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Abstract

According to the World Health Organisation (WHO), the number of people suffering from Alzheimer's disease (AD) worldwide is around 18 million. The prevalence of AD doubles every five years between 65 and 85 years of age and it is estimated that due to the ageing population, 34 million people will suffer from AD by 2025. The WHO has also stated that if AD onset were delayed by 5 years, the number of cases worldwide could be halved. Currently there are no curative or disease-stalling treatments for AD and a major research effort is underway in order to better understand the molecular and cellular details of the pathways that result in this devastating neurodegenerative disorder. This research is critical if effective therapeutics are to be developed.

Keywords

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Lipids and Alzheimer's disease

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According to the World Health Organisation (WHO), the number of people suffering from Alzheimer's disease (AD) worldwide is around 18 million. The prevalence of AD doubles every five years between 65 and 85 years of age and it is estimated that due to the ageing population, 34 million people will suffer from AD by 2025. The WHO has also stated that if AD onset were delayed by five years, the number of cases worldwide could be halved [1]. Currently there are no curative or disease-stalling treatments for AD and a major research effort is underway in order to better understand the molecular and cellular details of the pathways that result in this devastating neurodegenerative disorder. This research is critical if effective therapeutics are to be developed.

It is a well-known fact that the brain is a lipid-rich organ, with around 50% of its dry mass accounted for by lipids [2]. This is largely due to the myelin that ensheathes neuronal axons. In addition to the insulating function of myelin lipids it is abundantly clear that there are numerous additional pathways by which brain lipid homeostasis may have an impact on (or be altered as a consequence of) AD. The functions of lipids in brain cells include regulation of signalling, transcription, membrane structure, synaptic function, protein processing, protein-protein interactions and more; as will become clear in the brief introduction of the articles (below) appearing in this Special Issue of *BBA: Molecular and Cellular Biology of Lipids* dedicated to Lipids and Alzheimer's disease.

Although keyword searches are an imperfect means of assessing research activity in a particular field, it is interesting to note that in the last two decades the number of publications containing the searchable terms "lipid and Alzheimer" has increased rapidly compared to the number of publications containing each of these terms alone (Fig 1). There appears to be two "bursts" of research activity in the "lipids and AD field". The first was in the early to mid

1990's, a period that coincides with the discovery that APOE genotype is associated with AD risk [3], and the second in the early 2000s, a period that coincides with the discovery that (in retrospective studies) statin use appears to afford protection for AD [4]. Of course these are only examples of research findings that may have sparked further interest in the field; there were clearly many exciting developments in the last two decades that may have contributed to the escalating interest in the possible role that lipids may play in AD.

The goal of this Special Issue of *BBA: Molecular and Cellular Biology of Lipids* dedicated to Lipids and Alzheimer's disease is to provide an overview of current developments and new ideas that may not yet be fully explored. The contributions are in the form of reviews, primary research articles and in some cases a mixture of both. The emphasis for all contributions has been to provide current information that points towards future avenues of research that should be pursued to better understand the relationships between lipid metabolism and AD and, where possible, provide some insight regarding therapeutic targets for the disease. The 29 papers included in this Special Issue are loosely grouped into nine topics: 1. *Genetics, bioinformatics and cutting-edge technology*; 2. *Phospholipases and fatty acids*; 3. *Apolipoproteins and lipid transport*; 4. *Cell membranes and endo/lysosomal lipid transport*; 5. *Sphingolipid pathways*; 6. *Signalling and transcriptional regulation*; 7. *Lipid peroxidation*; 8. *Lipid changes in Alzheimer's disease brain*; 9. *Amyloid- β – lipid interactions and cross-talk*. An intriguing article reviewing the very early history of the lipid-AD connection (dating back to the seminal papers by Alois Alzheimer himself) is also included. These contributions are briefly summarised below.

1. Genetics, bioinformatics and cutting-edge technology

Jones and colleagues outline the rationale and strengths of genome-wide association studies (GWAS) and provide a current update of genes, including CLU (clusterin), associated with AD risk [5]. A surprisingly large number of genes identified by AD association studies are directly involved in lipid pathways and Wollmer has used a bioinformatics approach to interrogate the AmiGo gene ontology database and the AlzGene database in order to generate a comprehensive listing of genes involved in cholesterol metabolism that may be associated with AD risk [6]. Lipidomics has emerged as a powerful technique to identify changes in multiple lipid classes simultaneously. The article by Han sets out the principles of mass spectrometry-based shotgun lipidomics and goes on to report changes in brain ceramide and sulfatide levels in subjects with mild cognitive impairment or AD [7].

2. Phospholipases and fatty acids

Specific fatty acids are known to play important roles in neurobiology. Mucke and Sanchez-Mejia provide an overview of essential fatty acid (EFA) metabolism in the brain and provide evidence indicating altered Group IVA phospholipase A2 (GIVA-PLA₂) activity may contribute to A β -induced pathology in AD ([8], and see cover illustration). On a related subject, Oster and Pillot provide an overview of the multiple protective actions that one specific EFA, docosahexaenoic acid, may exert in the context of A β -induced neurotoxicity [9]. Oliveira and Di Paolo discuss the role of phospholipase D (PLD) in the brain and suggest that that through the regulation of APP processing (and other pathways), PLD isozymes may contribute to AD neurodegeneration [10].

3. Apolipoproteins and lipid transport

One of the seminal findings linking lipids to AD was the identification of the APOE ϵ 4 allele as a significant risk factor [3]. Recent studies shed light on the mechanisms by which apoE

may modulate AD and these findings are comprehensively reviewed by Vance and Hayashi [11]. LaDu and colleagues provide a concise overview of the factors that may be involved in lipoprotein remodelling in the parenchyma and highlight the research questions that should be addressed in order to better understand the processes regulating lipoprotein metabolism in the brain [12]. One area of lipoprotein biogenesis that has attracted attention in the AD context is the so-called LXR-ABCA1-APOE regulatory axis. Lefterov and colleagues review this area and highlight the important role that ABCA1-mediated apoE lipidation may play in regulating A β aggregation and clearance [13]. Kågedal and colleagues report that the intracellular cholesterol transport protein NPC1 is upregulated in AD hippocampal neurons; a finding that is recapitulated in amyloidogenic transgenic mice [14]. Although the physiological implications of increased NPC1 expression remain to be resolved, dysregulated lysosomal lipid trafficking in AD is an area that appears to warrant further attention.

4. Cell membranes and endo/lysosomal lipid transport

In an area linked to the lysosomal system, Potier and colleagues provide a review article dealing with methods for analysing subcellular changes in membrane cholesterol localization and the potential impact this may have on endosome size [15]. A research article by the same group reveals that changes in plasma membrane cholesterol levels may regulate clathrin-mediated APP endocytosis and A β production [16]. The topic of intracellular cholesterol transport and the impact this has on APP processing is explored further in the comprehensive review provided by Burns and Rebeck [17]. This is followed by a detailed review by Vetrivel and Thinakaran covering the important role that membrane lipid rafts play in APP processing in which particular emphasis is placed on the factors that regulate targeting of APP and the β - and γ -secretases to lipid rafts [18].

5. Sphingolipid pathways

Sphingolipids including sphingomyelin (SM) and glycosphingolipids (GSLs) are a component of myelin sheaths and are also highly enriched in lipid raft microdomains within cell membranes. Yanagisawa and colleagues review the role that ganglioside GM1 plays in the regulation of A β conformation and fibrillization [19]. The role that dysfunctional sphingolipid metabolism (particularly involving the production of ceramide and other bioactive metabolites) may play in regulating synaptic function and neurodegeneration in AD is comprehensively reviewed by Haughey and colleagues [20]. An article from my own laboratory demonstrates the potential anti-amyloidogenic action of several structurally related ceramide analogues that are known inhibitors of GSL synthesis [21].

6. Signalling and transcriptional regulation

The crucial function that lipids play in cellular signalling in health and disease is widely recognised. Eckert and colleagues provide a detailed overview of the role that isoprenoids play in regulating small GTPases and present an argument that alterations in protein prenylation may contribute to synaptic dysfunction and other aspects of AD [22]. The potential role that an array of biologically active nuclear lipid mediators may play in regulating gene transcription and the possible impact that this may have on pathways involving oxidative stress, inflammation and apoptosis is brought into the AD context in a thought-provoking article by Farooqui and colleagues [23]. Burris and colleagues provide evidence that 24-hydroxycholesterol binds to two members of the nuclear hormone receptor superfamily, ROR α and ROR γ , thereby suppressing their constitutive transcriptional activity [24]. It is proposed that this may underlie at least a proportion of the protective functions that have been previously ascribed to the LXR agonists such as T0901317 and GW3965 in AD animal models.

7. Lipid peroxidation

There has been a long-standing interest in the role that lipid peroxidation may play in AD pathogenesis. Butterfield and colleagues provide a detailed overview of the deleterious function that the aldehydic lipid peroxidation end-product, 4-hydroxynonenal (HNE), plays in AD pathogenesis by virtue of its capacity to derivitize specific amino acid side chains [25]. A concise review by Pratico highlights the mechanisms by which isoprostanes are formed in the AD brain and the pathways by which these products of arachidonic acid oxidation may induce cellular stress [26].

8. Lipid changes in Alzheimer's disease brain

In addition to changes in lipid peroxidation, there is mounting evidence that changes in lipid synthesis and metabolism are dysfunctional in the AD brain. Three papers focus on different aspects of sterol metabolism in the AD brain. Ledesma and colleagues review the factors that lead to altered cholesterol homeostasis in the ageing brain and the implications this has for AD pathogenesis and treatment [27]. Kolsch and colleagues provide data indicating levels of cholesterol and its precursors lanosterol, lathosterol and desmosterol are reduced in CSF derived from AD patients [28]. A study by Marx and colleagues focuses on the neurosteroids pregnenolone and dehydroepiandrosterone and show that both of these potentially neuroprotective molecules are reduced in AD temporal cortex as compared to control subjects [29].

9. Amyloid- β – lipid interactions and cross-talk

Possibly one of the most studied areas relating lipid metabolism to AD concerns the relationship (and in some instances the direct interaction) between membrane lipids and

processing of APP to generate A β . Bhattacharyya and Kovacs provide strong evidence suggesting that the inhibition of acyl-coenzyme A: cholesterol acyl transferase 1 to prevent intracellular cholesteryl ester accumulation may represent a novel strategy to lower A β generation and accumulation in the AD brain [30]. A review article from Hartmann and colleagues provides a detailed overview of the mechanisms by which membrane lipid structure may modulate APP processing and an intriguing regulatory feedback loop that involves the modulation of lipid homeostasis by APP cleavage products is described [31]. Sanders and colleagues describe another recently identified interaction between membrane lipid and APP that relies on the direct binding of the APP C99 C-terminal transmembrane domain to cholesterol; an interaction that favours C99 localization in lipid rafts thus enhancing amyloidogenic processing [32].

The papers listed in abovementioned sections of this Special Issue of *BBA: Molecular and Cellular Biology of Lipids* dedicated to Lipids and Alzheimer's disease are prefaced by an intriguing historical review article by Foley who examines the very earliest reports describing alterations in lipid levels associated with AD pathology [33]. Surprisingly, the earliest papers from Alois Alzheimer and others published a century ago dedicate substantial discussion to the occurrence of glial lipid inclusions in AD brain sections. It is only relatively recently though that powerful genetics studies combined with modern molecular and cell biology approaches are revealing the precise details of the pathways that may link lipid pathways with AD pathogenesis. The articles briefly introduced above provide a broad cross-section of the fertile "Lipids and AD field" which is now providing tangible leads for therapeutic exploitation.

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Figure legend

Figure 1. Relative number of publications appearing in PubMed

(<http://www.ncbi.nlm.nih.gov/pubmed>) that are identified by the term “Lipid” (blue line),

“Alzheimer” (green line) or “Lipid and Alzheimer” (red line) are plotted for the period

covering 1980 to 2009. The 2009 vales are arbitrarily assigned a value of 100. The numbers

of papers appearing in 2009 in each of the categories were: Lipid, 39,324; Alzheimer 3,702;

Lipid and Alzheimer, 436.

Figure 1

