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Evidence of altered phosphatidylcholine metabolism in Alzheimer's disease

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ABSTRACT

Abberant lipid metabolism is implicated in Alzheimer's disease (AD) pathophysiology, but the connections between AD and lipid metabolic pathways are not fully understood. To investigate plasma lipids in AD, a multiplatform screen (n = 35 by liquid chromatography–mass spectrometry and n = 35 by nuclear magnetic resonance) was developed, which enabled the comprehensive analysis of plasma from 3 groups (individuals with AD, individuals with mild cognitive impairment (MCI), and age-matched controls). This screen identified 3 phosphatidylcholine (PC) molecules that were significantly diminished in AD cases. In a subsequent validation study (n = 141), PC variation in a bigger sample set was investigated, and the same 3 PCs were found to be significantly lower in AD patients: PC 16:0/20:5 ($p < 0.001$), 16:0/22:6 ($p < 0.05$), and 18:0/22:6 ($p < 0.01$). A receiver operating characteristic (ROC) analysis of the PCs, combined with apolipoprotein E (ApoE) data, produced an area under the curve predictive value of 0.828. Confirmatory investigations into the background biochemistry indiciated no significant change in plasma levels of 3 additional PCs of similar structure, total choline containing compounds or total plasma omega fatty acids, adding to the evidence that specific PCs play a role in AD pathology.

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1. Introduction

It is estimated that there are 24 million persons worldwide with Alzheimer's disease (AD), a figure that is expected to double every 20 years until at least 2040 (Mayeux and Stern, 2012). The size of the affected population and the nature of the disease poses a huge challenge to patient health and care organizations around the world. However, the full physiological mechanism of AD is yet to be fully elucidated, and there is thus a need to identify both disease-relevant pathways for targeted treatment as well as molecular markers to aid in clinical diagnosis and monitoring disease progression (Jack et al., 2011).

Previous research has indicated that lipid molecules play a role in AD, and these have frequently been reported at abnormal concentrations in AD tissue (Bradley et al., 2012; Mangialasche et al., 2012; Wang et al., 2012). Many of these prior studies were conducted using a targeted experimental design, in which known pathways of disease were investigated in a focused manner, based on previous hypotheses of disease pathogenesis. Such targeted approaches have provided evidence suggesting a link between AD and high-density lipoproteins (HDLs) and related proteins in plasma (Di Paolo and Kim, 2011; Han et al., 2011; Lovestone et al., 1996; Orešič et al., 2011; Thambisetty et al., 2010; Whiley and Legido-Quigley, 2011). In addition, the lipoproteins apolioprotein E (ApoE) and apolipoprotein J (ApoJ) have been linked to AD via both genetic and proteomic studies

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(Shi et al., 2012; Thambisetty et al., 2010). ApoJ has been found as a component of HDL and is thought to be a chaperone of amyloid protein, a protein known to be heavily involved in the pathology of AD (Hye et al., 2006; Thambisetty et al., 2010).

An alternative to such targeted discovery is the use of non-targeted small-molecule analysis, commonly termed metabolomics. In contrast to targeted studies, metabolomics attempts to analyze an expansive range of lipids and small metabolites. In metabolomics studies, small-molecule (size <1000–1500 Da) fingerprints are collected, and subsequent data mining can provide unexpected leads into the biochemistry of the disease. The range of molecules studied depends on the analytical platform used and on the applied methodology, with certain combinations of techniques achieving higher specificities (Martin et al., 2007; Whiley et al., 2012).

Non-targeted analysis of AD has previously been reported (Greenberg et al., 2009; Han et al., 2011; Orešič et al., 2011). The majority of these previous studies focus on plasma samples, analyzed either by liquid chromatography–mass spectrometry (LC-MS) (Greenberg et al., 2009; Orešič et al., 2011) or direct infusion mass spectrometry (DIMS) (Han et al., 2011). Interestingly, the significant molecular features identified in these previous works were lipid molecules. One of these studies reported an increase in ceramide (CM16) levels and a decrease in sphingolipid (SP16) levels in the plasma of AD patients (Han et al., 2011). Another investigation identified a phosphatidylcholine (PC), PC 16:0/16:0, as 1 of a cluster of 3 metabolites thought to be predictive markers of AD development in individuals with mild cognitive impairment (MCI) (Orešič et al., 2011). The third example reported a number of bile acids (GCA, GDCA, and GCDCA) that increase in MCI and AD plasma (Greenberg et al., 2009). The latter publication went on to recommend further investigation into the lipid fraction of the AD metabolome.

With these previous results in mind, we developed a non-targeted lipidomics to investigate plasma lipid species in AD. In the study described here, an initial metabolite screen involving LC-MS and nuclear magnetic resonance (NMR) profiling was performed, and the resultant data were analyzed using multivariate statistical modeling. The results of this "screen" phase indicated that 3 lipid phosphatidylcholine molecules (PC16:0/20:5, PC16:0/22:6, and 18:0/22:6) significantly decrease in AD plasma compared to controls. We then performed a multiplatform "validation", designed to both confirm the findings, as well as provide further biological reasoning regarding the changes observed. Fig. 1 illustrates the overall study design and the individual analytical stages incorporated into each phase (screen and validation).

2. Methods

2.1. Sample cohorts

Plasma for the 2 experimental phases (screen and validation) was collected from 2 clinical cohorts, the AddNeuroMed cohort and the King's College London Dementia Case Register (DCR). Ethical approval was awarded for all cohorts in the corresponding centers of collection. The cohorts are described in full in the Supplementary Information section and are summarized in Supplementary Table S1. Further details regarding sample collection and the AddNueroMed and DCR cohorts can be found elsewhere (Hye et al., 2006; Lovestone et al., 2009; Simmons et al., 2009; Thambisetty et al., 2010).

2.2. Procedures

The study was divided into 2 major sections, designated throughout as "screen" (the initial screening phase) and "validation" (the subsequent confirmatory phase).

2.2.1. Screen phase

The screen phase of the study used 2 analytical platforms (LC-MS and NMR) to perform non-targeted analysis. LC-MS analysis was completed in a cohort of 35 age- and sex-matched human plasma samples (10 AD, 10 MCI, 15 control) (Supplementary Table S1). A complete method description is provided in the Supplementary Information section (under the heading "Screen LC-MS").

A separate set of 35 samples (13 AD, 12 MCI, 10 control) (Supplementary Table S1) was analyzed by ^{1}H-NMR spectroscopy at 600.29 MHz using a Bruker Advance 600 spectrometer (Bruker Biospin, Coventry, UK). Standard 1D, Carr-Purcell-Meiboom-Gill spin-echo (CPMG), and J-resolved (JRES) spectra were acquired for metabolomics and metabolite measurements. Further details regarding sample preparation and analysis are described in the Supplementary Information.

2.2.2. Validation phase

Validation was completed in 3 parts. First, a comprehensive LC-MS lipidomics method was applied to a larger sample set to confirm the initial PC observations from the screen phase; then,

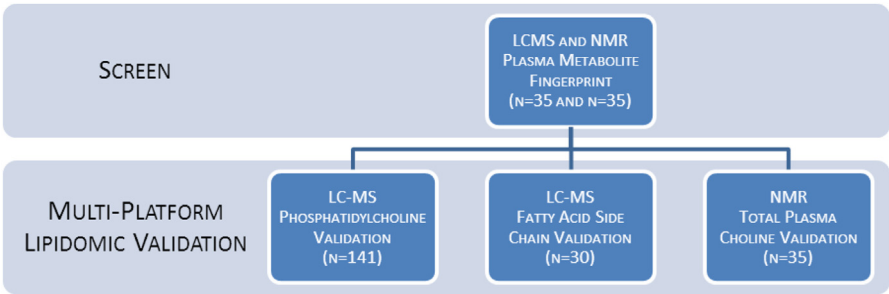

Fig. 1. Experimental pipeline overview. Initially a typical liquid chromatography–mass spectrometry (LC-MS) and nuclear magnetic resonance (NMR) metabolite screen led to the identification of 3 phosphatidylcholine (PC) molecules that significantly decrease in individuals with Alzheimer's disease (AD) compared to controls. This led to a comprehensive multiplatform lipidomic analysis consisting of 3 major components. During NMR analysis of patient plasma, particular attention was focused on total choline-containing molecules, a vital component of the phosphatidylcholine molecules identified in the screen experimental section. LC-MS analysis of plasma fatty acids (arachidonic acid, docosahexaenoic acid, and eicosapentaenoic acid) was also conducted. Again, as with NMR analysis of choline species, these fatty acid species are components of phosphatidylcholine structures indentified in the screen experimental section. Finally, comprehensive lipidomic validation was conducted with a large sample cohort. Here a specially developed lipidomic LC-MS method was applied to increased sample numbers. The method is able to detect >3000 lipid markers from a single plasma extraction.

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