Review

The Role of Lysophosphatidic Acid in Neuropsychiatric and Neurodegenerative Disorders

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Abstract: Individuals suffering from diverse neuropsychiatric and neurodegenerative disorders often have comparable symptoms, which may underline the implication of shared hereditary influences and the same biological processes. Lysophosphatidic acid (LPA) is a bioactive phospholipid and a crucial regulator of the development of adult neuronal systems; hence, it may play an important role in the onset of certain diseases such as Alzheimer's, Parkinson's disease, and schizophrenia. During development, LPA signaling regulates many cellular processes such as proliferation, survival, migration, differentiation, cytoskeleton reorganization, and DNA synthesis. So far, six lysophosphatidic acid receptors that respond to LPA have been discovered and categorized based on their homology. Despite the abundance of evidence relating LPA cellular activities to different pathological conditions, little is known about the involvement of LPA in the field of neuropsychiatric and neurodegenerative diseases. The purpose of this review is to define LPA activities related to the illnesses stated above in order to better understand these pathologies and provide future novel treatment strategies based on the latest data.

Keywords: lysophosphatidic acid (LPA); neuropsychiatric disorders; neurodegenerative disorders; major depressive disorder (MDD); schizophrenia (SCZ); Alzheimer's disease (AD); Parkinson's disease (PD)

1. Introduction

Neuropsychiatric and neurodegenerative diseases are a serious and growing global health concern. In 2016, more than one billion individuals worldwide were plagued by mental disorders, accounting for around 16% of the global population [1], while, in 2019, neurodegenerative disorders caused about 10 million fatalities and 349 million disability-adjusted life years, which is a measure of the healthy years of life lost [2]. The repercussions of new diseases, such as COVID-19, on mental health have been widely documented and include the exacerbation of new symptoms and the worsening of preexisting conditions [3,4]. Mental disorders often emerge in early or mid-adulthood and are often associated with the onset of neurodegenerative diseases later in life and, as a consequence, a life expectancy 10–15 years lower than that of the general population [5,6]. Patients with a mental disorder (i.e., major depression, schizophrenia, bipolar, and anxiety disorder), are up to four times more likely to develop dementia or neurodegenerative problems that affect cognition in adulthood, and 65% of people experience major psychological symptoms while suffering from a neurodegenerative disease [7]. Recently, the involvement of lysophosphatidic acid (LPA) in the pathologies of the central nervous system (CNS) has come to light. LPA is generated by a variety of metabolic routes in the intracellular and extracellular enzymatic systems, the most significant of which is the enzymatic action of autotaxin (ATX) [8]. The second essential mechanism consists of the synthesis of LPA from membrane phospholipids via the activity of phospholipases [9]. LPA acts as an extracellular signaling molecule

through its six different G protein-coupled receptors (GPCRs), (LPAR1, LPAR2, LPAR3, LPAR4, LPAR5, and LPAR6). These LPARs primarily activate the Gαq/11, Gα12/13, Gαi/o, or Gαs subunits and subsequently different downstream signaling mediators, mainly represented by the phospholipase C (PLC), Akt, mitogen-activated protein kinase (MAPK) [10], and Rho-associated protein kinase (Rho/ROCK) (Figure 1) [11], which are involved in cell proliferation [12], survival [13–15], migration [11], cerebral cortex formation, cognitive functions [16], and many other functions. It is known that impaired lipid metabolism and alterations in lipid content in the brain have been linked to aging as well as several CNS disorders [17], and LPA has been shown to have numerous roles in both development and disease [18]. Indeed, dysfunctions in LPA signaling have been linked to various neurological conditions, including major depressive disorder (MDD), schizophrenia (SCZ), Alzheimer's (AD), and Parkinson's disease (PD) [19–23]. The purpose of this review is to discuss the involvement of LPA in neuropsychiatric and neurodegenerative disorders in light of the most recent studies, to better understand these diseases and try to offer innovative approaches for future treatments (Figure 2).
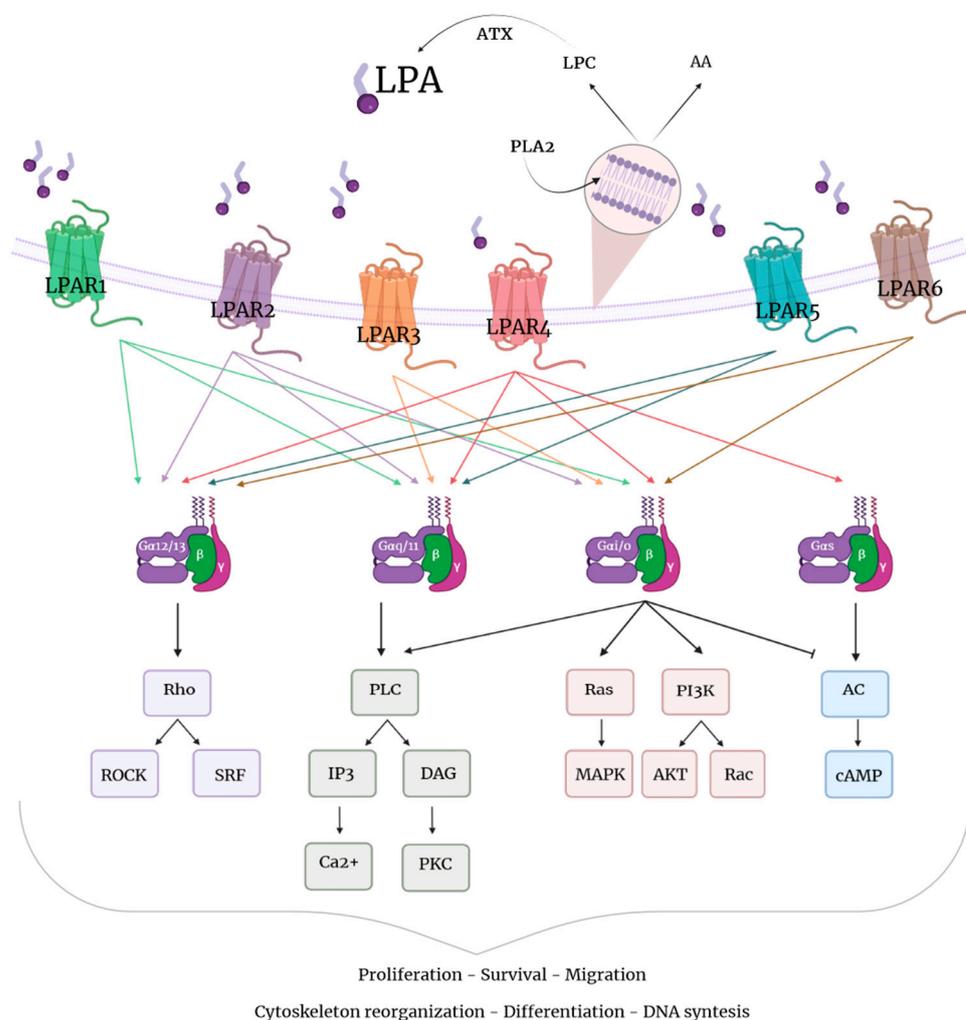

Figure 1. Schematic representation of LPA production and signaling. Phospholipase A2 (PLA2) generates lysophosphatidylcholine (LPC) from membrane lipids, which is then converted into lysophosphatidic acid (LPA) by autotaxin (ATX). LPA acts through six transmembrane G-coupled protein receptors (LPAR1-6), which activate several signaling pathways through the activation of different G proteins. The cellular responses elicited by LPA are involved in proliferation, survival, migration, cytoskeleton reorganization, differentiation, and DNA synthesis.
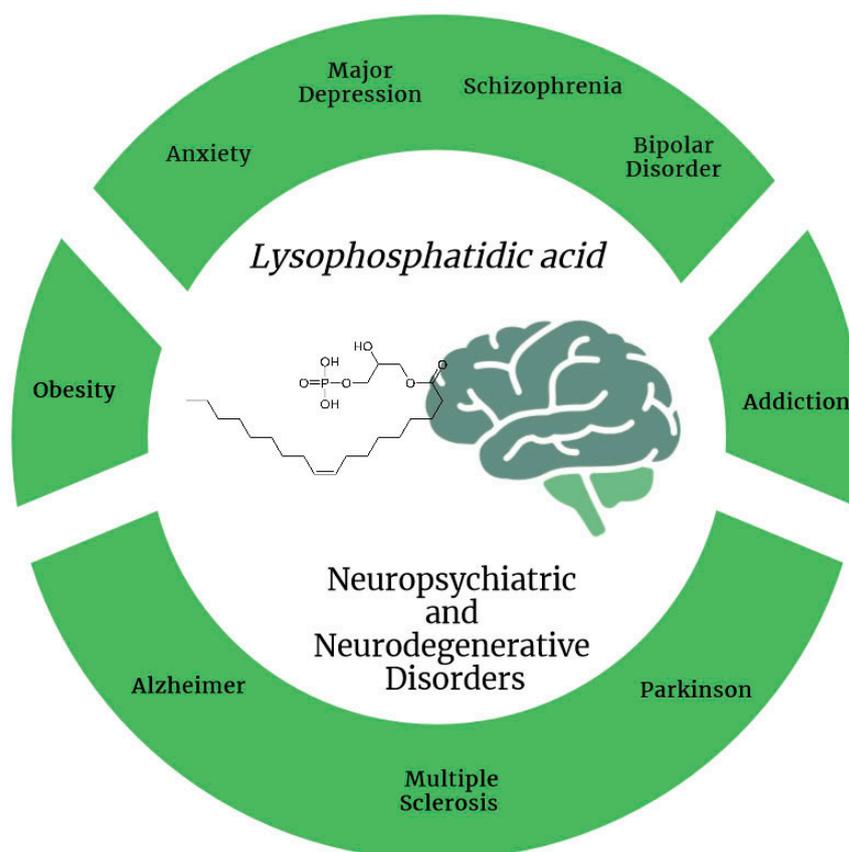
Figure 2. Illustration of LPA's potential involvement in neurodegenerative and neuropsychiatric disorders.

2. LPA and LPA Receptors: Overview

LPA was identified in 1957 as a glycerophospholipid [24]. This molecule is one of the most basic natural phospholipids, showing only one fatty acyl chain consisting of a glycerol backbone connected to a phosphate group. This lipid is water-soluble and, based on the acyl chain length, the molecular mass ranges between 430 and 480 Da. LPA species are composed of unsaturated (16:1, 18:1, 18:2, and 20:4) and saturated (16:0 and 18:0) fatty acids which have unique biological characteristics [25]. LPA is found in brain tissue, cerebrospinal fluid (CSF), and biological fluids such as saliva, urine, and seminal fluid [26,27]. LPA is also found in the plasma of people suffering from many pathological conditions such as chronic liver damage, nervous system disorders, and even obesity. The LPA concentrations in the plasma typically range from 0.7 to 80 nM, whereas in the serum, LPA concentrations can approach the micromolar level [28]. As signaling mediators and membrane components, LPA and the related precursor lysophosphatidylcholine (LPC) may be detected in the extracellular and intracellular compartments. LPARs are hypothesized to mediate the extracellular bioactive effects of LPA [29], while intracellular LPA seems to play a critical role in the manufacture of complex glycerolipids such as monoglycerides, diglycerides, and triglycerides [30]. To date, five primary mechanisms of LPA generation have been identified. The main known pathway is represented by the lysophospholipids–autotaxin (LPLs-ATX) pathway, in which LPLs generated from acidic phospholipids (PLs) by PLA1 or PLA2 are converted into LPA by plasmatic ATX. In the phosphatidic acid–phospholipase A1/A2 (PA-PLA1/PLA2) pathway, phosphatidic acid (PA) is initially synthesized from PLs or diacylglycerol by the activities of the phospholipase D enzymes (PLD1 and PLD2) and diacylglycerol kinase (DGK); subsequently, PLA1 or PLA2 eliminate one acyl group to generate LPA. In the de novo glycerophosphate acyltransferase (GPAT) synthesis pathway, GPATs promote the initial step in glycerolipid synthesis, converting glycerol-3-phosphate (G3P) into LPA via fatty acid transfer from acyl-CoA. The monoacylglycerol kinase (MAGK)

pathway consists of the dephosphorylation of LPA by lipid phosphate phosphatases (LPPs), resulting in the production of monoacylglycerol (MAG). MAG can then be phosphorylated by MAGK, resulting in another cycle of LPA signaling. LPA can also be produced according to the oxidative modification of low-density lipoprotein (LDL).

Once generated, LPA signals through different receptors, as mentioned above. LPAR1 (known as EDG2) was identified in 1996 by Hecht and collaborators, as the product encoded by ventricular zone gene-1, paving the way for the discovery of all other LPARs [31]. Based on the LPAR1 homology, two additional LPA receptors, LPAR2 and LPAR3 (known as EDG4 and EDG7), were found later. LPARs 1-3 are members of the endothelium differentiation gene (EDG) family, which exhibits 50% homology [27]. Three more LPA receptors (LPARs 4-6; non-EDG family) were found in recent years and are similar to purinergic receptors [32]. As mentioned above, LPARs communicate via G12/13, Gq/11, Gi/o, and Gs. LPA-mediated G12/13 activation influences cell motility, which is carefully regulated by the coordinated actions of Rho and Rac, affecting cytoskeletal reorganization, cell migration, and invasion. All these actions are supported via many signaling proteins, including c-Jun-N-terminal kinase (JNK) and the protein p38 via ROCK. LPA also activates Gq/11, controlling the balance of Ca^{2+} through the PLC, whilst the $G\beta\gamma$ and Gi/o subunits promote the activation of the PI3K/Akt pathway, which typically stimulates Rac. Rac controls the regulation of JNK and Ras activity, with subsequent activation of Raf and extracellular signal-regulated kinase (ERK). Gq/11 also stimulates the rapamycin (mTOR) signaling pathway. The PI3K and Ras-Raf-MEK-ERK pathways can likewise be activated by Gi/o. $G\alpha$ can enhance cAMP concentrations, although it should be noted that the same enzyme is also inhibited by Gi/o, demonstrating the intricacy of the signaling cascades activated by LPARs.

Roles of LPA in the Body

As mentioned above, LPA plays different roles in the body. It is widely expressed in the CNS and is involved in neurodevelopment. LPAR1 is expressed in Schwann cells and seems to be important in the onset of neuropathic pain, a form of chronic pain with few treatment options. For instance, in the fibromyalgia-like generalized pain paradigm, LPAR1 KO mice show no signs of pain, indicating the function of brain LPAR1 signaling in aberrant pain generation [33], and are resistant to diabetes-related neuropathic pain [34]. These mice also show alterations in alveolarization, likely depending on LPAR1 [35]. Furthermore, LPAR1M318R/M318R rats consistently show expanded alveoli [36]. LPAR1 KO mice present also alterations in their intestinal villi and in the migration and proliferation of their intestinal epithelial cells (IECs). LPAR1-KO mice possess bone and cartilaginous defects, including cranial malformations and improper rib-to-sternum attachment [37,38], as well as impaired mineralization and elevated bone porosity [39]. In addition, different studies highlighted the role of LPAR1 in vascular remodeling [40,41]. LPAR2 is involved in intestinal illness and injury protection. In a mouse radiation model, for instance, oral treatment of LPA decreased IEC apoptosis, and the absence of this protective effect in LPAR2 KO mice demonstrates the relevance of the LPA-LPAR2 axis. This axis is critical to intranodal T-cell migration, and LPAR2 KO T-cells being transplanted into wild-type mice lead to reduced lymph node mobility in the adoptive transfer tests [42]. Recently, it was shown that LPAR2 participates in exploratory and hyperphagic behaviors following fasting [43]. LPAR2 signaling has also recently been revealed in stroke penumbra damage [44], asthma [45], and myocardial infarction [46]. Female LPAR3 KO mice have significant reproductive abnormalities, including delayed implantation and abnormal embryo positioning [47]. In addition to the previously stated promoting function of LPAR1, also LPAR3 was shown to be involved in neuropathic pain. LPAR3 KO mice are protected from LPC- or LPA-induced demyelination [48]. The same KO mice have lower cardiac cell proliferation during the first week of life, although the deficits improve subsequently [49]. LPAR4 and LPAR6 are involved in vascular development. More specifically, LPAR4 seems to be responsible for the proangiogenic role of LPA and is implicated in cardiovascular

diseases such as atherosclerosis [50,51]. Moreover, LPAR4/LPAR6 double-KO mice show a deadly vascular phenotype [52]. LPAR4 is also involved in metabolic syndromes, and LPAR4 KO animals show higher levels of mitochondrial and adipogenesis genes in their fat tissue [53]. LPAR4 is implicated in bone development, as LPAR4 KO mice present an increased skeletal volume, trabecular thickness [54], and reduced hematopoietic stem cells in the spleen and in the bone marrow [55]. LPAR5 works as an inhibitory receptor in the T-cells [56]; indeed, LPA reduces T-cell-receptor-mediated CD8 T signaling and lethal function in vitro and in vivo. LPAR5 is abundant in the villous portion of the gut, is strongly expressed in IECs, protects against diarrhea, and is implicated in intestinal homeostasis [57,58]. Indeed, LPAR5 KO mice were either lifeless or died as a result of intestinal abnormalities, and, in numerous neuropathic pain models, they show decreased pain progression [59]. In 2008, LPAR6 was identified for the first time as the direct gene in human autosomal recessive woolly hair/hypotrichosis (ARWH/HT), and multiple articles reported ARWH/HT patients carrying various kinds of LPAR6 mutations [60]. Moreover, LPAR6 KO animals had faster oligodendrocyte development in the brain, indicating that endogenous LPA adversely affects oligodendrocyte growth [61]. LPA6 is abundant in ameloblasts and ameloblast cell lines, and it improves cell–cell adhesion and cortical actin production in a Rho-dependent way [62].

3. Involvement of LPA in Neuropsychiatric Disorders

3.1. Major Depressive Disorder: Clinical Studies

MDD is the most prevalent mental condition, characterized by a persistent low mood, feelings of melancholy, and a lack of interest in daily activities [60,63]. In 2019, was investigated whether ATX modifications occurred in MDD patients and whether those changes were related to the degree of depressive symptoms. The results showed that the ATX levels in CSF and serum were considerably lower in MDD patients in comparison to non-depressed individuals. Antidepressants did not appear to have a direct effect on ATX levels. However, serum ATX levels rose following electroconvulsive sessions, suggesting that changes in the ATX-LPA axis may be involved in the etiology and manifestation of MDD [64].

In the same year, a gender difference was detected in the LPA levels in the plasma and CSF of depressed patients, which were higher in females compared to males and not linked to the age of the individuals [20]. Subsequently, the relationship between LPA and depression was investigated using the Hamilton Rating Scale for Depression (HAMD) score, finding no link in the samples and suggesting that LPA would not be a useful biomarker for the evaluation of MDD diagnosis. One year later, Riya and collaborators investigated not only the roles and interactions of LPA but also the role of LPC in the serum of MDD patients [19]. No significant differences in LPA and LPC serum levels between MDD patients and healthy controls (HC) were detected, and no association was found in terms of patient characteristics. Omori, in 2021, focused on a precursor of LPA, LPA 22:6 (LPA docosahexaenoic acid), and ATX in MDD and SCZ patients. The LPA 22:6 levels in the CSF were considerably lower in individuals with MDD and SCZ, despite no significant variations in LPA content. Moreover, it was demonstrated that the LPA 22:6 levels were negatively correlated with the HAMD scores in individuals with MDD but not with any Positive and Negative Syndrome Scale (PANSS) score in subjects affected by SCZ. Furthermore, LPA 22:6 and ATX were not correlated with the symptoms of the MDD and SCZ patients. Interestingly, the ATX activity in the CSF of the MDD patients did not differ from that of the HC, contrary to the findings provided previously by the same group, which was explained by the fact that the LPA and LPC levels in the CSF were between normal and relatively low [65].

Major Depressive Disorder: Preclinical Studies

Animal research based on genetic manipulation also supports the alterations observed in patients. Indeed, in the Malaga variant of LPAR1-null mice (maLPA1-null mice), the dele-

tion of LPAR1 affected the functional brain map essential to appropriate hedonic behavior and stress coping, which may account for some of the maladaptive behaviors found in this genotype. Moreover, treatment with antidepressants resulted in behavioral improvements and functional brain normalization. Neurobiological changes linked to depression and anxiety were observed, with increased activity of the limbic system, which is comparable to that seen in depressed patients [66]. This aspect was further investigated by employing a Matrix-Assisted Laser Desorption/Ionization mass spectrometry technique to assess the impact of a LPAR1 deficit on the LPA levels in the hippocampus of maLPAR1-null mice [67]. In this LPAR1-deficient rat strain, variations in LPA 18:0 and 18:1 were observed, the most representative LPA species in the hippocampus, while LPA 20:4 was the least abundant. Specifically, in this study, an increase in the total concentration of LPA and alterations in the LPA species were observed in the hippocampus following an intensive stress procedure such as the restraint, indicating that hippocampal LPA is a primary target of stress. Thus, the elevated plus maze (EPM) was used to assess behavioral alterations after acute stress, which caused an anxiogenic phenotype and enhanced the concentration of LPA 18:2. The role of stress in the onset and progression of depression may be viewed as the outcome of numerous converging elements. In this context, it makes sense that the hippocampal LPA species might represent a target of stress and may have a role in the exacerbation of depression [68]. MRL/lpr mice, which are employed in neuropsychiatric systemic lupus erythematosus research, exhibit depression-like characteristics as well as microglial activation and blood–brain barrier (BBB) weakening. It was demonstrated that in the tail suspension test, LPA dramatically decreased the extended immobility period in MRL/lpr mice and greatly shortened the initial bout of immobility relative to the control mice. On the other hand, pretreatment with the Ki16425 inhibitor, a selective antagonist of LPAR1 and LPAR3, dramatically reversed the effects of LPA. Treatment with LPA improved the decreased performance during the Y-maze and novel object recognition tests. In addition, LPA reduced the expression of CD68, TMEM119, GFAP, and cleaved caspase 3 in the hippocampus and prefrontal cortex of the MRL/lpr animals with behavioral impairments and ameliorated behavioral abnormalities. Moreover, LPA therapy reduced the expression of interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) in the hippocampus. LPA treatment was also shown to improve the integrity of the BBB in MRL/lpr mice, as shown by the reduced leakage of sodium fluorescein into the brain of MRL/lpr animals after LPA administration without altering the plasma levels of anti-dsDNA antibody. These data suggested that treatment with LPA might alleviate depression-like behaviors by reducing BBB susceptibility [69].

Further evidence of the positive effect of LPA on depression comes from in vitro research, in which it was observed that antidepressants might exert their function through their action on LPA receptors. It was reported that tricyclic and tetracyclic antidepressants were able to activate endogenous LPAR1 in CHO-K1 fibroblasts and induce a pro-survival and proliferative response through the transactivation of insulin-like growth factor-1 and the stimulation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) [12]. These effects were also shown to protect glial cells against oxidative stress and hippocampal neurons against apoptosis mediated by TNF-α [14,15,70]. The same authors further characterized the effects of antidepressants on the LPA receptors using three lines of HEK stably expressing human LPAR1, LPAR2, or LPAR3. In this experiment, it was demonstrated that tricyclic and tetracyclic antidepressants in association with LPA were able to increase the Gi/o-mediated ERK1/2 phosphorylation in HEK-LPAR1, -LPAR2 and -LPAR3 cells, as well as in CHO-K1 fibroblasts and HT22 hippocampal neuroblasts, and this increase was paralleled by an augmentation of the phosphorylation of S6 ribosomal protein and cyclic-AMP response element-binding protein (CREB). Moreover, antidepressants also increased the phosphorylation of AMP-activated protein kinase in HEK expressing LPAR1 and LPAR3 while inhibiting the LPA-mediated activation of Rho in HEK-LPAR1 and LPAR2 [71]. These results indicate that LPAR1, LPAR2, and LPAR3 are molecular targets of antidepressants

and corroborate the hypothesis that alterations in LPA and its receptors might be involved in the pathophysiology of depression.

3.2. Schizophrenia: Clinical Studies Involving LPA and Its Receptors

LPA seems to be important to the pathophysiology of schizophrenia. A clinical study in which the CSF was collected from Japanese patients and age- and gender-matched HC, showed that patients with SCZ had considerably decreased levels of LPA and LPLs as well as the associated metabolic enzymes, and these levels were shown to be negatively correlated with a variety of clinical symptoms. The levels of LPA 22:6 in the CSF of the SCZ patients were considerably lower than in the HC, probably due to an anomaly in LPA 22:6 metabolism [62,65].

Schizophrenia: Preclinical Studies

The mutation of LPAR1 causes a variety of abnormalities similar to those seen in SCZ, which is connected to alterations in the neurotransmitters, reduced glutamate release, an altered startle response, and impairments in the prepulse inhibition (PPI) test in animals [21,72,73]. During development, abnormal LPAR signaling may trigger SCZ-like impairments and represent a pathway shared by different environmental risk factors. To demonstrate the validity of an SCZ-like model for neuropsychiatric disease, a prenatal brain hemorrhage model was employed [74]. Mouse embryos on embryonic day 13.5 (E13.5) were given intraventricular injections of a vehicle, LPA, or diluted serum. Between 10 and 12 postnatal weeks, adult rats treated at E13.5 were tested for cognitive and negative symptom impairments linked to a variety of neuropsychiatric diseases. When compared to the vehicle-exposed group, the serum- and LPA-exposed mice had considerably lower baseline locomotor activity. The female LPA- and serum-exposed mice had considerably lower PPI, but the males were unaffected. During prenatal bleeding, LPAR1 blockade appeared to cause anomalous glutamatergic and dopaminergic signaling related to behavioral abnormalities, such as altered exploratory-behavior-induced anxiety and PPI. Genome-wide transcriptome studies were then performed to evaluate the genes and networks influenced by prenatal serum and LPA exposure in the prefrontal cortex and midbrain of the female adult mice since the females showed the most pronounced phenotypic abnormalities. Around 1500 and 2100 differently expressed mRNA transcripts were observed between the brains of the adult females prenatally exposed to serum or LPA and those of the vehicle-exposed controls, as well as changes in numerous main canonical pathways linked to SCZ, including synaptic long-term potentiation, dopamine-DARPP32 feedback in cAMP signaling, and calcium signaling [74].

3.3. Anxiety and Bipolar Disorders: Clinical Evidence

The peripheral lipid profile was assessed in female patients affected by bipolar disorder (BD) and HC. In this study, plasma samples from 30 HC and 24 female BD patients were examined using liquid chromatography–mass spectrometry for complete lipid profiling and quantitative validation. Quantitative changes in numerous lipid classes were observed, which resulted in them being significantly elevated or downregulated in BD patients and favorably or negatively linked with the severity of their psychotic, affective, or mania symptoms. Furthermore, 55 lipids with significant variations were found, and 9 species were evaluated as supplementary biomarkers for the diagnosis of BD according to their correlation with clinical indicators [75].

Anxiety and Bipolar Disorders: Preclinical Studies

LPA injections into the brain have been found to cause emotional alterations in rats [76]. To go deeper into this aspect, 1-bromo-3(S)-hydroxy-4-(palmitoyloxy)-butyl phosphonate (BrP-LPA), a non-selective LPAR1-4 antagonist, was used to explore the receptors implicated in LPA-induced behavioral alterations [77]. BrP-LPA suppressed the increase induced by LPA in head-dip counts as well as the decrease in the percentage of time spent in the

open arms of the hole-board test and the EPM test, while LPA did not influence locomotor activity. These data stressed the role of LPA in producing anxiety-like behavior in mice via the LPA receptors. A loss of hippocampal GABAergic neurons was observed in adult maLPAR1-deficient mice, as well as calcium-binding proteins and neuropeptides such as somatostatin and neuropeptide Y, emphasizing the importance of LPAR1 in proper brain functioning [78]. Interestingly, when medial ganglionic eminence-derived interneuron progenitor cells were implanted into the hippocampus of adult maLPAR1-deficient mice, they could restore the environment of the hippocampus in the host, reduce anxiety-like behaviors, and neutralize passive coping while having no adverse effects on motor function, suggesting LPAR1 as a target for interneuron-related neuropsychiatric diseases.

3.4. Dysregulated Gene Sets in Neuropsychiatric Diseases in Humans

Multigene aberrant expression analysis, as well as consensus co-expression network analysis, were used to find similar dysregulated gene sets in the cortical regions of the brains of people with autism (AUT), SCZ, and BD. AUT, SCZ, and BD were shown to be linked in 156, 102, and 51 gene sets, respectively, starting from 17,786 Gene Set Enrichment Analysis (GSEA) [79]. In particular, the genetic set PID_LPA4_PATHWAY was matched with all three disorders. Shared genetic alterations might underline a common origin for several psychiatric conditions.

The investigation of the involvement of LPAR1 in mice shows that LPAR1-null mice display a range of negative behaviors, symptoms, and cognitive deficiencies, including features found in AUT and SCZ patients, whereas glutamatergic signaling defects are linked to AUT, SCZ, and other neuropsychiatric illnesses. Among the LPA receptors, LPAR1 was shown to be particularly related to neuropsychiatric illnesses, although other LPAR subtypes might also be relevant to similar diseases and provide new information in the complex of neuropsychiatric disorders [79].

4. LPA Involvement in Minor Neuropsychiatric Disorders

The field of neuropsychiatric diseases is significantly wider than what has been discussed so far. Naturally, MDD, SCZ, BD, and anxiety are the main investigated disorders, but many more minor neuropsychiatric conditions are influenced by LPA. Indeed, in recent years, the crucial functions exerted by this lipid have become increasingly evident, even in circumstances that were previously unconsidered.

4.1. Obesity: Preclinical Studies

Obesity has been linked to cognitive and behavioral disorders. Indeed, obese subjects are more likely to suffer from neuropsychiatric illnesses such as depression and dementia than non-obese people. Modifications in ATX-LPA signaling and activity have been linked with inflammatory conditions and obesity, which give rise to complications such as insulin resistance, and cardiovascular disease [80,81]. It was observed that FATX KO mice and mice treated with Ki16425 gained more weight and accumulated more adipose tissue than wild-type (WT) or control mice on a high-fat diet (HFD). These findings imply that LPA (through LPAR1) has a tonic inhibitory impact on adipose tissue growth, which might be due to LPA's anti-adipogenic action [82]. Later, the same group demonstrated that following a high-fat high-sucrose (HFHS) diet, male rodents with a heterozygous ATX deficit (ATX+/−) were protected from obesity, systemic insulin resistance, and cardiomyocyte dysfunction. ATX+/− mice fed an HFHS diet displayed higher levels of insulin-stimulated Akt phosphorylation in their white adipose tissue, hearts, skeletal muscles, and livers. In the absence of alterations in fat oxidation or ectopic lipid buildup, preserved insulin-stimulated glucose transport in the muscles of HFHS-fed ATX+/− mice was related to better mitochondrial pyruvate oxidation [83].

Similarly, LPA inhibited insulin-stimulated Akt phosphorylation and mitochondrial energy consumption in C2C12 myotubes at baseline and after palmitate-induced insulin resistance, indicating that the ATX-LPA pathway might play a role in obesity-induced

insulin resistance in metabolically important tissues and that LPA has a direct impact on skeletal muscle insulin signaling and mitochondrial function [84].

4.2. Addiction: Preclinical Studies

Memories of cocaine-induced stimuli are difficult to forget, and it is precisely because of this difficulty that the need to investigate other techniques and signaling pathways that may be effective in addiction rehabilitation arises. Improving adult hippocampal neurogenesis (AHN) to stimulate hippocampus plasticity is a viable method since adding new neurons can not only aid new learning but also modify old connections and diminish retrograde memories. The purpose of a study conducted on mice was to see whether modifying AHN after establishing cocaine-context correlations would alter the preservation of these relationships. The research was performed using cocaine training using the conditioned place preference (CPP) in mice. LPA, the LPAR1-3 inhibitor Ki16425, or a vehicle solution were given chronically with intracerebroventricular infusions, and the CPP was tested after 23 days. Long-term CPP retention was decreased in the LPA-treated animals, and the number of adult-born hippocampal cells that developed into mature neurons almost doubled. In an additional test, LPA was immediately administered to normal and LPAR1-deficient mice, revealing that LPAR1-mediated activation was essential to LPA-induced proliferative effects. These findings imply that the LPA/LPAR1 system operates as a powerful in vivo regulator of AHN and emphasizes the potential use of pro-AHN treatments for treating impaired cognition in cocaine addicts [85].

5. LPA in Neurodegenerative Disorders

5.1. Parkinson's Disease and LPA: Preclinical Evidence

PD is a neurodegenerative and progressive condition markedly characterized by a wide range of symptoms involving the CNS, the motor system, sensorial dysfunction, and beyond. The clinical traits of PD are accompanied by several molecular alterations that make this neurological condition challenging to understand. Considering the involvement of LPA in the pathophysiology of certain neurological disorders, in the last 10 years, scientists have focused on the investigation of a possible connection between LPA and PD. The role of LPA in the dopaminergic (DA) neurons, which are known to be degenerated in PD, particularly in the substantia nigra pars compacta (SNpc), was evaluated in a preclinical study [23]. The treatment of mesenchymal stem cells with LPA (at concentrations of 0, 10, 20, and 40 mol/L for 48 h) revealed morphological alterations linked to differentiation in the DA neurons, such as the production of tyrosine hydroxylase (TH). The number of LPAR1 and TH-positive cells decreased in the SNpc of the 6-OHDA rat model of PD, with an overall 86% loss of TH-positive neurons. Moreover, considering the involvement of the gastrointestinal tract in PD, the expression of LPAR1 in the myenteric nerve plexus of the 6-OHDA rats resultantly was significantly increased. Even though the precise involvement of LPA in the etiology of PD is today poorly understood, these results indicate that LPA contributed to the preservation of the DA neurons in an animal model of PD disease [23]. In vivo experiments in the Balb/c mouse model revealed that intraperitoneal treatment with the LPA receptor ligand gintonin (100 mg/kg) increased serum DA levels in these mice [86]. A few years later, Choi's group used the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD to investigate the protective role of gintonin in the disease [87]. Gintonin (50 or 100 mg/kg) was administered to the mice once a day for 12 days from 5 days before the first MPTP injection, generating two pre-treated MPTP mice groups (MPTP + GT 50 or MPTP + GT 100); the other groups were MPTP mice administered with saline 1 h before the MPTP injection (20 mg/kg, every 2 h × 4 times), mice administered with gintonin alone (100 mg/kg of gintonin) and finally the sham group. Motor impairments were assessed according to the mice's pole, rotarod, and nest-building behavior. Gintonin was shown to be beneficial in all three tests, and these findings were complemented by the effects of gintonin on a decrease in TH-positive neuronal cell loss in the SNpc and striatum of these mice. In addition, real-time PCR revealed the effect of 100 mg of gintonin in

reducing the expression of inflammatory mediators such as IL-6, cyclooxygenase (COX-2), and TNF-α. Moreover, gintonin was shown to be effective in the protection of the BBB after MPTP treatment, and in terms of a reduction in the activation of the MAPK and NF-kB pathways. The LPAR1-3 inhibitor Ki16425, administered to the mice once a day 30 min before MPTP treatment, abolished the ameliorating effects of gintonin on the behavioral tests and the activation of mediators of microglia activation, as well as the overexpression of LPAR1 and LPAR3 mediated by gintonin [87]. Overall, these findings suggest that LPA receptors, notably 1 and 3, may be involved in gintonin-mediated CNS anti-PD effects. PD is associated with an increased risk of developing seizures [88]. Considering the protective role of gintonin against PD, a mouse model of kainic acid (KA)-induced epilepsy was used to evaluate the likely positive effects of this compound on epilepsy [86]. Mice i.p. injected with 55 mg/kg of KA developed a typical seizure pattern. Interestingly, oral pre-administration of gintonin (50 or 100 mg/kg) ameliorated the seizures. The effect of gintonin was mediated by LPAR1-3 since it was abolished by the administration of Ki16425. The mice were also intracerebroventricularly injected (i.c.v) with 0.2 μg of KA to assess the effect of gintonin on glutamate-mediated excitotoxicity. The gintonin-treated animals had lower caspase-3 expression in the hippocampus and lower mRNA levels of IL-1, IL-6, COX-2, inducible nitric oxide synthase, and Iba-1-positive cells, a sign of microglial activation. The study suggested that gintonin probably participated in the anti-inflammatory and anti-oxidative effects mediated by KA through the activation of LPARs 1 and 3 [89]. Collectively, these results suggest that LPA may have a preventive function against the harmful processes that occur in PD.

Gintonin was also used to assess the catecholamine release in the PC12 cellular line. Hwang and colleagues showed that gintonin is able to increase the intracellular Ca^{2+} concentration through the LPARs [90]. The DA release allowed by the interaction between gintonin and the LPARs suggests the relevance of LPA in neurodegenerative pathologies that involve DA as the main neurotransmitter, like PD [89].

5.2. Multiple Sclerosis and LPA

MS is a long-term neurological disease that mostly affects the young population [91]. It is a complex and multifactorial illness whose etiology is related to genetical and environmental factors. MS's typical features are represented by central and peripheral lesions of the white matter, accompanied by clinical impairments involving the motor system. Considering the role that LPA plays in inflammation and apoptosis, today, increasing investigations are carried out to assess the involvement of LPA in neurodegenerative and immune-mediated diseases such as MS.

5.2.1. LPA Levels in MS Patients

One of the first pieces of evidence of the interplay between MS and LPA comes from a clinical study in which was observed that MS patients have higher levels of LPA compared with controls. The authors demonstrated that fingolimod (FTY720), an immunosuppressive drug used to treat the relapsing–remitting (RR) form of MS, was able to inhibit ATX [92]. Starting from this evidence, other studies have investigated the potential involvement of LPA in the initiation or progression of MS. A few years later, another group of researchers investigated the LPA levels in the CSF of RR-MS patients or patients in remission [93]. In the relapsing group, higher levels of LPA were registered both in serum and CSF samples compared with the remitting and control groups, who showed similar LPA concentrations in their serum and CSF. This finding revealed that the increase in LPA levels occurs during relapse. It is well known that people affected by MS have an imbalance in T-cell activity [94]. T-cells go through a variety of biological processes, and the activation process results in the release of reactive oxygen species (ROS) [95]. It has been shown that ATX increases in response to the release of oxidative species. In a study by Jiang et al., 2018, the treatment of patients with methylprednisolone, a corticosteroid used to treat inflammation, led to a decrease in the levels of LPA in the serum and CSF [93]. A possible mechanism behind

this effect is that methylprednisolone inhibits the survival of activated CD4+ T-cells, thus reducing the oxidative burden that might increase ATX activity and, consequently, LPA production [96].

5.2.2. Preclinical Studies Conducted in Animal Models of MS

Hyperalgesia is one of the characteristics observed in neurodegenerative diseases like MS but the exact mechanism underlying the increased pain sensitivity is unclear. Inoue et al., 2004, shed light on the importance of LPA receptors in mediating the initiation of neuropathic pain, allodynia, hyperalgesia, and demyelination in the dorsal roots of C57BL6/J mice [97]. A few years later, a group of scientists subjected mice to sciatic nerve ligation in the right limb, followed by LPA administration in the intrathecal space between L5 and L6, discovering that the grade of demyelination in the LPA-treated mice was significantly higher than in LPAR1−/− mice. LPA seemed to provoke dorsal root demyelination in the Remak bundles, as seen in ex vivo experiments [98]. The connection between demyelination and neuropathic pain remains still to be elucidated. However, some aspects of the connection between LPAR1 and MS were clarified using a potent inhibitor of ATX: compound-1. This compound was administered in a MOG-induced experimental autoimmune encephalomyelitis (EAE) model, which after the inhibitor administration, showed a reduction in the inflammation score in the spinal cord and a significant decrease in the disease score evaluated according to behavioral observations [99]. The authors also discovered that LPAR5 plays an important role in the neuropathic pain exhibited in a cuprizone (CPZ)-driven demyelination animal model of MS. After CPZ injection, LPAR5 was 15 times more prominent than the other LPA receptors in the corpus callosum, but it did not affect CPZ-induced demyelination. The animals were then stimulated with electrical frequencies. The WT mice showed a significant reduction in the pain threshold compared with the LPAR5 KO mice, who showed no changes in pain threshold, suggesting that LPAR5 mediated hyperalgesia through the Aδ-fibers in these animals but not in the WT mice [100]. The role of LPAR1 was investigated in the EAE mouse model of MS [101]. The LPAR1 antagonist VPC 32183-S was administered in both a genetic model maLPAR1-null, and a pharmacological model. At the age of seven weeks, female mice were immunized with the MOG35–55 peptide and were then compared to mice lacking LPAR1 to point out the role of LPAR1 in the clinical course of EAE. The WT and LPAR1-null mice showed an RR course of EAE, although, in the LPAR1-null strain, the symptoms were less severe. Moreover, a repeated dose of the LPAR1 antagonist VPC 32183-S determined an improvement in the symptomatology in the group of WT mice, suggesting that LPAR1 can worsen the clinical course of EAE. In addition, the group of LPAR1-null mice showed an increase in the expression of LPAR1 in the immune cells of the CNS and a two-fold increase in the blood's mononuclear cell count, and the expression was higher during relapse [101]. LPAR1 was also found to be increased in RR-MS patients during the first relapse, providing evidence of the involvement of LPAR1 in the inflammatory phase of the disease. In response to cues from their milieu, macrophages can adopt various functional programs through a process known as polarization. It has been shown that LPAR1 plays a role in the polarization of the macrophages in response to two different stimulations aimed at reproducing an inflammatory state, mediated by stimulation with lipopolysaccharide (LPS) + interferon γ (IFNγ), and a pro-regenerative state, using IFNβ or IL-4. LPAR1 upregulation was noticed during the pro-inflammatory state and was strongly linked with an increase in the transcripts of C-C Motif Chemokine Ligand 2 (CCL2), CCL20, CCL5, and Toll-like receptor type 2 (TLR2), which was abolished by the addition of Ki16425 [101]. Similarly, the LPA levels were shown to be elevated in a mouse model in which MOG35-55-inoculated mice were tracked until the 22nd day after vaccination to assess the development of the symptomatology associated with EAE [102]. A peak in the symptomatology was observed at day 15, on which the collection of plasma samples showed an increase in the ATX levels, as well as LPA. The heterozygous knockout ATX mice did not show differences in the incidence of EAE if compared to the transgenic mice over-expressing the ATX protein,

as well as in comparison to the control group. During the onset and remission phases, there was an increase in the levels of ATX mRNA in the spinal cord, while an increase in LPA was only observed during the remission phase. The increased levels of ATX were explained by the augmented PLA2 in the same region [102]. The role of LPA was also investigated in an animal model of MOG-induced EAE, in which Ki16425 was employed to test the effects of the agonist 1-oleoyl-LPA on motor activity and inflammation [103]. Eight- to nine-week-old C57BL/6J MOG35–55-immunized mice were divided into two groups. Low-EAE animals were given the LPAR1-3 antagonist Ki16425, while high-EAE mice were given the LPAR1-2 agonist 1-oleoyl-LPA. The low-EAE mice were i.p. injected with Ki16425, and the onset of symptoms was recorded on day 9 after immunization. The low-EAE group showed a significant motor impairment (especially at the dose of 30 mg of Ki16425). The levels of LPAR3 were increased in the spinal cord, a substantial grade of demyelination was observed, and withdrawal of the drug abolished the detrimental effects on the motor disability. In addition, the low-EAE group presented infiltrates of inflammatory and CD4+ T-cells and microglial activation in the spinal cord; moreover, an increase in the weight of the secondary lymphoid organs was registered. Ki16425 was seen to be effective in terms of the increase in the accumulation of Th1 and Th17 cells in the spinal cord of the low-EAE mice group and determined the degradation, as shown by the increase in the PECAM-1 and GFAP markers, whereas occludin and claudin-5 were decreased. Moreover, an enhancement in the ROS pathway was shown in the low-EAE mice [103]. In the same study, the effect of 1-oleoyl-LPA, an LPAR1-2 agonist, was assessed. High-EAE mice were injected with the drug starting at the onset of the symptoms. This administration resulted in decreased demyelination and an improvement in terms of motor disability, cellular inflammation, microglial activation, and oxidative stress damage, pointing out the probable beneficial effects of the activation of the LPAR1-2 pathway in mice under EAE conditions [103].

5.2.3. Comparative Study of LPA Levels between Patients and an Animal Model of MS

Unlike the two previous investigations, in a comparative clinical-preclinical study, was found an overall drop in LPA levels in serum samples from human MS patients and mice models [104]. The study aimed to assess the LPA and ATX levels in a group of MS patients and compare them with different strains of experimental mice models: SJL/S female mice, which represent the RR-EAE group; TCR1640 female mice for the spontaneous form of RR-EAE; C57BL6/J female mice; and LPAR2−/− mice and LPAR2+/+ littermates for the investigation of the primary progressive EAE (PP-EAE). When patients were divided into subgroups, the authors observed that the LPA serum levels were higher in the MS patients with relapse and acute relapse, while in the refractory relapse group, the LPA levels were significantly lower. All of the subjects (patients, EAE, and SLJ/S mice) were subsequently given fingolimod and natalizumab to evaluate their effect on the LPA concentration. The LPA levels were lower in patients who did not receive therapy, and a similar outcome was observed in the EAE animals. In both the MS patients and normal participants, their ATX levels followed the LPA trend linearly. The EAE mice were then tested to assess the functional implications of the LPA changes in the spleen, specifically in the white blood cells and the spinal cord. The authors observed a decrease in LPAR2-positive CD4+ T-cells and LPAR2-positive myeloid cells in the spleen. Moreover, LPAR2 and LPAR3 increased in the white blood cells and spinal cord, while LPAR5 increased in the spleen and spinal cord but not in the blood. An increase in LPAR1 mRNA in the spleen was also observed. Following the depletion of LPAR2 (LPAR2−/−), the mice developed severe primary progressive EAE conditions, accompanied by strong microglial activation, T-cell infiltration, a reduction in B lymphocytes, and higher levels of CD4+ T-cells. Finally, the RR-EAE mice were administered with the GRI 977143, an LPAR2 agonist (100 μg/mouse/d p.o.), which elicited an improvement in the EAE clinical scores and a significant reduction in the infiltration of the white matter, indicating that LPAR2 agonists might have a protective effect on the LPA endogenous loss observed in these mice [104].

5.3. LPA and Alzheimer's: In Vitro Main Evidence

As mentioned above, LPA is a signaling bioactive lipid derived from membrane phospholipids [105]. Increasing evidence suggests that the abnormal functioning of the ATX-LPA axis might be involved in the onset and progression of AD since these molecules have been linked with the main pathological manifestations of AD, including the intracellular deposition of neurofibrillary tangles (NFTs), extracellular aggregation of insoluble β-amyloid peptides (Aβ) (Aβ-40 and Aβ-42), and microglial activation [106]. NFTs are pathological intracellular accumulations of phosphorylated tau protein, and these aggregates compromise neuronal function and alter synaptic transmission, contributing to the onset of the severe symptomatology and cognitive abnormalities displayed by AD patients [107]. Tau is a microtubule-associated protein that modulates the stability and dynamicity of the microtubules, thus maintaining axonal integrity and proper functioning [108]. LPA was demonstrated to interfere with the structure of the cytoskeleton and cause neurite retraction, and this effect appears to be mediated by the G protein Gα12/13 [109], which is an upstream regulator of the small GTPase Rho [110,111], but its specific effect on the microtubular structure is still unclear. Sayas and his group demonstrated that LPA-induced neurite retraction was associated with an increase in the phosphorylation of tau protein in differentiated human neuroblastoma SY-SH5Y cells [112]. Two hours after treatment with LPA, almost all the cells had lost neurites and actin filaments, microtubules were disrupted, and tubulin accumulation was observed in the cell body. Moreover, the authors observed that tau phosphorylation increased 2–2.5-fold following the LPA treatment. The authors demonstrated that the effects of LPA on the differentiated SY-SH5Y cells were mediated by its binding to LPAR1 and used several kinase inhibitors to determine which kinase was responsible for the tau phosphorylation during neurite retraction. The treatment of cells with LiCl, an inhibitor of glycogen synthase kinase-3 (GSK-3), 2 h before LPA administration strongly reduced the tau phosphorylation and neurite retraction. Consistently, they reported an increase in GSK-3 activity after LPA treatment, with increased tyrosine phosphorylation of GSK-3, confirming its involvement in LPA-mediated neurite retraction [112,113]. A few years later, the same group used B103-LPAR1 neuronal cells, which constitutively express LPAR1, to investigate the molecular mechanism responsible for the LPA1-induced activation of GSK-3 [114]. The authors observed that the treatment of B103-LPA1 cells with 1-oleyl-LPA induced a rapid increase in the tyrosine phosphorylation of GSK-3β, which is known to elicit GSK-3β activation, and GSK-3β was demonstrated to form physical complexes with tau both in vivo and in vitro [115–120]. Starting from the consideration that LPA acts as a strong Ca^{2+} mobilizer in some cell types [121], Sayas and colleagues supposed that the PLC pathway might be involved in its effect on GSK-3β phosphorylation. Indeed, they observed that LPA treatment induced an increase in Ca^{2+} mobilization and a transient decrease in phosphatidylinositol-4,5-bisphosphate (PIP2), suggesting increased hydrolysis by PLC. All of these effects were blocked by the pretreatment of the cells with the pertussis toxin, an inhibitor of Gi, which also abrogated GSK-3β tyrosine phosphorylation, thus indicating that LPA-induced GSK-3β activation is mediated by the PCL-Ca^{2+} pathway [114]. In addition, they identified Pyk2, a Ca^{2+}-dependent proline-rich tyrosine kinase, as a mediator of GSK-3β tyrosine phosphorylation; indeed, Pyk2 inhibition was able to interfere with LPA-induced neurite retraction, confirming the involvement of the PCL-Ca^{2+}-Pyk2 pathway in mediating the effects of LPA on tau phosphorylation [114]. The role of GSK-3β activation on tau phosphorylation was further investigated in cultured rat hippocampal slices. In this context, it was demonstrated that the incubation of the slices with wortmannin, an inhibitor of phosphatidylinositol 3-kinase (PI3K), increased the tau phosphorylation in vivo [119], and GF-109203X (GFX), which inhibits protein kinase C (PKC), was able to increase tau phosphorylation and accumulation following an increase in GSK-3β activation: this effect was further increased when the two inhibitors were used in combination [122]. These results led to the hypothesis that the PI3K and PKC pathways also contribute to the regulation of GSK-3β activation and tau hyperphosphorylation, which leads to the pathological accumulation of NFTs in AD [122]. Further experiments using

a differentiated Neuro2A cell line showed that LPA-induced tau phosphorylation and neurite retraction were inhibited when the cells were treated with H98, which is a double inhibitor of CREB and cyclic-AMP dependent protein kinase (PKA) [123]. However, the hyperactivation of CREB alone did not alter the tau phosphorylation, suggesting a major effect of PKA in mediating the effect of LPA on this protein. To further clarify which specific pathways were involved in tau phosphorylation and neurite retraction after LPA treatment, they used different pharmacological inhibitors, including Y27632, a ROCK inhibitor which significantly reduced the LPA-mediated neurite retraction and tau phosphorylation. Interestingly, pretreatment of the Neuro2A cells with the p38 MAPK inhibitor SB203580 was able to inhibit neurite retraction without reducing tau phosphorylation, suggesting that other mechanisms can mediate neurite retraction following LPA treatment [123]. Altogether, these data indicate that LPA can induce tau phosphorylation and accumulation through the activation of GSK-3β, thus suggesting that an abnormal LPA metabolism might be involved in the formation of the NFTs typical of AD (Figure 3). Moreover, GSK-3 activity has also been correlated with the generation of Aβ peptide and its toxicity in AD [124,125], and elevated levels of GSK-3 have been found in the post-mortem brains of AD patients [126]. Considering the ability of LPA to induce GSK-3β activation and the increased levels of ATX found in the brain and CSF of AD patients [127,128], abnormalities in the metabolism of LPA might have a causal role in the pathogenesis of AD [129]. Moreover, a recent work by Ahmad and colleagues demonstrated the existence of an association between LPAs and some biomarkers correlated with AD progression [22]. Specifically, they observed that five different LPAs (16:0, 16:1, 22:4, 22:6, and 22:5) were positively correlated with the CSF levels of the Aβ-42 peptide, tau phosphorylation, and total tau, while two other LPAs (14:0 and 20:1) were associated only with the Aβ-42 peptide. Moreover, other LPAs, such as LPA 20:1 and alkyl-LPA 18:1, were positively correlated with biomarkers of tau pathology. Interestingly, some LPAs were also associated with the progression of dementia in AD patients, further corroborating the hypothesis that these bioactive lipids might have a role in the pathogenesis of AD [22]. In addition, LPA 18:2 was suggested as a possible mediator of metabolic changes in AD [130]. The accumulation of the insoluble Aβ peptide is one of the hallmarks of AD pathogenesis [131]. This pathogenic peptide is produced from amyloid precursor protein (APP) thanks to the action of two enzymes, specifically β- and γ-secretases [132]. There is evidence that some vascular factors, such as oxidized low-density lipoprotein (oxLDL), might be correlated with the accumulation of Aβ peptides and the risk of developing AD [133]. Consistently, increased oxidative damage to lipids has been observed in AD and the levels of oxLDL correlated with the Aβ levels in the CSF of AD patients [134,135]. It was demonstrated that LPA, one of the most biologically active components of oxLDL, is able to increase the production of Aβ peptides in a mouse neuroblastoma cell line that stably expresses the genes APP and presenilin 1, which encodes for the catalytic subunit of γ-secretase [136]. The authors showed that LPA treatment increased the expression levels of β-secretase, also known as beta-site APP-cleaving enzyme 1 (BACE1), without affecting APP or γ-secretase. LPA treatment also increased the activation and binding activity of CREB, and this transcriptional factor is thought to be responsible for the LPA-induced upregulation of BACE1 gene expression and Aβ production. Moreover, Shi's group investigated the signaling cascade involved in BACE1 activation and demonstrated that LPA can activate several kinases, including PKCδ, MAPK, MEK, and p90SRK. Sequential experiments using different inhibitors allowed the authors to determine the order of the molecular activation that leads to BACE1 upregulation and confirmed that LPA-induced BACE1 transcriptional activation is mediated by the PKCδ-MEK-MAPK-p90SRK signaling pathway, which ultimately activates CREB and consequently BACE1 gene transcription, thus increasing Aβ production [136]. These data represent compelling evidence that LPA might contribute to the origin of two major hallmarks of AD pathogenesis, namely tau phosphorylation and the consequent aggregation of NFTs and Aβ peptide accumulation (Figure 3). Further evidence of this hypothesis is that ATX is increased in the frontal cortex of AD patients [128]. Moreover,

ATX was proposed to be a marker of brain metabolic dysfunctions in AD, and its levels might predict AD outcomes [137]. Indeed, ATX levels have been inversely correlated with the metabolism in the prefrontal cortex and performance in memory tasks and executive function [137]. Recent evidence suggests that the ATX-LPA axis, besides its many biological functions [138], might also have a role in the regulation of microglial responses. It is known that abnormal activation of the microglia is a contributing factor to the pathogenesis of AD. Indeed, the microglia are responsible for the clearance of Aβ peptides, and microglial hyperactivation can increase Aβ and tau protein formation, which are, in turn, activators of the microglia [139]. Awada and his group observed that the treatment of microglial BV2 cells with an oxidative stress effector such as hydrogen peroxide (H_2O_2) evoked an increase in ATX expression and the production of LPA [140]. Moreover, overexpression of ATX in these cells reduced the expression of CD11b, a surface marker of microglial activation, in response to H_2O_2, and improved the cell viability, protecting microglia from H_2O_2 toxicity. ATX overexpression in BV2 cells also decreased the levels of ROS and signals of oxidative stress damage; indeed, it reduced the accumulation of carbonylated proteins and proteasomal activity. This protection against oxidative stress was abolished when the cells were treated with an LPAR1 antagonist, confirming that LPA is the mediator of the effects of ATX on the microglia [140]. Further research from the same authors also revealed that the treatment of microglial BV2 cells with LPS, which mimics a bacterial infection, significantly increased the expression of ATX and LPAR1 and LPA production. Moreover, the expression levels of some proinflammatory cytokines, such as TNF-α and IL-6, and markers of microglial activation, such as CD14, CD11b, B7.1, and B7.2, decreased upon LPS treatment in cells overexpressing ATX, while the anti-inflammatory cytokine IL-10 levels increased. These results suggest that a hyperactivation of the ATX-LPA axis not only prevents microglial activation but also promotes microglial inactivation through the induction of IL-10 expression [141]. However, the opposite results were observed in another study, in which LPAR1 overexpression led to microglial activation and increased TNF-α production in the BV2 cells after LPS treatment [142]. This effect was confirmed in primary mouse microglial cultures, in which the pharmacological blocking of LPAR1 inhibited the LPS-mediated upregulation of TNF-α but not of IL-6 and IL-1β, and in vivo, using mice systemically injected with LPS, in which LPAR1 gene knockdown was able to reduce microglial activation and proliferation. The authors identified the ERK1/2 pathway, and not the Akt or p38 MAPK pathways, as the effector of LPAR1-induced microglial activation [142]. Moreover, a more recent study reported that LPA can induce microglial activation via LPAR5, which was demonstrated to mediate the activation of the microglia through the action of protein-kinase D (PKD) in BV2 cells and primary mouse microglial cultures [143]. Plastira's group reported that the LPA-LPAR5-PKD pathway regulates microglial morphology and motility and is involved in the activation of proinflammatory transcription factors like STAT3 and p65-NF-kB. Moreover, a PKD inhibitor was able to inhibit the LPA-induced microglial production of inflammatory molecules and chemokines, such as COX-2, TNF-α, IL-1β, IL-6, CXCL10, CXCL2, and CCL5, as well as oxidative stress mediators such as ROS and nitric oxide. In this study, the authors identified the potential role of the ERK1/2, Akt, and p38 MAPK pathways in LPA-LPAR5-PKD-mediated microglial activation [143], and the involvement of the MAPK pathway was then confirmed in a more recent study from the same authors, in which they observed that MAPK antagonists reduced the microglial production of inflammatory and oxidative stress molecules (Figure 3) [144]. The literature suggests that the ATX-LPA axis has a potentially determining role in the origin of the most recognized hallmarks of AD, such as tau phosphorylation and NFT formation, Aβ accumulation, and microglial activation, thus making it a potential pharmacological target for the treatment of AD [138]. Interestingly, it was demonstrated that gintonin, an LPA-receptor-activating ligand derived from ginseng, is able to ameliorate AD neuropathology through the inhibition of the amyloidogenic process in both SH-SY5Y neuroblastoma cells transfected with mutant APP and a mouse model of Aβ neuropathol-

ogy [90]. This evidence indicates that more studies are necessary to clarify the exact role of LPA in the pathogenesis and progression of AD.
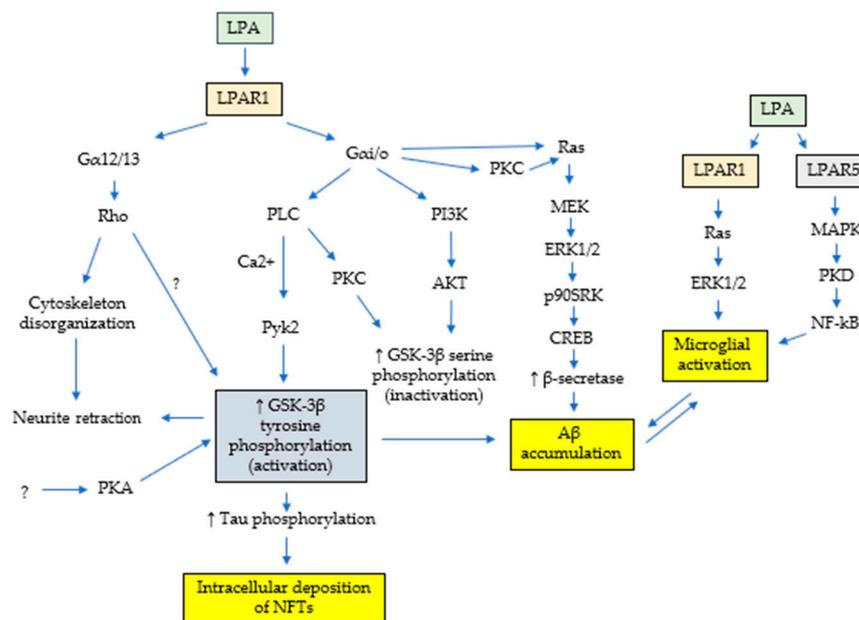

Figure 3. Schematic representation of the LPA signaling cascades involved in the pathogenesis of Alzheimer's disease.

6. Conclusions

This review aimed to assess the current progress in understanding the role of LPA as an active lipid mediator and its relevance in neuropsychiatric and neurodegenerative illnesses in light of the most recent discoveries. LPA is a highly pleiotropic molecule, and the pharmacological modulation of its production and receptors represents a crucial tool for understanding the multiple biological effects it evokes through each receptor. However, the precise modulation of a specific LPAR is complicated by the cross-reactivity presented by most compounds due to the high receptor homology and by the fact that each receptor can couple to more than one G protein, thus leading to diverse and often contrasting effects. Despite these complications, in recent years, several analogues of LPA and receptor antagonists were synthesized that efficaciously modulated the activity of LPARs, mainly concerning antitumoral therapy, fibrosis, inflammation, cardiovascular diseases, and neuropathic pain [145,146]. However, not much is known regarding the use of LPAR modulators for neurodegenerative and neuropsychiatric disorders. To date, the literature suggests LPAR1 as the most involved LPAR in the pathophysiology of disorders of the CNS, making its modulation an interesting therapeutic option for different neurological disorders. Among LPAR1 agonists, it is worth mentioning UCM-05194, a non-lipid LPA agonist that was proven to exert therapeutical effects in disorders like AD, MS, neuropathic pain, and dementia [147]. LPAR1 antagonists such as Ki16425, Ki16198, and other thiazole derivatives [148,149], which also affect LPAR2 and LPAR3 to a lesser extent, are mainly studied for cancer and pulmonary fibrosis treatment; however, there is evidence pointing out their potentially beneficial effect in nociception [150]. Moreover, the LPAR1 antagonist AM095 was shown to inhibit microglial activation and attenuate neurological deficits after ischemic brain damage [151]. The use of ATX inhibitors as modulators of the LPA concentration also needs to be considered. For example, the ATX inhibitor HA130 demonstrated to have an anti-inflammatory effect in hepatic encephalopathy [152]. Recently, the simultaneous inhibition of ATX and LPAR1 using dual ATX-LPAR1 inhibitors has started to emerge as more effective against certain kinds of cancers compared to single therapy and represents an interesting starting point for future research. However, the use

of dual inhibitors is still quite limited due to the high level of co-expression of different LPARs, which reduces the target specificity [153]. Besides LPAR1, also LPAR5 might be relevant to neuropsychiatric and neurodegenerative disorders since it was demonstrated to be involved in the regulation of microglial activation. Interestingly, the LPAR5 antagonist AS2717638 effectively inhibited the LPA-induced production of pro-inflammatory cytokines and chemokines in murine microglial cells [154], suggesting that LPAR5 inhibitors might be helpful for neurological conditions characterized by neuroinflammation. An extensive discussion of LPAR modulation is beyond the scope of this review. For a complete and detailed description of the pharmacological modulation of LPARs, we recommend the readers refer to these comprehensive review articles on this specific subject: [145,146]. The development of drugs with high specificity toward each LPAR remains the biggest challenge in completely understanding the functions of LPA and its many signaling pathways in the CNS and unraveling the real therapeutic potential of its modulation, considering the crucial role of this molecule in so many biological functions. As life expectancy rises, the incidence of neuropsychiatric and neurodegenerative disorders is destined to increase consistently. As a result, the hunt for fresh alternative approaches is becoming increasingly important, and new and innovative research is pivotal to shed light on new therapeutic targets for treating these complex conditions.

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