Evidence of altered phosphatidylcholine metabolism in Alzheimer's disease


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; Oresic et al., 2011; Thambisetty et al., 2010; Whiley and Legido-Quigley, 2011). In addition, the lipoproteins apolipoprotein E (ApoE) and apolipoprotein J (ApoJ) have been linked to AD via both genetic and proteomic studies.
method was applied to increased sample numbers. The method is able to detect
infusion mass spectrometry (DIMS) (Han et al., 2011). Interestingly,
plasma compared to controls. We then performed a multiplat-
certain combinations of tech-
the range of molecules studied depends on the analytical platform used and
on the applied methodology, with certain combinations of tech-
achieve higher specificities (Martin et al., 2007; Whitey et al., 2012).
Non-targeted analysis of AD has previously been reported
(LC-MS) (Greenberg et al., 2009; Orešić et al., 2011). The majority of these previous studies focus on plasma samples, analyzed either by liquid chromatography–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 pre-
dictive markers of AD development in individuals with mild
cognitive impairment (MCI) (Orešić et al., 2011). The third example
screen analyzed 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
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 multi-
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 Add-
NeuroMed 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 1H-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,
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