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Exploring Lipid Biomarkers of Alzheimer's Disease Using Advanced LC–MS/MS-Based Metabolomic Approaches

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ABSTRACT

Alzheimer's Disease (AD) is a progressive neurodegenerative disease that results in the loss of memory, motor function, ability to think, and other basic functions required for day-to-day life. The causes of the disease are still being investigated, but scientists and researchers have mostly agreed on one of the major genetic contributions to the disease. The excess buildup of two proteins, Tau and β-amyloid, limits communication between nerve cells or neurons. The buildup of these proteins only increases with the progression of the disease. This paper will discuss the genetic causes of AD, the process behind the formation of neurofibrillary tangles and amyloid plaques, recent neuroimaging techniques that help diagnose the disease, current symptomatic treatments, and upcoming future treatments that may be able to slow the progression of the disease significantly.

Keywords: Alzheimer's Disease, Lipidomics, LC-MS/MS, Biomarker Discovery.

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INTRODUCTION

Alzheimer's disease (AD), the predominant form of dementia, exhibits similar epidemiological trends and represents an urgent and escalating challenge worldwide. In the United States, approximately one in nine individuals (10.8%) age 65 and older suffer from AD, with an annual incidence of 1275 new cases per 100,000 persons.[1,2]

Current challenges

Patients with AD exhibit a substantial accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) within their brains, accompanied by a cascade of pathological processes such as neuroinflammation, synaptic dysfunction, mitochondrial and bio-energetic disturbances, as well as vascular abnormalities. Collectively these processes may; https://doi.org/10.1038/s41392-024-01911-3 ultimately lead to the death of neurons.[3,4] AD can be categorized into two types: early-onset familial Alzheimer's disease (FAD) and late-onset Alzheimer's disease (LOAD). FAD is rare (approximately 5% of AD cases) with typical disease onset at 65 years or younger, usually caused by gene variants of amyloid pre cursor protein (APP), presenilin (PSEN1) and PSEN2. LOAD is more common (~ 95% of AD cases) with disease onset older than 65 years and is associated with a combination of genetic (such as apolipo-protein E ε4 allele), environmental, and lifestyle factors [5]. In addition to these pathological hall marks, multiple alterations converge in the pathogenesis of AD. Elevated levels of inflammatory markers in AD patients indicate that neuroinflammation plays a significant role in disease pathogenesis [6] additionally, mitochondrial defects have been implicated in the exhaustion of nerve cells [7]. The disease is further characterized by disrupted production of trophic factors, neurotransmitters, and neuromodulators [8], as well as impaired degradation pathways, including endolysosomal anomalies [9,10], autophagy defects [11], and dysfunction of the ubiquitin-proteasome system [12].

Role of lipids

Lipids are key biological molecules that mediate cellular and organismal processes. It's been widely recognized that lipids are multi-functional. For instance, they serve as essential structurecomponents of cellular membranes, creating a selective barrier that separates the cell from its surroundings and ensures the compartmentalization within the cell [13]. Lipids are also crucial in energy metabolism, providing the cell with necessary fuel [14]. Moreover, they actively participate in signal transduction, either by functioning directly as signaling molecules or indirectly by influencing membrane fluidity, enabling post-translational modifications, or facilitating allosteric modulations [15]

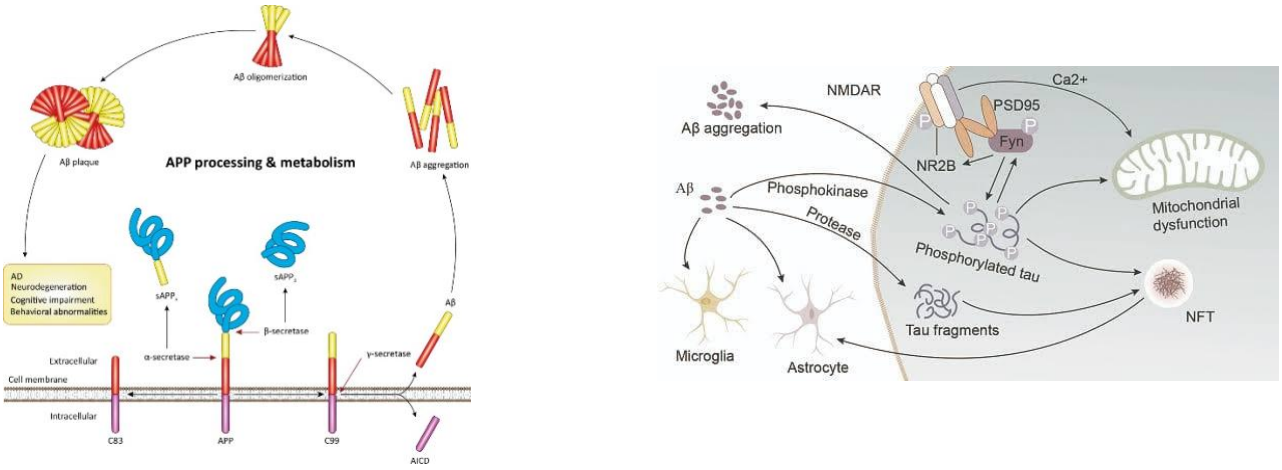

Figure 1: Interaction between AB and Tau in the pathogenesis of Alzheimer's Disease)

Lipid-related risk genes

In addition to senile plaques and neurofibrillary tangles, a third pathological hallmark in AD brain tissue, "adi pose inclusions" or "lipoid granules", was described in Dr. Alois Alzheimer's original report of AD in 1907 [16], this early suggestion of aberrant lipid metabolism has largely remainunderstudied over the past century, partially due to limited techniques for pursuing this direction, as well as the intensive focus on other disease hypotheses (such as Aβ and tau). A large body of emerging data including the recent genome-wide association studies (GWAS) [17,18],

Scope

In this review, we will first consider the role of apolipoprotein E (apoE) in lipid homeostasis in the central nervous system (CNS). We will then summarize data on the effects of APOE genotype on apoE function and lipid trafficking in normal functions and in pathogenesis. Finally, we will speculate on ways to increase lipidation of apoE with the goal to decrease apoE-associated CNS impairments

Methods

The participants' classification was accomplished according to a neuropsychological evaluation (AD Co-operative Study ADL Scale for Mild Cognitive Impairment (ADCS ADL-MCI) [19], Clinical Dementia Rating (CDR) [20], Functionality Assessment Questionnaire (FAQ) [21], Mini-Mental State Examination (MMSE) [22], Repeatable Battery for the Assessment of Neuropsychological Status-Delayed Memory (RBANS.DM) [23] and CSF biomarkers (ß-amyloid-42, total tau (t-tau) and phosphorylated tau (p-tau)), following the recommendations of the National Institute on Aging-Alzheimer's Association (NIA-AA) [24]

Lipid Peroxidation Compounds Determination and Samples Analysis.

Blood samples from participants were collected between 8 and 10 a.m. following the established clinical procedures, and were centrifuged for 10 min at 2000 × g. The plasma fraction was separated in a new tube with butylated hydroxytoluene (BHT) as the antioxidant, and stored at −80°C before analysis. The treatment and analysis of the samples were carried out as described by Peña-Bautista et al.[25]

Lipidomics in Alzheimer's disease

Lipids are made up of a wide range of chemically unique molecules that have different backbone structures and are made up of combinations of long chain fatty acids that are soluble in organic solvents but not in water. Currently, lipids are divided into eight categories that each comprise several types and subclasses of molecules: glycerol phospholipids, fatty sphingolipids acyls, (also glycerolipids, linked to mitochondrial dysfunction in type 2 diabetes and insulin resistance) ,[26]

Lipidomics has been increasingly being employed to investigate lipid dysfunction in conjunction with clinical treatment and to offer important information for the pathophysiology of various disorders [27]

Biomarkers

The NIA-AA and the International Working Group (IWG) consider AD as a slowly progressive neurological disease that begins before the onset of clinical symptoms. Indeed, AD is represented as a continuum that evolves in three stages, asymptomatic (preclinical AD), predementia (MCI due to AD), and dementia (due to AD) [28,29,30].

Among the pathophysiological markers of AD [31] include the specific presence of amyloid pathology (decreased Aβ1-42 peptide CSF levels or accumulation of the amyloid tracer in PET imaging) and Tau pathology (elevated Tau and phosphorylated Tau protein CSF levels or accumulation of the Tau tracer in PET imaging). Moreover, topographical markers for AD include volume modifications in the brain (temporo-parietal, hippocampal atrophy, cortical thickness) assessed by magnetic resonance imaging (MRI) and glucose hypo-metabolism measured by fluoro-deoxy-glucose (FDG)-PET [32]

Research Models Used

In order to both study the underlying mechanisms and to test and identify possible preventative strategies, AD models [33] range from in vitro cell culture models (two dimensional (2D) or three-dimensional (3D)) to animal models. Generally, 2D cell culture models lack cues provided by the extracellular matrix (ECM). These models are easy to maintain and cost-effective but do not allow the study of glia-neuron communication and crosstalk [34]. 3D models include neurospheroids [35], organ-on-a-chip devices [36], and engineered brain tissue [37], mimicking the brain's

complexity; however, they are more difficult to engineer and maintain. Animal models are required for studying both physiological and behavioral mechanisms of AD, but interspecies differences may result in unexpected results in clinical trials [38,39].

Current Treatments and Prevention Strategies for Alzheimer's Disease

Drug Treatments

Current drug treatments for AD are symptomatic-based rather than curative to limit the progression of cognitive symptoms and behavioral and psychological symptoms of dementia (BPSD). Four drugs (donepezil, memantine, galantamine, rivastigmine) are approved on the market and belong to two families: anticholinesterase inhibitors and anti-glutaminergics. These treatments are delivered through the oral or transdermal route [40,41].

The BBB represents a challenge for CNS drug delivery, and many strategies have been developed to address this challenge [42]. Drug efficacy may also be reduced due to age-related modifications in neuronal membranes and membrane receptors, which is not necessarily considered in pre-clinical studies. Indeed, a recent study showed changes in the microdomains of synaptosomes isolated from aged mice, which increased their response to amyloid stress and inhibited the neuroprotective effects of the ciliary neurotrophic factor [43].

Prevention Strategies for Alzheimer's Disease

A review of the current literature highlights the interest in prevention and non-drug therapies, specifically for MCI or the preclinical stage. As discussed above, AD abnormalities such as Abeta-induced synaptic dysfunctions or endosomal pathway blockade occur early, progressing with time, even over decades, by which time the available treatments have only modest effects. The decreased cognitive performance begins around midlife from 45 years [44] and increases with age due to structural and functional changes in the brain (for instance, regional brain volumes and integrity of the white matter, reduction in the fluidity of brain membranes, and changes in lipid composition) [45,46–48].

Biomarker Related Diagnostic Techniques

The use of non-invasive imaging biomarkers for the monitoring and development assessment of AD grips important clinical application. Neuroimaging techniques have the advantages to provide noninvasive insights into brain functionality, metabolic process and anatomy. Several non-invasive and highly sensitive imaging techniques have been explored for the early diagnosis of AD, such as PET, FDG (fluorode-oxyglucose)-PET, magnetic resonance imaging (MRI), and Computed tomography (CT). These methods are valued for their simplicity, rapid response, and accuracy [49–53]. Moreover, it is also considered a novel route to use in the case of high-risk people

affected by AD. Prof. E.D. Smith Dphil et al. successfully checked the performance of CT in several AD patients [54].

Clinical applications of biomarkers

The diagnosis of AD has evolved in recent years, transitioning from a syndromal framework to a biological basis. In 2024, the National Institute on Aging and the Alzheimer's Association (NIA-AA) workgroup published updated research guidelines for the diagnosis and staging of AD,[55]

Challenges

The on-time monitoring of AD with the help of diagnostic tools on the basis of effective nanoparticles have attracted more attention from researchers. Plasmap-tau231andp-tau217 are blood-based biomarkers strongly linked to AD pathology, reflecting both early Aβ buildup and advanced tau deposition [56]. Although blood-based biomarkers testing is less invasive, moreaccessible, and cost-effective than PET imaging or lumbar puncture [57], its clinical application is hindered by the ultra-low concentrations of biomarkers, and the difficulty is differentiating pathological signals from normal physiological levels [58]. Moreover, identifying accurate and specific biomarkers from neuroimaging data presents a significant challenge, particularly when aiming to characterize distinct populations and brain regions [59]. Likewise, obesity and metabolic syndrome have been linked to reduced plasma NFL concentrations, potentially attributable to increased blood volume in affected persons, which may dilute biomarkers levels. However, t-tau concentrations show a positive correlation with body index, indicating that metabolic factors may influence specific biomarkers in distinct ways [60,61].

Future Perspective

Future perspectives in lipidomics A remarkable expansion in lipidomics technologies, supported by the parallel development of computational tools, has positioned lipidomics and its applications at the forefront of modern biology and biomedicine. However, several open questions remain and define future directions in technological development (Box 6). Among these, a key challenge is the functional interpretation of lipid compositional changes. Current views on lipid functions are largely centred around biochemical pathways[62], biophysical ontologies[63], and fragmented knowledge of lipid-protein interactions in signalling. However, lipids rarely act at the level of individual species; instead, they function as supramolecular assemblies in the form of organelle-specific membranes and specialized membrane domains. Such lipid collectives most likely represent the true functional units responsible for biological activity; however, they remain challenging to define both qualitatively and quantitatively[64,65].

CONCLUSION

The recent failure of clinical trials aimed to control Aβ production has redirected the focus of preclinical drug discovery and academic research to the identification of new therapeutic targets and early causes of AD, including altered brain energetics and mitochondrial dysfunction. The use of metabolomics in AD research is gaining momentum because it enables the monitoring of changes in numerous interconnected networks that are crucial for comprehending complex metabolic abnormalities.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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