LPAR2. Mice missing LPAR2 had enhanced motor abilities and myelin sparing following SCI. *In vitro* cell culture experiments showed that LPAR2 activation of microglia resulted in oligodendrocyte cell death and the cytotoxic effects of the microglial LPA-LPAR2 axis were caused by purine release by microglia and receptor activation P2X7 affects oligodendrocytes. This work sheds fresh light on the involvement of LPAR2 in SCI [43] (Table 1).

As previously highlighted, studies have shifted towards focusing on the critical role of LPAR1 and LPAR2 in SCI pathology. Inhibiting these receptors holds promise in reducing inflammation, neuronal loss, and promoting functional recovery, paving the way for targeted therapies to enhance SCI outcomes. Experimental findings showed that inhibiting LPAR1 might ameliorate the negative consequences of SCI, providing a possible treatment path. Understanding the processes that underpin LPAR1 activation and its downstream consequences gives important insights for creating targeted therapies to improve outcomes for people with SCI [44]. The discovery of LPAR1 as a major mediator in SCI pathophysiology opens up possibilities for targeted treatment therapies and the use of LPAR1 antagonist receptors showed promising results as a therapy option for SCI's consequences, including inflammation, neuronal loss, and delayed regeneration [43]. Further evidence of the involvement of LPAR2 in the consequences of SCI was given by a study in which UCM-14216, a new LPAR2 antagonist, administered to mice with SCI, successfully reduced the severity of the damage and improved the recovery of the functions. This study confirms the LPAR2 therapeutic potential of drugs targeting LPA receptors for improving spinal cord injury-induced pathology and increasing recovery [60].

2.1.3 Cerebellar Ataxia

CA is a neurological condition characterized by a loss of coordination, uneven walking, and difficulty with speech and eye movements caused by an injury to the cerebellum, the brain's motor control center [61].

New studies show a relationship between CA and LPA signaling [62,63]. Lipidomic studies revealed that alterations in genes regulating lipogenesis and lipolysis may alter lipid composition such as phospholipids, sphingolipids, and cholesterol levels, and contribute to the onset of hereditary CA and other ataxic disorders through the dysregulation of mitochondrial function, oxidative stress, and neuronal survival. Understanding the role of lipid dysregulation in disease etiology may provide new treatment strategies for these devastating neurodegenerative illnesses [62]. Recently, researchers investigated the link between a ho-

mozygous mutation in the *DDHD2* gene, which is involved in the production of a phospholipase, and the development of late-onset spastic ataxia. This mutation was shown to be correlated with a significant decrease in the activity of phospholipase A1 and, consequently, of LPA production, suggesting that a main mutation involved in the onset of CA is directly linked to LPA signaling and metabolism [63].

2.1.4 Cerebral Ischemia

Cerebral ischemia is a prominent cause of death and morbidity globally, frequently resulting in devastating neurological impairments, and is distinguished by insufficient blood flow to the brain [64]. The most prevalent kind of cerebral ischemia is ischemic stroke, which accounts for roughly 80% of all strokes worldwide, with considerable differences in incidence and prevalence across demographic and geographic locations. It happens when a cerebral artery gets clogged, triggering a series of events that include energy failure, excitotoxicity, oxidative stress, inflammation, and, eventually, neuronal cell death [65–67]. The study of cerebral ischemia has benefited from a variety of experimental models, such as transient or permanent occlusion of cerebral blood vessels in animal models, *in vitro* ischemia-reperfusion models, and advances in neuroimaging techniques for assessing cerebral perfusion and metabolism in humans. In addition, accumulating data shows that cerebral ischemia is more than just a localized phenomenon; it also involves extensive changes in neuronal connections and network dynamics, which contribute to cognitive impairment and other long-term effects [68].

LPAR1 might be an important target for cerebral ischemia, due to its ability to evoke microglial activation. In a recent study, researchers used a mouse model of transient middle cerebral artery occlusion (tMCAO) to evaluate the contribution of LPAR1 to ischemic damage. LPAR1 was shown to be implicated in brain infarction and neurological deficits, as well as neuroinflammation and microglial activation [69]. Other LPA receptors were also investigated in cerebral ischemia. To unravel the involvement of LPAR5 in the pathogenesis of cerebral ischemia, LPAR5 expression was characterized in the brains of mice exposed to tMCAO to model cerebral ischemia. Immunohistochemical research showed that LPAR5 expression was upregulated in the ischemic area, particularly in microglia, which was correlated with increased production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [45]. Further evidence of the involvement of LPA in ischemic damage comes from a study in which the authors highlighted increased LPA expression in the ischemic area following middle cerebral artery occlusion (MCAO) in rats. The LPA increase was followed by increased production of proinflammatory cytokines via nuclear factor-kappa B (NF-κB) signaling. Moreover, the authors speculate that there might be a connection between the increased LPA and the decreased expression of liver X receptor (LXR) after cere-

bral ischemia and suggest that the LPA-induced reduction of LXR might contribute to the ischemic pathophysiology [46] (Table 1).

Modulating the LPA system, particularly through antagonizing its receptors, has emerged as a promising strategy for reducing cerebral ischemic damage by regulating key factors in ischemia such as neuroinflammation and neuronal apoptosis. The antagonization of LPAR1 both through treatment with AM095, an LPAR1 antagonist, and a specific LPAR1 shRNA lentivirus, led to reduced neurological deficits and brain infarction, as well as microglial activation and production of proinflammatory cytokines, NF-κB, and MAPK activation [69]. Antagonizing LPAR1 activity also reduced the activity of NLRP3 inflammasome [70]. These results confirmed the importance of LPA-regulated inflammatory processes in ischemic damage. In another study, researchers treated tMCAO-exposed animals with the LPAR5 antagonist TCLPA5. TCLPA5-treated animals had smaller infarcts, reduced neuronal apoptosis and better neurological function, according to behavioral and histological tests. The neuroinflammatory reaction after ischemia was also shown to be reduced after the treatment, with reduced microglial activation and decreased expression of proinflammatory cytokines. This study identifies the antagonism of LPAR5 as a potential tool to prevent cerebral ischemic damage [45] (Table 1). It was previously shown that exogenous LPA was able to increase infarct size after cerebral ischemia-reperfusion due to an increase in the permeability of the BBB [71]. A recent study deepened this aspect by examining the influence of endothelium-specific Autotaxin (ATX) deletion on the effects of stroke and ischemic reperfusion ice with endothelial-specific ATX deletion and wild-type controls were subjected to MCAO to model stroke and the stroke outcome was evaluated by measuring infarct volume, microglial activation, and BBB integrity. In animals missing endothelial ATX, LPA levels were significantly reduced, as well as infarct size and microglial activation. Moreover, permeability analysis showed that the integrity of the BBB was preserved in the brains of endothelial-specific ATX knockout mice, as shown by reduced Evans Blue dye leakage. Endothelial-specific ATX excision provides neurological protection by maintaining BBB integrity regulating signaling pathways involved in the dysfunction of the vascular system and, reducing neuroinflammation demonstrating that blocking endothelial ATX is a potential therapeutic strategy for improving the effects of stroke and reducing cerebrovascular consequences [72].

2.2 LPA in Neurodegenerative Disorders

2.2.1 Huntington's Disease

HD is a progressive neurodegenerative ailment marked by physical impairment, cognitive decline, and mental symptoms. It is triggered by a genetic mutation in the huntingtin (*HTT*) gene, which produces a mutant hunt-

ingtin protein (mHTT) [73]. Deposition of mHTT in neurons causes neuronal malfunction, atrophy, and eventually cell death, particularly in areas of the brain important in motor control and cognition. HD usually appears in mid-adulthood, with symptoms deteriorating over time and resulting in substantial impairment and untimely mortality.

Recent research has found differences in LPA levels and LPA receptor expression in the brains of HD patients and animal models of illness [74]. LPA signaling has also been demonstrated to affect the pathophysiology of HD by regulating neuroinflammation, excitotoxicity, and synaptic function. Targeting the LPA signaling system might be a promising therapeutic method for reducing neuronal damage and cognitive impairment in HD [57]. So far, few very recent publications focused on LPA involvement in HD. The knock-in Q140/Q140 rodent model, which mimics essential aspects of HD, was used for lipid extraction with liquid chromatography combined with simultaneous mass spectrometry (LC-MS/MS) to measure glycerophospholipid constituents. Glycerophospholipid profiles differed significantly between HD and wild-type mouse brains. PA and LPA were shown to be dysregulated in the brains of HD mice when compared with controls [74]. Since PA is a precursor of LPA, the reduction of PA synthesis that is observed in these animals could underlie the increase seen in LPA species, therefore indicating that lipid signaling, metabolism, and cellular homeostasis disruptions could be linked with Huntington's disease pathology [74]. The function of sphingolipids was also evaluated in the etiology of HD and how they affect cellular reactions to hypoxic stress, examining how dysregulated sphingolipid metabolism causes neuronal dysfunction and vulnerability in HD. It was shown that some sphingolipid species, such sphingosine-1-phosphate (S1P), a bioactive lipid similar to LPA, and ceramide, had abnormal regulation in HD and altered cellular reactions after hypoxic stress. Irregular sphingolipid signaling pathways lead to oxidative stress, inflammation, and mitochondrial dysfunction, worsening neurons' sensitivity to hypoxic insults in HD [75].

The function of gintonin in neurological dysfunction and striatal cytotoxicity through the modulation of LPA signaling was examined in an HD mice model produced by 3-nitropropionic acid (3-NPA). The pretreatment with gintonin of animals treated with 3-NPA, an irreversible inhibitor of complex II in the mitochondria, to model HD ameliorated the outcome by blocking mitochondrial dysfunction, inflammation, and microglia activation due to the activation of Kelch-like ECH-associated protein 1 (Keap1)-Nuclear factor erythroid 2-related factor 2 (Nrf2) pathways and up-regulation of LPA in the striatum. The beneficial effects of gintonin were annulled by antagonizing LPAR1-3 using Ki16425, corroborating the importance of the LPA system for brain functioning. It was additionally looked into the beneficial effect of gintonin (GT) in STHdh cells, an *in vitro* model of HD, and an adeno-associated viral (AAV) vector-infected mouse model of HD, with the posi-

6

tive effect of gintonin demonstrated by the inhibition of formation of mutant HTT aggregates and reduced cell death. Probably, gintonin could be evaluated as a novel future therapeutic agent for HD by activating Keap1-Nrf2 signaling through the LPA signaling pathway [76].

2.2.2 Amyotrophic Lateral Sclerosis

ALS, sometimes known as Lou Gehrig's disease, is a degenerative neurological disease marked by a slow decline and destruction of motor neurons in the brain and spinal cord. This deadly ailment causes gradual muscular weakening, paralysis, and, eventually, respiratory failure, usually ending in death within a few years after the symptoms start. Because of its devastating effect and complicated genesis, ALS has sparked widespread interest in both the medical and scientific sectors. While the exact origin of ALS remains unknown, recent research reveals a complex interaction of genetic, environmental, and lifestyle variables. Approximately 5–10% of ALS cases are inherited, with the remainder being sporadic, showing a complicated genetic contribution along with environmental effects [77]. The prevalence of ALS differs widely, with greater rates recorded in some areas. Typically, ALS affects 1 to 2 persons per hundred thousand globally each year, with modest variances among individuals [78]. While ALS can develop at any age, it primarily affects persons between the ages of 40 to 70, with the typical age of manifestation at 55 years [79]. The cause of ALS is an intricate connection of numerous molecular processes, comprising excitability, oxidative stress, dysfunction in the mitochondria, decreased axonal transport, and neuroinflammation [80]. These mechanisms lead to the gradual degradation of motor neurons, which leads to the loss of muscular function seen in ALS patients. Recent discoveries in neurobiology have emphasized the probable significance of LPA in ALS etiology. Altered LPA signaling has been linked to neuroinflammatory reactions, axonal decay, and neuronal death, indicating its possible role in ALS pathophysiology [81].

LPA binding to LPAR1 regulates a variety of cellular functions associated with ALS pathogenesis. The therapeutic potential of targeting LPA receptor LPAR1 signaling was investigated using superoxide dismutase 1 (SOD1)-G93A transgenic mice, a well-established ALS animal model. SOD1-G93A transgenic mice received therapy with the LPAR1 antagonist AM095 at early disease phases, and the progression of the disease was evaluated as delayed disease development in SOD1-G93A mice compared to controls, revealing preserved motor neurons and reduced glial inflammation, neuroinflammation, and oxidative stress, indicating attenuated disease pathology. These findings imply that LPA-mediated pathways play a role in ALS pathogenesis and give a basis for additional research into LPA receptor antagonists as possible ALS therapeutics [47] (Table 1). On the other hand, gintonin was proven to be effective in ameliorating the symptoms, preventing motor dysfunction,

and increasing survival in SOD1-G93A mice, suggesting that the role of LPA-LPAR1/3 signaling in ALS needs to be further investigated [82]. Using the same transgenic animal paradigm deficient in LPAR2, the influence of LPAR2 on ALS evolution was evaluated, as LPAR2 mRNA levels were found to be elevated in post-mortem spinal cord samples from ALS patients [48]. *LPAR2* gene deletion enhanced microglial activation but did not cause demyelination or degeneration of motor axons, protecting against muscular atrophy. The deletion of the LPAR2 decreased macrophage infiltration into the skeletal muscle in transgenic mice, connecting LPAR2 signaling to muscle inflammation and atrophy in ALS demonstrating for the first time that LPAR2 might contribute to ALS, and that its genetic deletion has protective effects. More research into the underlying mechanisms of LPAR2-mediated neuroprotection is needed [48] (Table 1).

2.3 LPA in Genetic Neurological Disorders

2.3.1 Autism Spectrum Disorders

ASD is a diverse collection of neurodevelopmental conditions distinguished by impaired social communication, repetitive behaviors, and limited interests. With an estimated frequency of 1 in 54 children in the United States [83], ASD places a considerable burden on affected people and society. ASD's etiology is complicated, with intricate relationships involving predisposition to the disorder, variables in the environment, and abnormal neurodevelopmental mechanisms. Numerous susceptibility genes and chromosomal anomalies have been linked to ASD, including changes in synaptic function, neural connection, and neurotransmitter signaling [84]. Furthermore, prenatal and postnatal variables such as maternal illness, exposure to environmental chemicals, and maternal metabolic abnormalities increase the chance of ASD [85].

Emerging data points to a possible relationship between LPA imbalance and ASD pathogenesis. Children with ASD exhibit altered levels of LPA, indicating that LPA may have a role in modifying synaptic function, neuronal connection, and neuroinflammatory processes involved in ASD etiology [86]. A case-control study was conducted to explore immunological abnormalities during mid-gestation in women of children with autism spectrum disorder (ASD). The focus was on the potential relationship to LPA signaling, which gave insight into the immunological changes associated with ASD and their possible link to LPA dysregulation. The study evaluated maternal levels of cytokines in mid-gestation across women who had kids with ASD and typical controls. The investigation discovered that mothers of children with ASD had substantially higher levels of interferon (IFN)-γ, IL-4, and IL-5 compared to controls. Women carrying a child with ASD experience midgestational immunological dysfunction, which is manifested by a T helper (Th)1/Th2 cytokine dysregulation and heightened inflammatory responses. Imbalanced LPA signals may af-

fect maternal-fetal immunological responses during gestation, resulting in abnormal levels of cytokines and elevated ASD risk in children. A direct link connecting abnormalities of LPA signaling and ASD has not yet been identified. However, considering the involvement of LPA in regulating inflammatory processes, this research emphasizes the value of understanding targeting LPA signaling pathways and immunological dysfunction during pregnancy to understand its effect on neurodevelopment [87].

High-throughput mass spectrometry and chromatography technologies found unique metabolic characteristics in people with ASD in comparison to controls, as evidenced by changes in numerous metabolite types such as amino acids, lipids, and organic acids. The researchers used bioinformatics and statistical modeling to discover particular metabolites with variable abundance in ASD samples [49] (Table 1). In particular, changes of LPA 18:2 levels were detected in blood samples from children with ASD, which was considered as a predictor of the disease [85]. Altered LPA signaling may affect neuronal growth, synaptic activity, and neuroinflammatory responses, all of which have been linked to ASD etiology. Furthermore, altered LPA metabolism could lead to neurological abnormalities, interpersonal challenges, and intellectual disabilities seen in ASD phenotypes. Additional study is needed to assess the safety and effectiveness of LPA-targeted future treatments in clinical trials for ASD patients.

2.3.2 Hutchinson-Gilford Progeria Syndrome and LPA

HGPS is a rare genetic condition that results in accelerated aging caused by mutations in the *LMNA* gene, which encodes the lamin A protein. Patients with HGPS show signs of premature aging, such as vascular dysfunction, hair loss, and skin abnormalities, and oxidative stress is thought to play a role in disease progression [88]. Based on the oxidative stress and aging theory, as well as how the increase in LPA signaling can protect against cell damage induced by reactive oxygen species (ROS) [88], investigating the LPA system and its implication in the premature aging process of HGPS could provide valuable pathological and therapeutic insights into premature cellular senescence.

At the end of the 90's, the involvement of LPAR3 in reducing oxidative stress and cellular senescence in HGPS was investigated. Using HGPS-specific cellular models, scientists show that LPAR3 activation reduces oxidative stress and aging characteristics. LPAR3 activation increases antioxidant mechanisms of defense, improves mitochondrial activity, and suppresses DNA damage and the senescence-associated secretory phenotype (SASP) in HGPS cells [50] (Table 1). Moreover, the same authors confirmed the ability of LPAR3 signaling to reduce oxidative stress through the complex regulation of mitochondrial homeostasis [51] (Table 1). The findings imply that targeting LPAR3 signaling pathways might be a promising treatment method for reducing cellular senescence and prema-

ture aging in HGPS. Activation of LPAR3 shows promise for combating oxidative stress and preserving cellular function in HGPS and perhaps other age-related diseases (Table 1).

2.4 LPA and Other Neurological Conditions

2.4.1 Seizures

Seizures are a sign of aberrant synchronous neuronal activity in the brain, which causes a variety of clinical symptoms and behaviors [89]. It is a prevalent neurological condition that affects people of all ages, with a global prevalence of around 1% [90,91]. Seizures can occur as single episodes or as part of a recurring pattern known as epilepsy, which affects approximately 70 million individuals worldwide [92]. Understanding the processes that cause epileptic seizures is critical for accurate diagnosis, efficient treatment, and better quality of life for people affected. Disruptions in ion channels, neurotransmitter systems, and neural networks all play important roles in seizure production and propagation [93]. Genetic investigations have found various mutations in ion channels, neurotransmitter receptors, and synaptic proteins related to epilepsy syndromes, underscoring the disorder's genetic variability [94]. Environmental factors such as head trauma, stroke, brain infections, and developmental anomalies can all raise the risk of seizures by interfering with normal brain function and circuits. Advanced neuroimaging methods give useful information on the anatomical and functional abnormalities that cause epileptic seizures, assisting in the localization of epileptogenic lesions and directing surgical procedures where necessary [95]. Pharmacological treatments, nutritional therapy, neuromodulation methods, and surgical procedures are all used to manage seizures and epilepsy, and they are adapted to the needs of each patient [96]. Despite optimum medical treatment, a considerable minority of patients continue to suffer uncontrolled seizures, emphasizing the need for alternative therapeutic options and continuous research efforts.

The LPAR1 expression in the hippocampus after seizure induction was studied. Immunohistochemical research demonstrates that LPAR1 is upregulated particularly in reactive neural stem cells (NSCs) in the hippocampus neurogenic niche. This suggests that LPAR1 may be involved in the identification of seizure-induced activation of NSCs. Knockout mice missing LPAR1 in NSCs were treated to induce seizure and the loss of LPAR1 caused altered differentiation dynamics and proliferation of NSCs, emphasizing its regulatory function in NSCs behavior. Modulation of LPAR1 activity modifies seizure susceptibility and severity, implying that LPAR1-mediated control of NSCs plays a role in the pathophysiology of epileptic seizures determining the function of LPAR1 in identifying and modulating the organization of seizure-induced reactive NSCs in the hippocampus. LPAR1 appears as a significant molecular indicator and modulator of NSC be-

havior in the context of seizures, providing prospective avenues for therapy for controlling epileptogenesis and boosting neurogenesis in epileptic circumstances [52] (Table 1). In addition, when investigating epilepsy, a study has found that the genetic deletion of the Plasticity Related Gene-1 (*PRG-1*), a membrane protein related to lipid phosphate phosphatases, can lead to epileptic seizures [97]. This outcome was directly linked to LPA. PRG-1 can interact with LPA by controlling its levels at the synaptic level by nonenzymatic mechanisms. LPAR2 knockout animal model further confirmed that LPA-LPAR2 interaction is implicated in hyperexcitability while PRG-1 acts to counteract it [97]. This emphasizes that LPA-LPAR2 interaction is involved in the regulation of excitatory synaptic transmission in the hippocampus, implying that the disruption of this pathway can result in hyperexcitability and seizures.

On the other hand, gintonin's regulatory effect on LPA signaling and its potential to mitigate excitotoxicity-induced neuronal damage and inflammation were investigated by using a mouse model of kainic acid-induced seizures. Gintonin was delivered to mice by intraperitoneal methods, followed by behavioral evaluations, histological investigations, and biochemical assays to determine its impact on seizure outcomes and neuronal survival. The results show that gintonin pretreatment significantly lowers seizure frequency, duration, and severity in kainic acid-treated rats in comparison with untreated controls. Gintonin treatment reduces neuronal cell death and preserves hippocampus structure, indicating neuroprotective properties against excitotoxicity-induced neuronal damage. As gintonin is a specific ligand for LPA receptors, the work sheds light on the role of LPA receptors in mediating its neuroprotective properties. Experimental inhibition of LPA receptors reduces the therapeutic effects of gintonin, emphasizing the relevance of the stimulation of LPA receptors 1 and 3 in regulating its neuroprotective properties. Gintonin suppresses the activity of microglial cells, reduces inflammatory mediators, and cytokine production, and inhibits NF-κB signaling in the hippocampus. Furthermore, gintonin has antioxidant capabilities via reducing ROS, increasing the activity of antioxidant enzymes, and protecting hippocampal neurons. Gintonin, which targets LPA receptors and modulates anti-inflammatory, and antioxidant processes, provides prospective possibilities for the establishment of treatments for neurological illnesses which include excitotoxicity, neurological inflammation, and oxidative damage [98].

2.4.2 Migraine

Migraine is one of the most common neurological diseases globally, impacting millions of people and causing significant impairment. It is a complicated neurological illness defined by recurring headaches that are frequently accompanied by photophobia nausea, and disorientation [99].

Despite the lack of direct evidence connecting LPA signaling with migraine, several evidence links LPA abnormalities with neuropathic and chronic pain. Indeed, LPA was shown to be involved in the initiation and maintenance of neuropathic pain and also fibromyalgia through demyelination of the dorsal root mediated by LPAR1, an increase in inflammatory mechanisms regulated by LPAR3, and an increase in central LPA production through an overactivation of glial cells [11]. An interesting study revealed that LPA levels in the CSF of patients diagnosed with neuropathic pain were correlated with the intensity and duration of pain. LPA 18:1 and 20:4 in particular were shown to be the most correlated with the symptoms [100].

Moreover, it is important to consider the antagonism of LPAR1/3 as a potential therapeutic approach to treat pain. Indeed, LPAR1/3 antagonists were shown to be effective against chronic pain caused by a variety of occurrences, such as chemotherapy, nerve and spinal cord injury, diabetes, cerebral ischemia, and fibromyalgia caused by cold or several other stressors [101]. Considering the nature of migraine, which is characterized among other symptoms by severe episodes of pain, it could be speculated that LPA signaling might be involved in the onset or worsening of the symptoms. Moreover, migraine is also correlated with neuroinflammation and vascular abnormalities [102,103], all factors that are known to be regulated by LPA signaling. However, more specific research is needed to provide clear evidence of the involvement of LPA in migraine and develop effective treatments for this strongly debilitating disorder.

2.4.3 Human Immunodeficiency Virus Associated Neurocognitive Disorders

HIV is part of the Retroviridae family. It targets CD4+ T cells, leading to a gradual suppression of the immune system, and consequently resulting in immunodeficiency that eventually leads to death due to the increased susceptibility to opportunistic infections [104]. Recent research has highlighted the involvement of LPA in the pathophysiology of HIV, particularly concerning infection and HIV-associated complications.

LPA can significantly influence the survival and function of CD4+ T cells. It has been reported that LPA signaling can lead to apoptosis, or programmed cell death, of CD4+ T cells, contributing to the depletion of these crucial immune cells during HIV infection. This loss of CD4+ T cells is a key factor in the progression of HIV to AIDS [105]. A study by Le Hingrat and colleagues [105] investigated the effects of sustained CD4+ T-cell depletion in the context of simian immunodeficiency virus (SIV) infection in African green monkeys (AGMs). AGMs are natural hosts for SIV and typically do not progress to AIDS, even with high viral loads [106]. The study found that despite significant depletion of both circulating and mucosal CD4+ T cells, these monkeys did not progress to AIDS, offering valuable insights into the mechanisms of immune resilience. In addition to LPA's role in im-

mune cell depletion, the HIV-1 trans-activator of transcription (Tat) protein has been recognized for contributing to HIV-induced white matter damage. The viral Tat protein was shown to reduce the lysophospholipase D activity of ATX, leading to decreased LPA synthesis. This reduction in LPA impairs the growth of oligodendrocyte precursor cells and is associated with reduced oligodendrocyte differentiation, which may negatively impact myelination processes. Such disruptions could contribute to the neurological defects observed in HIV-associated neurocognitive disorders (HAND) [106,107]. Furthermore, before the initiation of combination antiretroviral therapy (cART), HIV-infected individuals were found to have higher levels of LPA compared to healthy controls. During the first year of cART, LPA levels remained unchanged even as viral load decreased, and immune function improved. This suggests that while cART is effective in controlling viral replication, it may not fully normalize lipid metabolism, particularly in terms of LPA production and regulation. Consequently, LPA has been proposed as a potential marker of persistent metabolic abnormalities in HIV patients [53] (Table 1). Gaining knowledge about LPA's function in neuroinflammation and neurodegeneration opens up new avenues for research into the mechanisms behind HAND and points to possible treatment options. One intriguing tactic to lessen neuroinflammation and stave off cognitive loss in HIV-positive persons may be to target LPA signaling pathways with therapeutic approaches including the use of LPA receptor antagonists or inhibitors of LPA synthesis to modulate the inflammatory response and preserve neuronal function.

3. Conclusions

The therapeutic potential of targeting LPA signaling in neurological disorders offers a promising avenue for innovative treatments, yet significant challenges remain to ensure clinical success. Anti-LPA antibodies and receptor antagonists have shown efficacy in preclinical models of TBI, ALS, and seizures by reducing neuroinflammation, promoting neuronal survival, and enhancing recovery outcomes [38,47,69,108]. However, translating these findings into human therapies is complicated by potential off-target effects, as LPA is critical to physiological processes such as vascular integrity and immune regulation, raising concerns about systemic side effects [56]. The heterogeneity of LPA's roles across disorders further necessitates tailored therapeutic approaches, given its distinct contributions to the pathophysiology of conditions such as cerebral ischemia, migraines, and spinal cord injury [42,65,102]. Additionally, pharmacokinetic challenges, such as ensuring effective BBB penetration and avoiding systemic degradation, must be addressed [38,72]. Compensatory mechanisms in lipid signaling networks may also reduce the long-term efficacy of LPA-targeted interventions, highlighting the need for robust monitoring and biomarker development

during clinical trials [81]. Despite these obstacles, advancements in understanding LPA signaling pathways and innovative delivery mechanisms provide a foundation for developing safer and more effective therapies. Addressing these risks and refining disease-specific strategies could transform LPA signaling modulation into a viable therapeutic avenue for diverse neurological conditions [9,48].

Author Contributions

Writing—original draft preparation, SD; Supervision, SD, and VA; Review, editing and substantial contributions to the conception or design of the work, SD, VA, MCO, PO. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Conflict of Interest

All authors declare no conflicts of interest. Although Maria C. Olianas and Pierluigi Onali are employees of ExplorePharma s.r.l., they did not receive sponsorship from ExplorePharma s.r.l., and the judgments in data interpretation and writing were not influenced by this relationship. Given her role as the Guest Editor, Simona Dedoni had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Hongquan Wang.

References

[1] World Health Organization. Neurological Disorders: Public Health Challenges. 2006. https://iris.who.int/handle/10665/43605 (Accessed: 1 August 2024).

[2] Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JPA. Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses. Parkinsonism & Related Disorders. 2016; 23: 1–9. https://doi.org/10.1016/j.parkreldis.2015.12.008.

[3] Nazzi C, Avenanti A, Battaglia S. The Involvement of Antioxidants in Cognitive Decline and Neurodegeneration: *Mens Sana in Corpore Sano*. Antioxidants (Basel, Switzerland). 2024; 13: 701. https://doi.org/10.3390/antiox13060701.

[4] Gregorio FD, Battaglia S. The intricate brain-body interaction in psychiatric and neurological diseases. Advances in Clinical and Experimental Medicine: Official Organ Wroclaw Medical University. 2024; 33: 321–326. https://doi.org/10.17219/acem/185689.

[5] Di Paolo G, Kim TW. Linking lipids to Alzheimer's disease: cholesterol and beyond. Nature Reviews. Neuroscience. 2011; 12: 284–296. https://doi.org/10.1038/nrn3012.

[6] Singh A, Kukal S, Kanojia N, Singh M, Saso L, Kukreti S, et al. Lipid mediated brain disorders: A perspective. Prostaglandins & other Lipid Mediators. 2023; 167: 106737. https://doi.org/10.1016/j.prostaglandins.2023.106737.

[7] Estes RE, Lin B, Khera A, Davis MY. Lipid Metabolism Influence on Neurodegenerative Disease Progression: Is the Vehicle as Important as the Cargo? Frontiers in Molecular Neuroscience. 2021; 14: 788695. https://doi.org/10.3389/fnmol.2021.788695.

[8] Dedoni S, Camoglio C, Siddi C, Scherma M, Fratta W, Fadda P. The Role of Lysophosphatidic Acid in Neuropsychiatric and Neurodegenerative Disorders. Future Pharmacol. 2024; 4: 199–221. https://doi.org/10.3390/futurepharmacol4010014.

[9] Geraldo LHM, Spohr TCLDS, Amaral RFD, Fonseca ACCD, Garcia C, Mendes FDA, et al. Role of lysophosphatidic acid and its receptors in health and disease: novel therapeutic strategies. Signal Transduction and Targeted Therapy. 2021; 6: 45. https://doi.org/10.1038/s41392-020-00367-5.

[10] Chakraborty A, Kamat SS. Lysophosphatidylserine: A Signaling Lipid with Implications in Human Diseases. Chemical Reviews. 2024; 124: 5470–5504. https://doi.org/10.1021/acs.chemrev.3c00701.

[11] Ueda H. LPA receptor signaling as a therapeutic target for radical treatment of neuropathic pain and fibromyalgia. Pain Management. 2020; 10: 43–53. https://doi.org/10.2217/pmt-2019-0036.

[12] Ueda H, Neyama H, Matsushita Y. Lysophosphatidic Acid Receptor 1- and 3-Mediated Hyperalgesia and Hypoalgesia in Diabetic Neuropathic Pain Models in Mice. Cells. 2020; 9: 1906. https://doi.org/10.3390/cells9081906.

[13] Funke M, Knudsen L, Lagares D, Ebener S, Probst CK, Fontaine BA, et al. Lysophosphatidic Acid Signaling through the Lysophosphatidic Acid-1 Receptor Is Required for Alveolarization. American Journal of Respiratory Cell and Molecular Biology. 2016; 55: 105–116. https://doi.org/10.1165/rcmb.2015-0152OC.

[14] Gennero I, Laurencin-Dalicieux S, Conte-Auriol F, Briand-Mésange F, Laurencin D, Rue J, et al. Absence of the lysophosphatidic acid receptor LPA1 results in abnormal bone development and decreased bone mass. Bone. 2011; 49: 395–403. https://doi.org/10.1016/j.bone.2011.04.018.

[15] Alioli CA, Demesmay L, Laurencin-Dalacieux S, Beton N, Farlay D, Follet H, et al. Expression of the type 1 lysophosphatidic acid receptor in osteoblastic cell lineage controls both bone mineralization and osteocyte specification. Biochimica et Biophysica Acta. Molecular and Cell Biology of Lipids. 2020; 1865: 158715. https://doi.org/10.1016/j.bbalip.2020.158715.

[16] Hao F, Zhang F, Wu DD, An D, Shi J, Li G, et al. Lysophosphatidic acid-induced vascular neointimal formation in mouse carotid arteries is mediated by the matricellular protein CCN1/Cyr61. American Journal of Physiology. Cell Physiology. 2016; 311: C975–C984. https://doi.org/10.1152/ajpcell.00227.2016.

[17] Takeda A, Kobayashi D, Aoi K, Sasaki N, Sugiura Y, Igarashi H, et al. Fibroblastic reticular cell-derived lysophosphatidic acid regulates confined intranodal T-cell motility. eLife. 2016; 5: e10561. https://doi.org/10.7554/eLife.10561.

[18] Endle H, Horta G, Stutz B, Muthuraman M, Tegeder I, Schreiber Y, et al. AgRP neurons control feeding behaviour at cortical synapses via peripherally derived lysophospholipids. Nature Metabolism. 2022; 4: 683–692. https://doi.org/10.1038/s42255-022-00589-7.

[19] Bitar L, Uphaus T, Thalman C, Muthuraman M, Gyr L, Ji H, et al. Inhibition of the enzyme autotaxin reduces cortical excitability and ameliorates the outcome in stroke. Science Translational Medicine. 2022; 14: eabk0135. https://doi.org/10.1126/scitranslmed.abk0135.

[20] Pei J, Cai L, Wang F, Xu C, Pei S, Guo H, et al. LPA$_2$ Contributes to Vascular Endothelium Homeostasis and Cardiac Remodeling After Myocardial Infarction. Circulation Research. 2022; 131: 388–403. https://doi.org/10.1161/CIRCRESAHA.122.321036.

[21] Ye X, Hama K, Contos JJA, Anliker B, Inoue A, Skinner MK, et al. LPA3-mediated lysophosphatidic acid signalling in embryo implantation and spacing. Nature. 2005; 435: 104–108. https://doi.org/10.1038/nature03505.

[22] Ma L, Uchida H, Nagai J, Inoue M, Chun J, Aoki J, et al. Lysophosphatidic acid-3 receptor-mediated feed-forward production of lysophosphatidic acid: an initiator of nerve injury-induced neuropathic pain. Molecular Pain. 2009; 5: 64. https://doi.org/10.1186/1744-8069-5-64.

[23] Sumida H, Noguchi K, Kihara Y, Abe M, Yanagida K, Hamano F, et al. LPA4 regulates blood and lymphatic vessel formation during mouse embryogenesis. Blood. 2010; 116: 5060–5070. https://doi.org/10.1182/blood-2010-03-272443.

[24] Yasuda D, Kobayashi D, Akahoshi N, Ohto-Nakanishi T, Yoshioka K, Takuwa Y, et al. Lysophosphatidic acid-induced YAP/TAZ activation promotes developmental angiogenesis by repressing Notch ligand Dll4. The Journal of Clinical Investigation. 2019; 129: 4332–4349. https://doi.org/10.1172/JCI121955.

[25] Yanagida K, Igarashi H, Yasuda D, Kobayashi D, Ohto-Nakanishi T, Akahoshi N, et al. The Gα12/13-coupled receptor LPA4 limits proper adipose tissue expansion and remodeling in diet-induced obesity. JCI Insight. 2018; 3: e97293. https://doi.org/10.1172/jci.insight.97293.

[26] Jenkin KA, He P, Yun CC. Expression of lysophosphatidic acid receptor 5 is necessary for the regulation of intestinal Na$^+$/H$^+$ exchanger 3 by lysophosphatidic acid in vivo. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2018; 315: G433–G442. https://doi.org/10.1152/ajpgi.00130.2018.

[27] Wang M, He P, Han Y, Dong L, Yun CC. Control of Intestinal Epithelial Permeability by Lysophosphatidic Acid Receptor 5. Cellular and Molecular Gastroenterology and Hepatology. 2021; 12: 1073–1092. https://doi.org/10.1016/j.jcmgh.2021.05.003.

[28] Spencer SA, Suárez-Pozos E, Soto-Verdugo J, Wang H, Afshari FS, Li G, et al. Lysophosphatidic acid signaling via LPA$_6$: A negative modulator of developmental oligodendrocyte maturation. Journal of Neurochemistry. 2022; 163: 478–499. https://doi.org/10.1111/jnc.15696.

[29] Estivill-Torrús G, Llebrez-Zayas P, Matas-Rico E, Santín L, Pedraza C, De Diego I, et al. Absence of LPA1 signaling results in defective cortical development. Cerebral Cortex (New York, N.Y.: 1991). 2008; 18: 938–950. https://doi.org/10.1093/cercor/bhm132.

[30] Fukushima N, Ishii I, Habara Y, Allen CB, Chun J. Dual regulation of actin rearrangement through lysophosphatidic acid receptor in neuroblast cell lines: actin depolymerization by Ca(2+)-alpha-actinin and polymerization by rho. Molecular Biology of the Cell. 2002; 13: 2692–2705. https://doi.org/10.1091/mbc.01-09-0465.

[31] Fukushima N, Morita Y. Actomyosin-dependent microtubule rearrangement in lysophosphatidic acid-induced neurite remodeling of young cortical neurons. Brain Research. 2006; 1094: 65–75. https://doi.org/10.1016/j.brainres.2006.04.007.

[32] Gaire BP, Choi JW. Critical Roles of Lysophospholipid Receptors in Activation of Neuroglia and Their Neuroinflammatory Responses. International Journal of Molecular Sciences. 2021; 22: 7864. https://doi.org/10.3390/ijms22157864.

[33] Peterson AB, Xu L, Daugherty J, Breiding MJ. Surveillance report of traumatic brain injury-related emergency department visits, hospitalizations, and deaths, United States, 2014. 2019. Available at: https://stacks.cdc.gov/view/cdc/78062 (Accessed:

1 August 2024).

[34] Chun J, Weiner JA, Fukushima N, Contos JJ, Zhang G, Kimura Y, *et al*. Neurobiology of receptor-mediated lysophospholipid signaling. From the first lysophospholipid receptor to roles in nervous system function and development. Annals of the New York Academy of Sciences. 2000; 905: 110–117. https://doi.org/10.1111/j.1749-6632.2000.tb06543.x.

[35] Plastira I, Bernhart E, Joshi L, Koyani CN, Strohmaier H, Reicher H, *et al*. MAPK signaling determines lysophosphatidic acid (LPA)-induced inflammation in microglia. Journal of Neuroinflammation. 2020; 17: 127. https://doi.org/10.1186/s12974-020-01809-1.

[36] Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2007 and 2013. Morbidity and Mortality Weekly Report. Surveillance Summaries (Washington, D.C.: 2002). 2017; 66: 1–16. https://doi.org/10.15585/mmwr.ss6609a1.

[37] Peterson AB, Zhou H, Thomas KE. Disparities in traumatic brain injury-related deaths-United States, 2020. Journal of Safety Research. 2022; 83: 419–426. https://doi.org/10.1016/j.jsr.2022.10.001.

[38] Crack PJ, Zhang M, Morganti-Kossmann MC, Morris AJ, Wojciak JM, Fleming JK, *et al*. Anti-lysophosphatidic acid antibodies improve traumatic brain injury outcomes. Journal of Neuroinflammation. 2014; 11: 37. https://doi.org/10.1186/1742-2094-11-37.

[39] García-Morales V, Montero F, González-Forero D, Rodríguez-Bey G, Gómez-Pérez L, Medialdea-Wandossell MJ, *et al*. Membrane-derived phospholipids control synaptic neurotransmission and plasticity. PLoS Biology. 2015; 13: e1002153. https://doi.org/10.1371/journal.pbio.1002153.

[40] Arun P, Wilder DM, Morris AJ, Sabbadini R, Long JB. Cerebrospinal Fluid Levels of Lysophosphatidic Acids Can Provide Suitable Biomarkers of Blast-Induced Traumatic Brain Injury. Journal of Neurotrauma. 2023; 10.1089/neu.2023.0087. https://doi.org/10.1089/neu.2023.0087.

[41] McDonald WS, Jones EE, Wojciak JM, Drake RR, Sabbadini RA, Harris NG. Matrix-Assisted Laser Desorption Ionization Mapping of Lysophosphatidic Acid Changes after Traumatic Brain Injury and the Relationship to Cellular Pathology. The American Journal of Pathology. 2018; 188: 1779–1793. https://doi.org/10.1016/j.ajpath.2018.05.005.

[42] Ueda H, Matsunaga H, Olaposi OI, Nagai J. Lysophosphatidic acid: chemical signature of neuropathic pain. Biochimica et Biophysica Acta. 2013; 1831: 61–73. https://doi.org/10.1016/j.bbalip.2012.08.014.

[43] López-Serrano C, Santos-Nogueira E, Francos-Quijorna I, Coll-Miró M, Chun J, López-Vales R. Lysophosphatidic acid receptor type 2 activation contributes to secondary damage after spinal cord injury in mice. Brain, Behavior, and Immunity. 2019; 76: 258–267. https://doi.org/10.1016/j.bbi.2018.12.007.

[44] Santos-Nogueira E, López-Serrano C, Hernández J, Lago N, Astudillo AM, Balsinde J, *et al*. Activation of Lysophosphatidic Acid Receptor Type 1 Contributes to Pathophysiology of Spinal Cord Injury. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2015; 35: 10224–10235. https://doi.org/10.1523/JNEUROSCI.4703-14.2015.

[45] Sapkota A, Lee CH, Park SJ, Choi JW. Lysophosphatidic Acid Receptor 5 Plays a Pathogenic Role in Brain Damage after Focal Cerebral Ischemia by Modulating Neuroinflammatory Responses. Cells. 2020; 9: 1446. https://doi.org/10.3390/cells9061446.

[46] Zeng X, Luo Z, Wu J, Zhou J, Shan Y, Zhu Y, *et al*. Cerebral Ischemia-Reperfusion Injury: Lysophosphatidic Acid Mediates Inflammation by Decreasing the Expression of Liver X Receptor. Journal of Molecular Neuroscience: MN. 2020; 70: 1376–

1384. https://doi.org/10.1007/s12031-020-01554-3.

[47] Gento-Caro Á, Vilches-Herrando E, García-Morales V, Portillo F, Rodríguez-Bey G, González-Forero D, *et al*. Interfering with lysophosphatidic acid receptor edg2/lpa$_1$ signalling slows down disease progression in SOD1-G93A transgenic mice. Neuropathology and Applied Neurobiology. 2021; 47: 1004–1018. https://doi.org/10.1111/nan.12699.

[48] Puigdomenech-Poch M, Martínez-Muriana A, Andrés-Benito P, Ferrer I, Chun J, López-Vales R. Dual Role of Lysophosphatidic Acid Receptor 2 (LPA$_2$) in Amyotrophic Lateral Sclerosis. Frontiers in Cellular Neuroscience. 2021; 15: 600872. https://doi.org/10.3389/fncel.2021.600872.

[49] Likhitweerawong N, Thonusin C, Boonchooduang N, Louthrenoo O, Nookaew I, Chattipakorn N, *et al*. Profiles of urine and blood metabolomics in autism spectrum disorders. Metabolic Brain Disease. 2021; 36: 1641–1671. https://doi.org/10.1007/s11011-021-00788-3.

[50] Chen WM, Chiang JC, Lin YC, Lin YN, Chuang PY, Chang YC, *et al*. Lysophosphatidic acid receptor LPA$_3$ prevents oxidative stress and cellular senescence in Hutchinson-Gilford progeria syndrome. Aging Cell. 2020; 19: e13064. https://doi.org/10.1111/acel.13064.

[51] Chiang JC, Chen WM, Newman C, Chen BPC, Lee H. Lysophosphatidic Acid Receptor 3 Promotes Mitochondrial Homeostasis against Oxidative Stress: Potential Therapeutic Approaches for Hutchinson-Gilford Progeria Syndrome. Antioxidants (Basel, Switzerland). 2022; 11: 351. https://doi.org/10.3390/antiox11020351.

[52] Valcárcel-Martín R, Martín-Suárez S, Muro-García T, Pastor-Alonso O, Rodríguez de Fonseca F, Estivill-Torrús G, *et al*. Lysophosphatidic Acid Receptor 1 Specifically Labels Seizure-Induced Hippocampal Reactive Neural Stem Cells and Regulates Their Division. Frontiers in Neuroscience. 2020; 14: 811. https://doi.org/10.3389/fnins.2020.00811.

[53] Peltenburg NC, Schoeman JC, Hou J, Mora F, Harms AC, Lowe SH, *et al*. Persistent metabolic changes in HIV-infected patients during the first year of combination antiretroviral therapy. Scientific Reports. 2018; 8: 16947. https://doi.org/10.1038/s41598-018-35271-0.

[54] Eisenried A, Meidahl ACN, Klukinov M, Tzabazis AZ, Sabbadini RA, Clark JD, *et al*. Nervous system delivery of antilysophosphatidic acid antibody by nasal application attenuates mechanical allodynia after traumatic brain injury in rats. Pain. 2017; 158: 2181–2188. https://doi.org/10.1097/j.pain.0000000000001019.

[55] Wojciak J, Sabbadini R, Crack P, Morganti-Kossmann C, Zhang M, Pebay A, *et al*. Role of lysophosphatidic acid in traumatic brain injury: anti-LPA antibodies are neuroprotective after experimental TBI (999.3). The FASEB Journal. 2014; 28: 999.3. https://doi.org/10.1096/fasebj.28.1_supplement.999.3.

[56] Yung YC, Stoddard NC, Chun J. LPA receptor signaling: pharmacology, physiology, and pathophysiology. Journal of Lipid Research. 2014; 55: 1192–1214. https://doi.org/10.1194/jlr.R046458.

[57] Choi JW, Chun J. Lysophospholipids and their receptors in the central nervous system. Biochimica et Biophysica Acta. 2013; 1831: 20–32. https://doi.org/10.1016/j.bbalip.2012.07.015.

[58] Xiao D, Su X, Gao H, Li X, Qu Y. The Roles of Lpar1 in Central Nervous System Disorders and Diseases. Frontiers in Neuroscience. 2021; 15: 710473. https://doi.org/10.3389/fnins.2021.710473.

[59] Yung YC, Stoddard NC, Mirendil H, Chun J. Lysophosphatidic Acid signaling in the nervous system. Neuron. 2015; 85: 669–682. https://doi.org/10.1016/j.neuron.2015.01.009.

[60] Khiar-Fernández N, Zian D, Vázquez-Villa H, Martínez RF, Escobar-Peña A, Foronda-Sainz R, *et al*. Novel Antagonist of the Type 2 Lysophosphatidic Acid Receptor (LPA$_2$), UCM-14216,

Ameliorates Spinal Cord Injury in Mice. Journal of Medicinal Chemistry. 2022; 65: 10956–10974. https://doi.org/10.1021/acs.jmedchem.2c00046.

[61] Marsden JF. Cerebellar ataxia. Handbook of Clinical Neurology. 2018; 159: 261–281. https://doi.org/10.1016/B978-0-444-63916-5.00017-3.

[62] Zhao J, Zhang H, Fan X, Yu X, Huai J. Lipid Dyshomeostasis and Inherited Cerebellar Ataxia. Molecular Neurobiology. 2022; 59: 3800–3828. https://doi.org/10.1007/s12035-022-02826-2.

[63] Doi H, Ushiyama M, Baba T, Tani K, Shiina M, Ogata K, et al. Late-onset spastic ataxia phenotype in a patient with a homozygous DDHD2 mutation. Scientific Reports. 2014; 4: 7132. https://doi.org/10.1038/srep07132.

[64] Pluta R. Cerebral Ischemia [Internet]. Exon Publications: Brisbane (AU). 2021. https://doi.org/10.36255/exonpublications.cerebralischemia.2021.

[65] Lai TW, Zhang S, Wang YT. Excitotoxicity and stroke: identifying novel targets for neuroprotection. Progress in Neurobiology. 2014; 115: 157–188. https://doi.org/10.1016/j.pneurobio.2013.11.006.

[66] Dong XX, Wang Y, Qin ZH. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta Pharmacologica Sinica. 2009; 30: 379–387. https://doi.org/10.1038/aps.2009.24.

[67] Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. Journal of Leukocyte Biology. 2010; 87: 779–789. https://doi.org/10.1189/jlb.1109766.

[68] Jiang X, Mu D, Manabat C, Koshy AA, Christen S, Täuber MG, et al. Differential vulnerability of immature murine neurons to oxygen-glucose deprivation. Experimental Neurology. 2004; 190: 224–232. https://doi.org/10.1016/j.expneurol.2004.07.010.

[69] Gaire BP, Sapkota A, Song MR, Choi JW. Lysophosphatidic acid receptor 1 (LPA$_1$) plays critical roles in microglial activation and brain damage after transient focal cerebral ischemia. Journal of Neuroinflammation. 2019; 16: 170. https://doi.org/10.1186/s12974-019-1555-8.

[70] Lee CH, Sapkota A, Gaire BP, Choi JW. NLRP3 Inflammasome Activation Is Involved in LPA$_1$-Mediated Brain Injury after Transient Focal Cerebral Ischemia. International Journal of Molecular Sciences. 2020; 21: 8595. https://doi.org/10.3390/ijms21228595.

[71] Chi OZ, Mellender SJ, Kiss GK, Chiricolo A, Liu X, Patel N, et al. Lysophosphatidic acid increased infarct size in the early stage of cerebral ischemia-reperfusion with increased BBB permeability. Journal of Stroke and Cerebrovascular Diseases: the Official Journal of National Stroke Association. 2020; 29: 105029. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105029.

[72] Bhattarai S, Subedi U, Manikandan S, Sharma S, Sharma P, Miller C, et al. Endothelial Specific Deletion of Autotaxin Improves Stroke Outcomes. Cells. 2023; 12: 511. https://doi.org/10.3390/cells12030511.

[73] Bano D, Zanetti F, Mende Y, Nicotera P. Neurodegenerative processes in Huntington's disease. Cell Death & Disease. 2011; 2: e228. https://doi.org/10.1038/cddis.2011.112.

[74] Vodicka P, Mo S, Tousley A, Green KM, Sapp E, Iuliano M, et al. Mass Spectrometry Analysis of Wild-Type and Knock-in Q140/Q140 Huntington's Disease Mouse Brains Reveals Changes in Glycerophospholipids Including Alterations in Phosphatidic Acid and Lyso-Phosphatidic Acid. Journal of Huntington's Disease. 2015; 4: 187–201. https://doi.org/10.3233/JHD-150149.

[75] Burtscher J, Pepe G, Maharjan N, Riguet N, Di Pardo A, Maglione V, et al. Sphingolipids and impaired hypoxic stress responses in Huntington disease. Progress in Lipid Research. 2023; 90: 101224. https://doi.org/10.1016/j.plipres.2023.101224.

[76] Jang M, Choi JH, Chang Y, Lee SJ, Nah SY, Cho IH. Gintonin, a ginseng-derived ingredient, as a novel therapeutic strategy for Huntington's disease: Activation of the Nrf2 pathway through lysophosphatidic acid receptors. Brain, Behavior, and Immunity. 2019; 80: 146–162. https://doi.org/10.1016/j.bbi.2019.03.001.

[77] Taylor JP, Brown RH, Jr, Cleveland DW. Decoding ALS: from genes to mechanism. Nature. 2016; 539: 197–206. https://doi.org/10.1038/nature20413.

[78] Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. Nature Reviews. Neurology. 2013; 9: 617–628. https://doi.org/10.1038/nrneurol.2013.203.

[79] Logroscino G, Traynor BJ, Hardiman O, Chiò A, Mitchell D, Swingler RJ, et al. Incidence of amyotrophic lateral sclerosis in Europe. Journal of Neurology, Neurosurgery, and Psychiatry. 2010; 81: 385–390. https://doi.org/10.1136/jnnp.2009.183525.

[80] Brown RH, Al-Chalabi A. Amyotrophic Lateral Sclerosis. The New England Journal of Medicine. 2017; 377: 162–172. https://doi.org/10.1056/NEJMra1603471.

[81] Ueda H. Lysophosphatidic acid signaling is the definitive mechanism underlying neuropathic pain. Pain. 2017; 158 Suppl 1: S55–S65. https://doi.org/10.1097/j.pain.0000000000000813.

[82] Nam SM, Choi JH, Choi SH, Cho HJ, Cho YJ, Rhim H, et al. Ginseng gintonin alleviates neurological symptoms in the G93A-SOD1 transgenic mouse model of amyotrophic lateral sclerosis through lysophosphatidic acid 1 receptor. Journal of Ginseng Research. 2021; 45: 390–400. https://doi.org/10.1016/j.jgr.2020.04.002.

[83] Maenner MJ, Shaw KA, Baio J, EdS1, Washington A, Patrick M, et al. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. Morbidity and Mortality Weekly Report. Surveillance Summaries (Washington, D.C.: 2002). 2020; 69: 1–12. https://doi.org/10.15585/mmwr.ss6904a1.

[84] Geschwind DH. Genetics of autism spectrum disorders. Trends in Cognitive Sciences. 2011; 15: 409–416. https://doi.org/10.1016/j.tics.2011.07.003.

[85] Krakowiak P, Walker CK, Bremer AA, Baker AS, Ozonoff S, Hansen RL, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics. 2012; 129: e1121–e1128. https://doi.org/10.1542/peds.2011-2583.

[86] Wang H, Liang S, Wang M, Gao J, Sun C, Wang J, et al. Potential serum biomarkers from a metabolomics study of autism. Journal of Psychiatry & Neuroscience: JPN. 2016; 41: 27–37. https://doi.org/10.1503/jpn.140009.

[87] Goines PE, Croen LA, Braunschweig D, Yoshida CK, Grether J, Hansen R, et al. Increased midgestational IFN-γ, IL-4 and IL-5 in women bearing a child with autism: A case-control study. Molecular Autism. 2011; 2: 13. https://doi.org/10.1186/2040-2392-2-13.

[88] Lamis A, Siddiqui SW, Ashok T, Patni N, Fatima M, Aneef AN. Hutchinson-Gilford Progeria Syndrome: A Literature Review. Cureus. 2022; 14: e28629. https://doi.org/10.7759/cureus.28629.

[89] Huff JS, Murr NI. Seizure. StatPearls Publishing: Treasure Island (FL). 2025.

[90] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014; 55: 475–482. https://doi.org/10.1111/epi.12550.

[91] Zhang YJ, Kong XM, Lv JJ, Yang CH, Li XY, Yang XT, et al. Analysis of the global burden of disease study highlights the global, regional, and national trends of idiopathic epilepsy epidemiology from 1990 to 2019. Preventive Medicine Re-

ports. 2023; 36: 102522. https://doi.org/10.1016/j.pmedr.2023.102522.

[92] Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. Lancet (London, England). 2019; 393: 689–701. https://doi.org/10.1016/S0140-6736(18)32596-0.

[93] Löscher W, Potschka H, Sisodiya SM, Vezzani A. Drug Resistance in Epilepsy: Clinical Impact, Potential Mechanisms, and New Innovative Treatment Options. Pharmacological Reviews. 2020; 72: 606–638. https://doi.org/10.1124/pr.120.019539.

[94] Møller RS, Larsen LHG, Johannesen KM, Talvik I, Talvik T, Vaher U, et al. Gene Panel Testing in Epileptic Encephalopathies and Familial Epilepsies. Molecular Syndromology. 2016; 7: 210–219. https://doi.org/10.1159/000448369.

[95] Duncan JS, Winston GP, Koepp MJ, Ourselin S. Brain imaging in the assessment for epilepsy surgery. The Lancet. Neurology. 2016; 15: 420–433. https://doi.org/10.1016/S1474-4422(15)00383-X.

[96] Ghosh S, Sinha JK, Khan T, Devaraju KS, Singh P, Vaibhav K, et al. Pharmacological and Therapeutic Approaches in the Treatment of Epilepsy. Biomedicines. 2021; 9: 470. https://doi.org/10.3390/biomedicines9050470.

[97] Trimbuch T, Beed P, Vogt J, Schuchmann S, Maier N, Kintscher M, et al. Synaptic PRG-1 modulates excitatory transmission via lipid phosphate-mediated signaling. Cell. 2009; 138: 1222–1235. https://doi.org/10.1016/j.cell.2009.06.050.

[98] Choi JH, Kwon TW, Jo HS, Ha Y, Cho IH. Gintonin, a *Panax* ginseng-derived LPA receptor ligand, attenuates kainic acid-induced seizures and neuronal cell death in the hippocampus via anti-inflammatory and anti-oxidant activities. Journal of Ginseng Research. 2023; 47: 390–399. https://doi.org/10.1016/j.jgr.2022.11.001.

[99] Aguilar-Shea AL, Membrilla Md JA, Diaz-de-Teran J. Migraine review for general practice. Atencion Primaria. 2022; 54: 102208. https://doi.org/10.1016/j.aprim.2021.102208.

[100] Ueda H. Pathogenic mechanisms of lipid mediator lysophosphatidic acid in chronic pain. Progress in Lipid Research. 2021; 81: 101079. https://doi.org/10.1016/j.plipres.2020.101079.

[101] Kuwajima K, Sumitani M, Kurano M, Kano K, Nishikawa M, Uranbileg B, et al. Lysophosphatidic acid is associated with neuropathic pain intensity in humans: An exploratory study. PloS One. 2018; 13: e0207310. https://doi.org/10.1371/journal.pone.0207310.

[102] Kursun O, Yemisci M, van den Maagdenberg AMJM, Karatas H. Migraine and neuroinflammation: the inflammasome perspective. The Journal of Headache and Pain. 2021; 22: 55. https://doi.org/10.1186/s10194-021-01271-1.

[103] Raposio E, Raposio G, Del Duchetto D, Tagliatti E, Cortese K. Morphologic vascular anomalies detected during migraine surgery. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS. 2022; 75: 4069–4073. https://doi.org/10.1016/j.bjps.2022.08.036.

[104] Deeks SG, Overbaugh J, Phillips A, Buchbinder S. HIV infection. Nature Reviews. Disease Primers. 2015; 1: 15035. https://doi.org/10.1038/nrdp.2015.35.

[105] Le Hingrat Q, Sette P, Xu C, Rahmberg AR, Tarnus L, Annapureddy H, et al. Prolonged experimental $CD4^+$ T-cell depletion does not cause disease progression in SIV-infected African green monkeys. Nature Communications. 2023; 14: 979. https://doi.org/10.1038/s41467-023-36379-2.

[106] Wheeler NA, Fuss B, Knapp PE, Zou S. HIV-1 Tat Inhibits Autotaxin Lysophospholipase D Activity and Modulates Oligodendrocyte Differentiation. ASN Neuro. 2016; 8: 1759091416669618. https://doi.org/10.1177/1759091416669618.

[107] Marino J, Maubert ME, Mele AR, Spector C, Wigdahl B, Nonnemacher MR. Functional impact of HIV-1 Tat on cells of the CNS and its role in HAND. Cellular and Molecular Life Sciences: CMLS. 2020; 77: 5079–5099. https://doi.org/10.1007/s00018-020-03561-4.

[108] Olianas MC, Dedoni S, Onali P. Inhibition of TNF-α-induced neuronal apoptosis by antidepressants acting through the lysophosphatidic acid receptor LPA_1. Apoptosis: an International Journal on Programmed Cell Death. 2019; 24: 478–498. https://doi.org/10.1007/s10495-019-01530-2.