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Review

# Glycerophospholipids and glycerophospholipid-derived lipid mediators: A complex meshwork in Alzheimer's disease pathology

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ABSTRACT

An increasing body of evidence suggested that intracellular lipid metabolism is dramatically perturbed in various cardiovascular and neurodegenerative diseases with genetic and lifestyle components (e.g., dietary factors). Therefore, a lipidomic approach was also developed to suggest possible mechanisms underlying Alzheimer's disease (AD). Neural membranes contain several classes of glycerophospholipids (GPs), that not only constitute their backbone but also provide the membrane with a suitable environment, fluidity, and ion permeability. In this review article, we focused our attention on GP and GP-derived lipid mediators suggested to be involved in AD pathology. Degradation of GPs by phospholipase $A_2$ can release two important brain polyunsaturated fatty acids (PUFAs), e.g., arachidonic acid and docosahexaenoic acid, linked together by a delicate equilibrium. Non-enzymatic and enzymatic oxidation of these PUFAs produces several lipid mediators, all closely associated with neuronal pathways involved in AD neurobiology, suggesting that an interplay among lipids occurs in brain tissue. In this complex GP meshwork, the search for a specific modulating enzyme able to shift the metabolic pathway towards a neuroprotective role as well as a better knowledge about how lipid dietary modulation may act to slow the neurodegenerative processes, represent an essential step to delay the onset of AD and its progression. Also, in this way it may be possible to suggest new preventive or therapeutic options that can beneficially modify the course of this devastating disease.



*Abbreviations:* 2-AG, 2-arachidonoylglycerol; 4-HNE, 4-hydroxynonenals; 4-HHE, 4-hydroxyhexenal; AA, arachidonic acid; Aβ, β-amyloid; ADAM, A Disintegrin And Metalloprotease; ADAPT, Alzheimer's Disease Anti-inflammatory Prevention trial; AD, Alzheimer's disease; AEA, arachidonyl-ethanolamide (anandamide); APP, amyloid precursor protein; BACE1, β-site APP cleavage enzyme; BAD, BCL-2-associated death promoter; BAX, BCL-2-associated X protein; BBB, blood–brain barrier; BCL-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; CA1, cornu ammonius 1; $CB_1$, cannabinoid receptors of type 1; $CB_2$, cannabinoid receptors of type 2; CNS, central nervous system; COX, cyclooxygenase; $cPLA_2$, cytosolic phospholipase $A_2$; DHA, docosahexaenoic acid; EC, endocannabinoid; EPA, eicosapentaenoic acid; EPOX, epoxygenases; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; FAAH, fatty acid amidohydrolase; GP, glycerophospholipid; CSF, cerebrospinal fluid; GSK-3, glycogen synthase kinase 3; HETE, hydroxyeicosatetraenoic acid; isoF, isofuran; isoK, isoketal; isoP, isoprostane; IL, interleukin; JNK/SAPK, c-Jun N-terminal kinase/stress-activated protein kinase; LA, linoleic acid; LC-ESI-MS, liquid chromatography electrospray ionization mass spectrometry; LC-FACS, long-chain fatty acyl-CoA synthetase; LOX, lipoxygenases; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; LPI, lysophosphatidylinositol; LPS, lysophosphatidylserine; LT, leukotriene; LTP, long term potentiation; LX, lipoxin; MAPK, mitogen-activated protein kinase; MCI, mild cognitive impairment; MDA, malondialdehyde; mGluR, metabotropic glutamate receptor; MaR, maresin; NF-kB, nuclear factor-kappa B; NF, neurofuran; NFT, neurofibrillary tangle; NK, neuroketal; NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate glutamate receptor subtype; NOS, nitric oxide synthase; NP, neuroprostane; NP, neuroprotectin; NSAID, non-steroidal anti-inflammatory drug; PAF, platelet activating factor; PAFR, platelet activator factor receptor; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PKC, protein kinase C; $PLA_2$, phospholipase $A_2$; PG, prostaglandin; PI, phosphatidylinositol; PMN, polymorphonuclear neutrophils; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; RAR, retinoic acid receptor; rCBF, regional cerebral blood flow; ROS, reactive oxygen species; RPE, retinal pigment epithelium; Rv, resolvin; RXR, retinoid X receptor; SP, senile plaque; $sPLA_2$, secretory phospholipase $A_2$; TNF-α, tumor necrosis factor-α; TRPV1, transient receptor potential vanilloid 1; TX, thromboxane.

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**Contents**



## 1. Introduction

It has long been known that in several chronic diseases with genetic and lifestyle components (e.g., dietary factors), there is also a perturbed intracellular lipid metabolism. Therefore, a lipidomic approach was recently developed to better understand the lipid molecular profile not only in cardiovascular but also in neurodegenerative diseases [1]. Alzheimer's disease (AD) is the most common form of dementia and, at present, there is still no a curative treatment for this devastating disease [2]. Actually, the lack of effective treatments is due to complexity of the pathophysiology of the disease that may have multifactorial components. Growing evidence supported the influence of lipid changes in the process of normal cognitive aging and in the etiology of age-related neurodegenerative diseases, although it remains open the question if altered brain lipids levels are cause or consequence of aging and/or AD or if there is a threshold in these changes which may result in normal or pathological conditions [3].

Dementia is not considered only a neurological disease but a scary and alarming social problem, especially if we consider the impressive proportions that it will reach in the next years especially when one considers the staggering proportions that will reach in the coming years. In fact, the 2010 estimates suggested 5.3 million of AD cases in the US [4], with >26 million patients with AD worldwide, and an expected increase to more than 106 million by 2050 [5]. From a neuropathological view, AD involves aberrant protein processing and is characterized by the presence of both intraneuronal protein clusters composed of extracellular aggregates of β-amyloid (Aβ) [senile plaques (SPs)], by endoproteolytic processing of the amyloid precursor protein (APP), and paired helical filaments of hyperphosphorilated tau protein [neurofibrillary tangles (NFTs)]. Hyperphosphorylation of tau protein causes neuronal synapse dysfunction and loss of cell-cell communication, whereas disturbed Aβ kinetics may be pivotal for pro-inflammatory pathways that affect cellular integrity [6]. At present, it is difficult to equivocally delineate if these pathological features of AD are causative or consequential, and the therapeutic challenge needs firstly of identifying the way-triggers that compromise cellular integrity [7]. Aβ induces lipid peroxidation and its sequelae could lead to neuroapoptosis [8], but it is equally true that the altered lipid signaling could exacerbate the pathological features of disease. However, the hypothesis that Aβ is the key pathologic factor affecting the disease process is strongly challenged by the finding that immunization with pre-aggregated $A\beta_{1-42}$ (AN1792) resulted in almost complete removal of the SPs from the brain of the patients but did not prevent progressive cognitive and clinical decay [9]. These negative finding have been recently echoed by the failure in two large Phase III clinical trials of semagacestat, a compound that inhibits γ -secretase, the pivotal enzyme that generates Aβ, although the drug showed to dramatically reduce the production of Aβ in the central nervous system (CNS) of humans [10]. Indeed, Aβ may have a physiological role in modulating synaptic plasticity and hippocampal neurogenesis [11]. Aβ deposition may simply represent a host response to an upstream pathophysiologic process or serve a protective function likely as an antioxidant/metal chelator [11].

In neurodegenerative process, the large attention devoted to lipids has ancient origin. In fact, Alois Alzheimer first described "the extraordinarily strong accumulation of lipoid material in the ganglion cells, glia and vascular wall cells" in the human brain of demented patient [12]. However, only in recent years thanks to impressive progress in imaging mass spectrometry (IMS), especially matrix-assisted laser desorption and ionization (MALDI)–IMS, it was possible to visualize in tissue sections the distribution of various lipid bio-molecules [13] and their endogenous metabolites, so creating an increasingly important research area around the role of cholesterol and other lipid components into pathogenesis of cognitive disorders. In fact, the brain is the most cholesterol-rich organ in the body, containing approximately 25% of total [14] where it is unesterified and it resides in the myelin sheaths and in the plasma membranes of astrocytes and neurons. Furthermore, neural membranes are composed of glycerophospholipids (GPs), sphingolipids, and proteins asymmetrically distributed between the two leaflets of lipid bilayers. In addition to structural integrity role to neural membranes, GPs, sphingolipids, and cholesterol belong to the signal transduction network that conveys extracellular signals from the cell surface to the nucleus inducing a biological response at the gene level. This is performed by second messengers (bioactive lipid mediators) through nuclear pores (large proteinaceous assemblies) that provide the sole gateway for the exchange of material between cytoplasm and nucleus lipid mediators [15]. Levels of GPs are decreased in brain autopsy samples from AD patients compared to age-matched controls [16] accompanied by increased activities of lipolytic enzymes and elevated concentrations of phospholipid degradation metabolites [17]. This emphasizes the possibility that a specific diet, in particular the Mediterranean dietary pattern and its nutraceutical properties, could modify the progression of AD by interfering with