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FOCUSED REVIEW

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Neurolipid systems: A new target for the treatment of dementia

Gorka Pereira-Castelo[1] | **Iker Bengoetxea de Tena**[1] | **Jonatan Martínez-Gardeazabal**[1] | **Marta Moreno-Rodríguez**[2] | **Estibaliz González de San Román**[1] | **Iván Manuel**[1,3] | **Rafael Rodríguez-Puertas**[1,3]

[1]Department of Pharmacology, University of the Basque Country (UPV/EHU), Leioa, Spain

[2]Department of Translational Neuroscience, Barrow Neurological Institute, Phoenix, Arizona, USA

[3]Neurodegenerative Diseases, BioBizkaia Health Research Institute, Barakaldo, Spain

Correspondence
Iván Manuel, Department of Pharmacology, University of the Basque Country (UPV/EHU), Leioa, Spain.
Email: ivan.manuel@ehu.eus

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Abstract

Neurolipids comprise a diverse class of bioactive lipids that include molecules capable of activating G protein-coupled receptors, thereby inducing systemic effects that contribute to the maintenance of homeostasis. Dementia, a non-specific brain disorder characterized by a common set of signs and symptoms, usually arises subsequent to brain injuries or diseases and is often associated with the aging process. Individuals affected by dementia suffer from the disruption of several neurotransmitter and neuromodulatory systems, among which neurolipids play an important role, including the endocannabinoid, lysophosphatidic acid and sphingosine 1-phosphate systems. In this review, we present an overview of the most recent and pertinent findings regarding the involvement of these neurolipidic systems in dementia, including data from a wide range of both in vitro and in vivo experiments as well as clinical trials.

KEYWORDS
dementia, endocannabinoid, lysophosphatidic acid, neurolipid, sphingosine 1-phosphate

Plain English Summary

Lipids, apart from the classical functions attributed to them, also have a function as molecules with neurotransmitter activity; these are called neurolipids. Neurolipids exert their function through G protein-coupled receptors and are involved in many physiological processes. In this review, we approach possible treatments involving the modulation of neurotransmitter systems by neurolipids, focusing on the cannabinoid, lysophosphatidic acid and sphingosine 1-phosphate systems in diseases in which dementia appears, such as Alzheimer's disease, Parkinson's disease and Huntington's disease. Given the lack of effective treatments for these diseases, neurolipids emerge as molecules with great therapeutic potential.

1 | INTRODUCTION

Dementia is a nonspecific brain disorder characterized by a set of common signs and symptoms that frequently appears after brain damage caused by injury or disease and is heavily related to aging. Along with neurodegenerative signs and neurological symptoms, such as impairments in progressive learning and memory, other symptoms are usually observed related to difficulties in behavioural, motor or emotional aspects, including language problems and depression. These signs may vary based on the type of dementia and the characteristics of each patient, which generates a large and heterogeneous group of different clinical profiles requiring individualized treatments.[1] Several neurodegenerative disorders are accompanied by different symptoms of dementia, including Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD). Currently, there are few effective pharmacological treatments indicated for these diseases, and they are generally focused on symptomatic relief rather than targeting the neurodegenerative process. Moreover, there is a lack of early diagnostic biomarkers for early detection.

AD, the most common dementia worldwide, is characterized by a progressive cognitive impairment of learning and memory, with fatal consequences for the patient. While the classical histopathological hallmarks of AD include extracellular amyloid-β plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein, synaptic loss is the parameter that best correlates with disease progression.[2] Neurotransmitter systems specifically affected in AD include cholinergic pathways and also lipid-based neurotransmitter systems such as the endocannabinoid (eCB).[3] Currently, the only approved treatments for the disease are inhibitors of acetylcholinesterase, antagonists of NMDA receptors, and more recently, anti-amyloid-β peptide antibodies; the last one is not exempt from controversy, and all of them show very limited improvements.

PD is principally a motor disorder that often courses with cognitive impairment. Recently, some types of PD have been defined neuropathologically as an alpha synucleinopathy showing accumulation of alpha synuclein protein in dopaminergic neurons of the *substantia nigra* that may lead to neuronal death and progressive impairment of the motor cognition of the patient. PD patients can develop a specific type of dementia, which is characterized by cognitive impairment, visual hallucinations and, more importantly, parkinsonism, defined by bradykinesia, gait impairment and rest tremor, among other symptoms.[4] As is the case with other neurodegenerative diseases, it has no healing treatment, being L-Dopa the most effective drug to mitigate the motor symptoms.

Unlike AD and PD, HD is a hereditary neurodegenerative disease, being the most common form of genetic-associated dementia. It is caused by a cytosine-adenine-guanine (CAG) trinucleotide repetition in the gene that encodes the huntingtin protein on chromosome 4.[5] Chorea, characterized by brief, semi-directed and irregular movements, is the most characteristic symptom of HD, and the treatment lies in antipsychotics and benzodiazepines, which do not reverse nor protect the patient from neurodegeneration.[6]

Therefore, new and innovative treatments are necessary for these three neurodegenerative diseases.

2 | NEUROLIPIDS AND THEIR ROLE IN THE MOST COMMON DEMENTIAS

Lipids are widely recognized for their roles in providing structure, energy storage and thermoregulation to the organism. However, it is important to broaden our perspective on lipids, as some of them also possess signalling capabilities in the CNS through binding and activation to G protein-coupled receptors (GPCRs).[7] There is a large variety of lipids in the CNS classified according to their chemical structures, such as sphingolipids, phospholipids, cholesterol and glycosphingolipids.[8] Few of them can be considered integral members of the extensive family of neurotransmitters and/or neuromodulators. Since peptides with these properties are called 'neuropeptides', lipids could be named as 'neurolipids'.[9] The discovery of

new lipid-based neurotransmitter systems, such as eCBs, lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P), shifts the focus to the relevance of these systems in both neurophysiological status and neurological disorders.

Neurolipids are typically synthesized in a calcium-dependent manner, as needed. This synthesis occurs through the enzymatic processing from membrane lipid precursors by phospholipases, sphingomyelinases or cytochrome P450 hydroxylases.[10] Precursors are located mainly at the cell membranes of the pre- or post-synaptic compartments. Endogenous ligands for neurolipids have the capability to interact with their respective receptors either in an autocrine manner, where they directly engage with their specific receptor within the lipid bilayer, or in a paracrine way. Their amphipathic properties allow them to easily cross the lipid bilayer, allowing them to function also in the cytoplasm[11] (Figure 1). Regarding their physiological roles, neurolipids have been involved in multiple processes in both peripheral and central nervous systems (CNSs), as well as regulating immune responses. These neurolipid systems are also regulated during the abovementioned neurodegenerative diseases. Thus, receptors and enzymes involved in the synthesis and degradation of the endogenous neurotransmitters of these systems could be used not only as biomarkers for early diagnosis of the mentioned diseases but also as therapeutic targets.[12]

Therefore, we have reviewed three of the most studied lipid-based or neurolipid neurotransmitter systems, namely, eCB, LPA and S1P systems, and their roles in the context of dementia linked to AD, PD and HD (Table 1, Figure 2).

2.1 | Endocannabinoid system

The eCB system has a widespread distribution in the CNS, modulating multiple neural processes, including neurodevelopment, synaptic plasticity and adaptive responses.[39] The main eCB neurotransmitters are N-arachidonoylethanolamine (anandamide or AEA) and 2-arachidonoylglycerol (2-AG), which activate two different subtypes of $G_{i/o}$-proteins-coupled cannabinoid receptors, CB_1 and CB_2. Some of the enzymes involved in the synthesis of the eCB include N-acyl-phosphatidylethanolamine-specific phospholipase D (NAPE-PLD) for AEA and diacylglycerol lipase (DAGL) for 2-AG, and for degradation, these include fatty acid amide hydrolase-1 (FAAH) for AEA and monoacylglycerol lipase (MAGL) for 2-AG.[40]

The eCB system is involved in different neurodevelopmental, psychiatric and neurodegenerative disorders. Thus, cannabimimetic and cannabinoid-based drugs have been proposed for the treatment of anxiety, schizophrenia, epilepsy and many neurological diseases, including some genetic syndromes or others accompanied by dementia, such as AD, PD and HD.

The activity of CB_1 receptors is higher in brain regions such as the hippocampus and the frontal cortex, which are involved in learning and memory processes at initial phases of the AD, gradually decreasing in advanced stages.[41] In frontal cortex, the same tendency was observed using the [^{125}I]SD-7015 radioligand to measure CB_1 receptor density and, importantly, this parameter inversely correlates with Braak's tau-based classification.[42] A study performed using brain samples from late stages of AD (Braak V/VI) analysed both CB

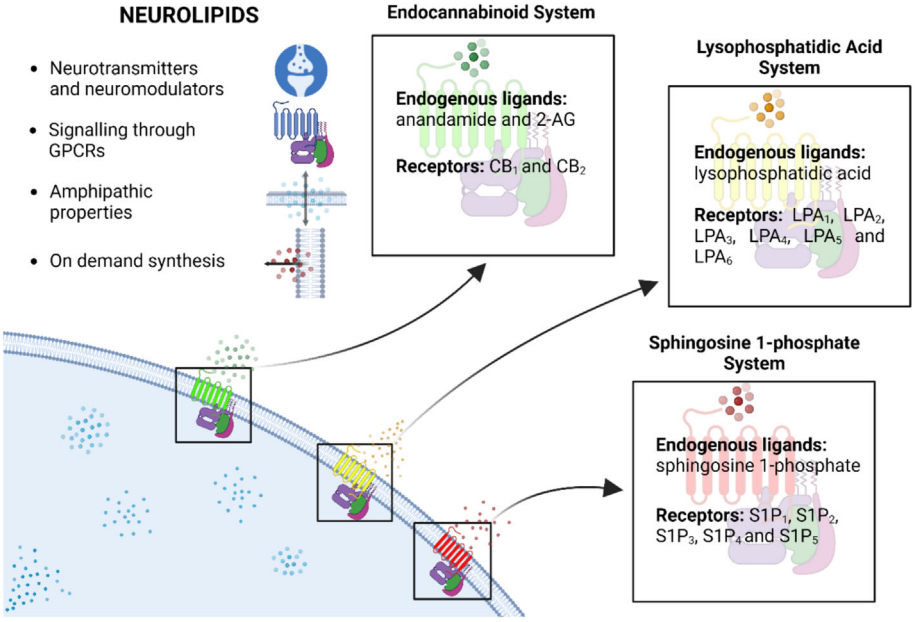

FIGURE 1 Schematic diagram illustrating the three main families of neurolipids: endocannabinoids, lysophosphatidic acids and sphingolipids. 2-AG, 2-araquidonoylglycerol; CB_{1-2}, cannabinoid receptor subtype 1–2; GPCR, G-protein coupled receptor; LPA, lysophosphatidic acid; LPA_{1-6}, lysophosphatidic acid receptor subtype 1–6; S1P, sphingosine 1-phosphate; $S1P_{1-5}$, sphingosine 1-phosphate receptor subtype 1–5.

TABLE 1 Novel neurolipidic treatments for Alzheimer's, Parkinson's and Huntington's diseases in different preclinical models and clinical trials.

Target disease	Study type	Treatment	Method	Findings	References
Alzheimer's disease	Patients	Cannabinoid extract	Mnemonic test	Improved mnemonic ability	13
	Experimental models	Fingolimod; SPHK1	MWM	Improved cognitive performance	14–16
		Botanical extracts (THC + CBD)	AAT, ELISA, immunohistochemistry, PCR, TORT and WB	Improved cognitive performance and decreased astrogliosis, microgliosis and neuroinflammation	17
		WIN55,212-2; JZL184	Autoradiographic studies and Immunohistochemistry	Increased CB_1 activity and density	18
		Gintonin	ELISA, immunohistochemistry, MWM, WB and YM	Improved cognitive performance and reduced β-amyloid levels	19
Parkinson's disease	Patients	CBD	Randomized, double-blinded, placebo-controlled, crossover clinical trial	Reduced anxiety and tremor amplitude	20
		Nabilone	Phase II placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal trial	Improvements in anxiety and sleeping problems	21
	Experimental models	Ponesimod	Immunohistochemistry, WB and YM	Spatial memory improvement, reduced TNF-α and CXCL10 levels and increased IL-33 levels	22
		S1P	Immunohistochemistry, PCR and WB	Increased SPHK1 levels and cell viability restoration	23
		Fingolimod	Actimeter, beam test, immunohistochemistry, pole test, rotarod, RT-PCR and WB	Motor improvement and increased BDNF levels.	24–26
		2-AG	Immunohistochemistry and HPLC	Neuroprotection	27
		URB597	Immunohistochemistry and rotarod	Motor improvement and increased anandamide levels	28
		Δ9-tetrahydrocannabivarin	CAA	Motor improvement	29
		VCE-004.8	CRT, immunohistochemistry and pole test	Increased dopaminergic neuron survival	30
		Gintonin	PCR, pole test, immunohistochemistry, rotarod and WB	Increased dopaminergic neuron survival and cognitive performance. Decreased inflammation	31

TABLE 1 (Continued)

Target disease	Study type	Treatment	Method	Findings	References
Huntington's disease	Patients	Sativex (THC + CBD)	Cohort study	No effect	32
	Experimental models	A-971432	Horizonal ladder task and rotarod	Motor improvement and increased lifespan	33
		K6PC-5	Clasping analysis, horizonal ladder task, PCR and rotarod	Motor improvement and increased S1P, $S1P_1$, $S1P_5$ and BDNF levels	34
		THI	Clasping analysis, horizontal ladder task, LC–MS/MS, negative geotaxic assay, rotarod, TEM and WB	Motor improvement, activation of pro-survival pathways, normalization of brain-derived neurotrophic factor levels, preservation of white matter integrity and stimulation synaptic functions	35
		CBD; CB_2 agonists	Immunohistochemistry, in situ hybridation, HPLC and PCR	Neuroprotection	36,37
		Gintonin	Immunohistochemistry and RT-PCR	Neuroprotection	38

Note: The articles included were selected on the basis of their scientific impact, novelty and relevance.
Abbreviations: 2-AG, 2-arachidonoylglycerol; AAT, active avoidance test; AD, Alzheimer's disease; BDNF, brain derived neurotrophic factor; CAA, computer aided acidimetry; CBD, cannabidiol; CRT, cylinder rearing test; ELISA, enzyme-linked immunosorbent assay; HPLC, high performance liquid chromatography; MWM, Morris water maze; PCR, polymerase chain reaction; PD, Parkinson's disease; S1P, sphingosine 1-phosphate; SPHK1, sphingosine kinase 1; TEM, transmission electron microscopy; THC, tetrahydrocannabinol; THI, 2-acetyl-5-tetrahydroxybutyl imidazole; TORT, two object recognition test; WB, western blot; YM, Y maze.

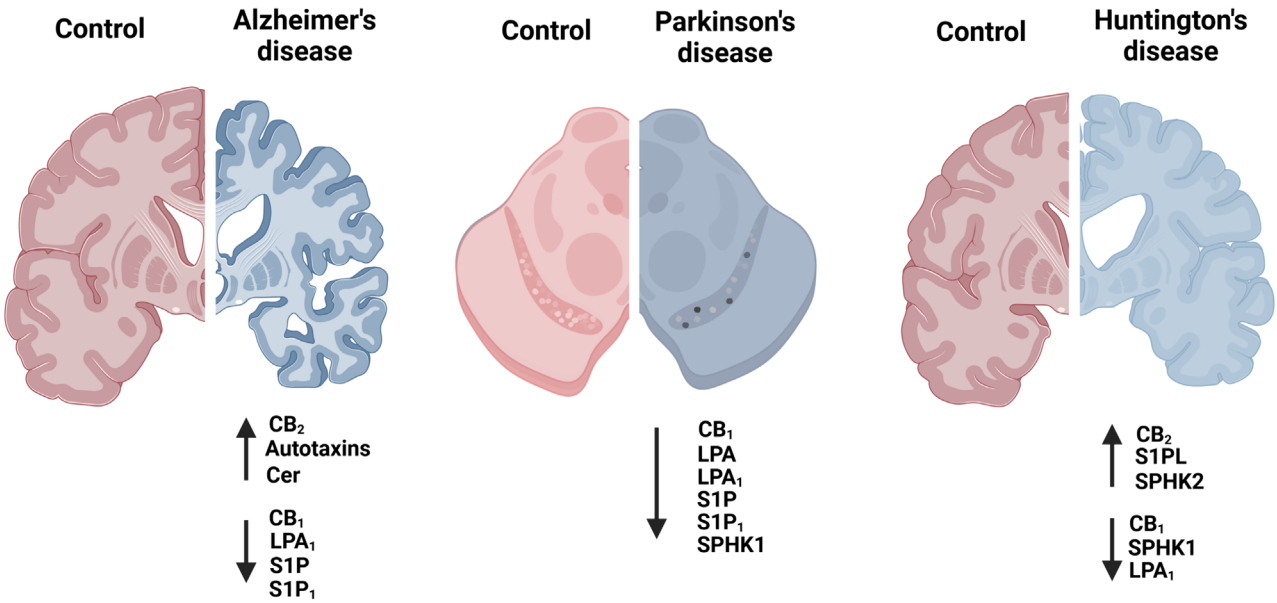

FIGURE 2 A schematic display of the major changes of the sphingosine 1-phosphate, endocannabinoid and lysophosphatidic acid systems in three of the most prominent neurodegenerative diseases, Alzheimer's disease, Parkinson's disease and Huntington's disease. CB_1, cannabinoid receptor subtype 1; CB_2, cannabinoid receptor subtype 2; Cer, ceramide; LPA, lysophosphatidic acid; LPA_1, lysophosphatidic acid receptor subtype 1; S1P, sphingosine 1-phosphate; $S1P_1$, sphingosine 1-phosphate receptor subtype 1; S1PL, sphingosine 1-phosphate lyase; SPHK, sphingosine kinase.

receptor subtypes using immunoblotting and reported a decrease in CB_1 receptor, in line with previous studies, while CB_2 density augmented probably as a consequence of inflammatory processes.[43]

Studies using a rat lesion model of basal forebrain cholinergic neurons (BFCNs) degeneration, which are selectively deleted in AD patients,[44] show increased activity of CB_1 receptors in cortical projection areas.[45,46] Similar alterations were also found in genetic AD models, such as the APP/PS1 double transgenic mice, in which CB_1 and CB_2 genes expression are altered in presymptomatic stages in the hippocampus and prefrontal cortex.[47] Importantly, a chronic administration of botanical extracts containing both Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in early disease stages of these same transgenic mice, reduced astrogliosis, microgliosis and neuroinflammation-related molecules, as well as improved cognitive performance.[17] In a subsequent study using older APP/PS1 mice, reduced memory impairment was equally observed following the treatment, but unlike mice treated at prodromal stages, there was no modulation of glial reactivity nor inflammatory markers. In contrast, cannabinoids altered the cortical excitatory/inhibitory balance only in aged mice.[48] In other transgenic models, like 5xFAD mice, CB_1 expression in the hippocampus was reduced, and this decrease was accompanied by cognitive impairment.[49] More recently, in a 5xFAD/$CB_2^{EGFP/f/f}$ mice model, microglial CB_1 receptor increase has been described.[50] In the 3xTg-AD model, alterations in CB_1 density and activity have been described. In line with the findings obtained from human AD samples, 4-month-old 3xTg-AD mice (prodromal stages) show upregulated CB_1 activity in areas such as the thalamus, which is decreased in areas such as the basal forebrain in older mice (15-month-old, advanced stages).[51] Seven-month-old mice (moderate pathological stage) express increased CB_1 receptor density and activity in various brain areas, particularly in the basolateral amygdala. This increase was reversed following the subchronic stimulation of the eCB system with either CB_1/CB_2 agonist WIN55,212-2 or JZL184, an inhibitor of MAGL, the main enzyme that catabolizes 2-AG.[18]

Together, these results indicate that CB_1 density and activity in AD are stage-dependent, up-regulated in the early stages of the disease and progressively reduced during neurodegeneration. This biphasic modulation raises controversy about the benefits and potential risks of CB treatments in the early *versus* late stages of the disease. Importantly, a case report published in 2022 described mnemonic improvement following a 22-month-long administration of cannabinoid extract microdoses to a 75-year-old patient presenting memory deficit, spatial and temporal disorientation, and impaired daily activity.[13] This report further highlights those biphasic effects of cannabinoid agonism on cognition and the beneficial effects of low as opposed to high doses, as well as the importance of the previous cognitive status of the patient receiving the drug.

In PD, receptors and enzymes, as well as endogenous ligands of the eCB system, are also altered[52] (Figure 2). Preclinical studies indicate that a modulation of this system exerts neuroprotective actions. A study using the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxin mouse model reported neuroprotective effects of increasing 2-AG levels.[27] Additionally, URB597, a FAAH inhibitor, effectively prevented motor impairment induced by MPTP. This protective effect was mediated through CB_1 and CB_2 signalling pathways by increasing anandamide levels. However, it did not maintain dopamine levels in the nigrostriatal pathway.[28] Δ9-tetrahydrocannabivarin, a non-psychoactive homologue of THC, demonstrates a dual mechanism of action in PD; it exerts symptoms of palliation by activating CB_2 receptors while simultaneously blocking CB_1 receptors in the 6-hydroxydopamine (6-OHDA) PD model. Additionally, it provides neuroprotection through antioxidant effects.[29] More recently, in the PD rat model of 6-OHDA, a CBD derivative, VCE-004.8, an agonist of the CB_2 receptor, was able to attenuate the toxin-induced loss of dopaminergic neurons in the *substantia nigra*.[30] Several clinical trials involving various cannabinoid-based drugs have been conducted, resulting in diverse outcomes. Some of these drugs exhibit motor effects, while others focus on neuropsychiatric improvement. The variability in results appears to depend on both the specific drug used and, more significantly, the methodology employed to assess these outcomes.[53] Some of the latest clinical trials include a randomized, double-blinded, placebo-controlled, crossover clinical trial, which concluded that CBD administration is associated with reduced anxiety and tremor amplitude in PD patients,[54] as well as a phase II placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal trial conducted with nabilone (a CB1 receptor agonist), which demonstrated improvements in anxiety and sleeping problems among PD patients.[55]

In HD, cannabinoid compounds could act as neuroprotective agents, at least in animal models. The mechanisms by which they exert neuroprotection vary depending on the animal model used. A study using a 3-nitropropionic acid (3-NPA) model reported neuroprotection of striatal projection neurons following CBD administration in a CB_1-independent manner, probably based on the antioxidant properties of CBD.[56] In a subsequent study in which an intra-striatal injection of the mitochondrial complex II inhibitor malonate was

performed, only CB_2 agonists protected striatal projection neurons from toxin-induced death.[57] In contrast with preclinical evidence, a double-blind study conducted with 24 HD patients indicated that Sativex, which contains both CBD and THC, did not affect disease progression.[32]

2.2 | Lysophosphatidic acid system

LPA is a metabolite of phospholipids biosynthesis in the cell membrane. The generic form of LPA (1- or 2-acyl-sn-glycero-3-phosphate) is composed of phosphate, a glycerol and a fatty acid, but there are different LPA species depending on the length of the fatty acid chain, saturation or position.[58] The actions of LPA are numerous and different. For instance, LPA produced by platelets is essential as a mediator of tissue regeneration.[59] LPA also allows different types of cellular responses, such as migration,[60] neurite contraction,[20] stimulation or inhibition of adenylyl cyclase,[21] or prevention of apoptosis.[61]

While the biosynthesis of LPA is not fully known, some enzymatic pathways have been described. The most important is the autotaxin enzymatic pathway, the second one, the production by phospholipase from membrane phospholipids, and, finally, the acyltransferase pathway.[62] LPA acts as a neurotransmitter through six different receptors, LPA_1-LPA_6 (Figure 1), and intracellularly these can be coupled to four different Gα subunits ($G\alpha_i$, $G\alpha_q$, $G\alpha_{12}$, $G\alpha_s$), and, consequently, different signalling routes can be activated.[63]

The extent of the involvement of LPA in neurodegenerative diseases is not precisely known, but a number of studies have established the relationship in one way or another between this neurolipid system and AD (Figure 2). Evidences show an increased expression of autotaxin, which in addition to being involved in synthesis, has an antioxidant effect in the prefrontal cortex of AD patients.[64] LPA levels are also found increased in patients suffering mild cognitive impairment (MCI).[65] In this context, there seems to be an association between various forms of LPA and $A\beta_{1-42}$, as LPA upregulates β-secretase activity.[66] Still, other authors have shown that administration of LPA agonists, such as gintonin, in transgenic models of AD reduces amyloid plaque deposition and improves memory.[19] Similarly, LPAs participate in the upregulation of glycogen synthase kinase-3 (GSK-3), an enzyme involved in tau phosphorylation, another hallmark of AD.[67] LPA appears to play a critical role in neurogenesis by modulating neuronal progenitors and in this regard, deficits in neurogenesis have been described.[68] Indeed, exogenous administration of LPA substantially improves memory in animal models, and this correlates with increased neurogenesis.[69] Regarding behaviour, LPA_1 receptor depletion causes symptoms in animals that mimic some of the symptoms that appear in AD type dementias, such as anxiety, memory impairment and motor disturbances.[70] These evidences, although inconclusive, seem to indicate the relationship between LPA and the development of AD and other dementias.

Regarding PD models in experimental animals, 6-OHDA-injured rats showed a significant reduction of LPA_1 density in the *substantia nigra* and differentiation of mesenchymal stem cells (MSCs) into dopamine neurons following LPA treatment, suggesting that LPA/LPA_1 signalling holds potential importance in the development and maintenance of dopaminergic neurons.[71] Furthermore, the oral administration of gintonin prevented the loss of dopaminergic cells in a PD model induced by MPTP injection. This treatment also exhibited anti-inflammatory and antioxidant properties and supported the preservation of the blood–brain barrier integrity, ultimately enhancing cognitive function. Importantly, these effects of gintonin were substantiated through co-administration with Ki16425, an antagonist targeting $LPA_{1/3}$ receptors, which completely nullified the benefits of gintonin.[31]

Regarding HD, elevated levels of LPA species were observed in the striatum of the Q140/Q140 HD mice model.[72] A treatment with gintonin exerted substantial protective effects in a 3-NPA model through the activation of LPA receptors and the nuclear factor erythroid 2-related factor 2 (Nrf-2) signalling pathway, along with the inhibition of the mitogen-activated protein kinases (MAPKs) and the nuclear factor-κB (NF-κB) signalling pathways. Moreover, gintonin demonstrates protective effects in STHdh cells and in an adeno-associated viral (AAV) vector-infected model of HD.[38]

2.3 | Sphingosine 1-phosphate system

The S1P system is a lipid-based neurotransmitter system that is located all along the organism. Five different transmembrane receptors, $S1P_{1-5}$, which are coupled to different G proteins ($G\alpha_{i/o}$, $G\alpha_{12/13}$, $G\alpha_s$ and/or $G\alpha_q$), have been described.[73] The endogenous ligand is S1P (Figure 1), a lipid signalling molecule that belongs to the family of sphingolipids. S1P is in constant balance with its precursor, ceramide, regulated by enzymatic processes. Ceramide is catabolized by ceramidases into sphingosine, which in turn is phosphorylated by sphingosine kinase enzymes (SPHK1/SPHK2) into S1P, and it can be catabolized by S1P lyase (S1PL). On the contrary, S1P can be dephosphorylated by sphingosine

phosphatases into sphingosine, to be later anabolized by ceramide synthases into ceramide.[36] Both neurolipids, S1P and ceramide, play an important role in cellular processes involved with survival, proliferation and differentiation; nevertheless, their effects are opposite. That is, while S1P acts as a positive modulator of cellular survival, displaying anti-apoptotic, proliferative and cell-trafficking effects, ceramide acts as a negative modulator, inducing apoptosis and cellular growth arrest.[37]

Aging, the main risk factor for AD development, has been linked with a disbalance in several sphingolipid molecules (Figure 2), highlighting S1P/sphingosine balance disruption in elderly people.[74] In a plasma samples study conducted within a longitudinal cohort involving healthy individuals, cognitively impaired non-demented individuals, AD patients and vascular dementia (VD) patients, it was observed that an increase in the ratio of d18:1 to d16:1 S1P correlated with cognitive deficits. Interestingly, despite these observed changes in the S1P ratios, the overall levels of S1P in plasma did not exhibit significant reductions.[75] In a subsequent study, a lipidomic analysis of plasma samples from control and both PD and AD patients showed a decrease in S1P levels and an increase in monohexylceramide and lactosylceramide levels in AD and PD groups compared with control groups.[76] Cerebrospinal fluid (CSF) lipid alterations have also been reported in PD and AD; sphingomyelins d18:1/18:0, which are precursors of ceramides and S1P, are increased in the CSF of patients that display pathological levels of $A\beta_{42}$, Tau and P-tau-181.[77]

A recent study indicates S1P metabolism dysregulation in the 5xFAD mouse model of AD, revealing a decrease in SPHK1/SPHK2 levels and an increase of S1PL levels, together with the increase of the $S1P_1$ receptor expression.[78] Strikingly, using the same model, a treatment of ponesimod, an agonist of S1P receptors, was able to offer neuroprotection by reducing tumor necrosis factor-alpha (TNF-α) and C-X-C motif chemokine ligand 10 (CXCL10) levels while increasing anti-inflammatory interleukin 33 (IL-33) levels and improving spatial memory.[22] Previous studies suggested that $S1P_1$ receptor activity is downregulated in several brain areas, including the hippocampus, in the 3xTg-AD mouse model.[7] Several studies also suggest that FTY720, commonly known as fingolimod, a functional antagonist of $S1P_1$ receptors, can provide neuroprotection against learning and memory deterioration in mouse and rat AD models. As an example, a subchronic treatment with fingolimod restored cognitive impairment as measured in the Morris water maze (MWM), using an AD-like rat model.[14] Moreover, a more recent study demonstrated that fingolimod exerted neuroprotection against cognitive impairment in 3xTg-AD mice in both novel object localization test and MWM.[15] Synthesis and degradation enzymes of the S1P system have also been reported to display an important role in neuroinflammatory processes; indeed, an elevation of SPHK1 improved AD-like pathology in the APP/PS1 model.[16]

Regarding PD, a clinical study showed that serum S1P levels were significantly depleted in PD patients compared to the control group. A sub-cohort of the same study demonstrated an association between decreased motor functions and decreased S1P serum levels.[79] In a 1-methyl-4-phenylpyridinium (MPP+) in vitro model, SPHK1 depletion diminished cell viability and could be restored by addition of S1P to the medium.[23] In the same way, using the aforementioned model, SPHK1 inhibition via targeting microRNA-6862 increases SPHK1 expression and protects neurons.[80] In various different in vivo models of PD, including models by intraparenchymal injection of rotenone, 6-OHDA or MPTP, as well as in GM2+/− transgenic mice, fingolimod or SEW-2871, a selective agonist of the $S1P_1$ receptor, improved motor function and provided neuroprotection through augmented brain-derived neurotrophic factor (BDNF)[24,25] and through the S1PR1/AKT/BNIP3/PINK1/Parkin axis.[26]

Concerning HD, *postmortem* HD patients show an aberrant metabolism of S1P where there is an increase in the expression and activity of S1PL and reduction of SPHK1.[81] In vivo experiments have described that the augmentation of SPHK1 or the inhibition of SPHK2 as well as S1PL has neuroprotective effects against huntingtin-evoked neurotoxicity.[82] A treatment with a specific agonist of $S1P_5$ receptors, A-971432, not only ameliorated motor dysfunction in the R6/2 mice model but also increased their lifespan.[33] In a further experiment, a treatment with an enhancer of SPHK1, K6PC-5, was able to increase S1P, BDNF, $S1P_1$ and $S1P_5$ expression while preventing motor dysfunction.[34] Interestingly, a study using both R6/2 mice model and fly models of HD treated with 2-acetyl-5-tetrahydroxybutyl imidazole, an SGLP1 inhibitor, recovered motor functions, BDNF levels and white matter integrity.[35] Nevertheless, no clinical trials have yet been made involving S1P drugs for the treatment of HD.

3 | CONCLUSIONS AND FUTURE PERSPECTIVES

Neurolipids are important signalling molecules with potential therapeutic effects against the most common dementias associated with the main neurodegenerative diseases, as has been demonstrated not only with preclinical in vitro and in vivo experiments but also with data from patients (Table 1). eCB and S1P drugs have shown relevant and interesting results in several animal models

of dementias from different origins, paving the way for clinical trials, although further data acquisition is needed in this regard. Despite the limited evidence regarding the involvement of LPA, it also plays an important role in the development of dementia and could be a potential coadjutant for future therapeutic approaches.

In summary, neurolipids represent a novel approach for the advancement of innovative therapies targeting the most prevalent forms of dementia, including AD, PD and HD. A deeper comprehension of these lipid systems holds the promise of enhancing our understanding of the aetiology, progression and potential treatments for these neurological conditions.

4 | LIMITATIONS OF THE REVIEW

The present review focuses on the description of the relationship of neurolipid systems in three specific diseases with dementia, such as AD, PD and HD. Among all the diseases that lead to dementia, these three are those that have attracted the most interest in the field of neurolipids. Although research on lipids that have neurotransmitter activity is a field that is expanding thanks to new techniques in the field of lipids that have been developed in recent years, there are currently not a large number of specific studies in the context of dementias, which may hinder a complete and thorough view of the subject. Much of the research in this field is conducted in animal models, limiting the direct extrapolation to human pathophysiology and its clinical relevance in dementias. A high heterogeneity has been observed in the design of the studies used for this review, and this may complicate the comparison and summarizing of the results, preventing a consensus on the usefulness of neurolipid treatments in these diseases. Due to the exponential growth of knowledge in this field, it is challenging to include every new publication within this article. Consequently, we have selectively included a limited number of the most pertinent, recent and innovative studies.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Iker Bengoetxea de Tena https://orcid.org/0000-0003-0586-1857

Iván Manuel https://orcid.org/0000-0003-0958-4738

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