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Altered brain high-energy phosphate metabolism in mild Alzheimer's disease: A 3-dimensional ^{31}P MR spectroscopic imaging study

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ABSTRACT

In Alzheimer's disease (AD), defects in essential metabolic processes for energy supply and phospholipid membrane function have been implicated in the pathological process. However, post-mortem investigations are generally limited to late stage disease and prone to tissue decay artifacts. In vivo assessments of high energy phosphates, tissue pH and phospholipid metabolites are possible by phosphorus MR spectroscopy (^{31}P–MRS), but so far only small studies, mostly focusing on single brain regions, have been performed. Therefore, we assessed phospholipid and energy metabolism in multiple brain regions of 31 early stage AD patients and 31 age- and gender-matched controls using ^{31}P–MRS imaging. An increase of phosphocreatine (PCr) was found in AD patients compared with controls in the retrosplenial cortex, and both hippocampi, but not in the anterior cingulate cortex. While PCr/inorganic phosphate and pH were also increased in AD, no changes were found for phospholipid metabolites. This study showed that PCr levels are specifically increased in regions that show early degeneration in AD. Together with an increased pH, this indicates an altered energy metabolism in mild AD.

1. Introduction

Alzheimer's disease (AD) is the main cause of dementia in the elderly, responsible for about half of the nearly 47 million dementia cases worldwide (Report, 2015). Although the disease is defined by the accumulation of amyloid beta plaques and neurofibrillary tau tangles in the brain (Braak and Braak, 1991), other pathological processes can be identified such as oxidative stress, vascular dysfunction, and inflammation (Akiyama et al., 2000; de la Torre, 2004; Markesbery, 1997). Additionally, defects in essential metabolic processes for energy supply and membrane function have been implicated in AD (Lynn et al., 2010; Nitsch et al., 1992).

The human brain is highly vulnerable to disturbances in energy metabolism, due to its relatively large energy consumption. Previous AD studies demonstrated alterations in global and cellular energy metabolism. FDG-PET studies have shown glucose hypometabolism in the retrosplenial cortex (RSC) and medial temporal lobe in people with mild cognitive impairment (MCI) and AD patients, as well as in cognitively normal carriers of the APOE ε4 allele (Nestor et al., 2003; Pietrini et al., 2000; Reiman et al., 2001; Reiman et al., 2005). Furthermore, the enzyme creatine kinase (CK), obtained from post-mortem AD tissue, shows reduced activity compared with samples that are free from neurological disease (Aksenov et al., 2000; David et al., 1998). The CK reaction, key to balance brain energy metabolism, can quickly replenish adenosine triphosphate (ATP) from the energy buffer phosphocreatine (PCr), when local energy demands suddenly increase (Lowe et al., 2015). This reaction also enhances the efficiency of mitochondrial oxidative phosphorylation (OXPHOS) by keeping adenosine diphosphate (ADP) sufficiently available (Schlattner et al., 2006) and prevents acidification by maintaining pH (for a review see

Abbreviations: ^{1}H, proton; ^{31}P–MRS, phosphorus magnetic resonance spectroscopy; AC, anterior commissure; ACC, anterior cingulate cortex; AD, Alzheimer's disease; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CK, creatine kinase; Cr, creatine; CSF, cerebrospinal fluid; GM, grey matter; GPCh, glycerophosphocholine; GPEth, glycerophosphoethanolamine; HL, left hippocampus; HR, right hippocampus; LS, least square; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; MRSI, magnetic resonance spectroscopic imaging; NAD(H), nicotinamide adenine dinucleotide; OXPHOS, oxidative phosphorylation; PC, posterior commissure; PCh, phosphocholine; PCr, phosphocreatine; PDE, phosphodiesters; PEth, phosphoethanolamine; Pi, inorganic phosphate; PME, phosphomonoesters; ROI, region of interest; RSC, retrosplenial cortex; WM, white matter

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Wallimann et al., 2011).

One of the earliest pathological changes in AD is synaptic dysfunction, which correlates well with cognitive dysfunction and disease severity (Terry et al., 1991). Alterations in neuronal membrane composition, vital for synaptic transmission, have been linked to synaptic dysfunction in AD (Pomponi et al., 2008). For instance, post mortem studies found reduced levels of the major membrane components phosphatidylcholine, phosphatidylethanolamine and phosphatidylinositol (Nitsch et al., 1992; Pettegrew et al., 2001), as well as altered activity of catabolic and anabolic enzymes, suggesting compensatory metabolic changes to reduce the rate of neuronal membrane loss (Ross et al., 1998).

High energy phosphates, such as ATP and PCr, and metabolites of phospholipid membrane metabolism can be assessed in vivo by phosphorus magnetic resonance spectroscopy (^{31}P–MRS). This technique has been applied in AD (e.g. Forlenza et al., 2002; Mandal et al., 2012; Pettegrew et al., 1994; Smith et al., 1995), but previous studies, essentially focusing on single brain regions, were severely hampered by small sample sizes and low spectral resolution, resulting in a wide disparity in findings. Furthermore, differences in the control groups that were used, in the brain regions that were studied and in the disease stages and medication statuses of the patients, may have contributed to apparent inconsistencies in the literature.

The aim of the current study was to investigate whether abnormal phospholipid and energy metabolism can be detected non-invasively in early stage AD patients by ^{31}P MR spectroscopic imaging (^{31}P–MRSI). This investigation was designed to overcome the limitations of previous studies. First, we performed the measurements at 3 T field strength with proton (^{1}H) decoupling to increase spectral resolution and sensitivity. Secondly, by applying ^{31}P–MRS in a 3-dimensional imaging mode we could investigate multiple brain regions simultaneously. We specifically addressed regions that are of interest in AD, namely, the hippocampus, the RSC, and the anterior cingulate cortex (ACC). Finally, we selected a well-defined drug-naïve patient group and an age- and gender-matched control group.

2. Materials and methods

2.1. Subjects and design

All visits of patients and controls to the Radboud university medical center (Nijmegen, the Netherlands) took place between 2012 and 2015. Patients aged ≥50 years with a diagnosis of possible or probable AD according to the revised National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association 2011 criteria (McKhann et al., 2011) with evidence of the pathophysiological process (i.e. from structural MRI or cerebrospinal fluid biomarker assays) and with a minimum Mini Mental State Examination (MMSE) score of 20, were recruited from the hospital's memory clinic or by referral from regional hospitals. All AD patients participated in a randomized controlled trial on the effect of a medical food on brain phospholipid metabolism (Rijpma et al., 2017; Dutch Trial Register 3346). Only baseline data were used in the current study. Healthy control subjects, age- and gender-matched to the AD group, were screened by telephone before being invited to the clinic. All subjects were drug-naïve for AD medication (cholinesterase inhibitors and NMDA-antagonists) and were free from neurological or psychiatric disorders (other than dementia, for the AD patients). Patients nor healthy controls used nutritional supplements containing docosahexaenoic acid, eicosapentaenoic acid or > 200% of the recommended daily allowance of vitamins B, C, or E. All subjects were screened for MRI contra-indications before inclusion in the study.

Written informed consent was obtained from all subjects and from the informal caregivers of the AD patients. The local ethics committee reviewed and approved the protocol and the study was conducted in accordance with the Declaration of Helsinki.

Medical history, medication use and MMSE were recorded from all subjects, as well as date of birth, sex, ethnicity, smoking habits, alcohol consumption, and family history of AD. Level of education was classified according to Verhage (Verhage, 1964) (comparable with the International Standard Classification of Education) and categorized in three groups: primary education or lower (low), junior vocational training (middle), and senior vocational or academic training (high).

2.2. MR acquisition

MRI and MRS were performed on a Magnetom Tim Trio 3T MR system (Siemens, Erlangen, Germany) with a dual-tuned ^{1}H/^{31}P volume head coil (Rapid Biomedical, Wuerzburg, Germany). High resolution MR images were acquired with a T1-weighted magnetisation-prepared rapid gradient-echo sequence (TR = 2300 ms, TE = 3.16 ms, TI = 1100 ms, 15° flip-angle, 176 sagittal slices, slice-matrix size = 256 × 256 mm, slice thickness = 1 mm, voxel-size = 1 × 1 × 1 mm, TA = 6:25 min).

^{31}P-MR spectra were acquired with whole brain 3D MRSI (a pulse-acquire sequence with 40° flip-angle, acquisition delay of 0.7 ms including 0.3-ms gradient phase encoding time, 512 ms acquisition duration with WALTZ4 ^{1}H decoupling during the first 256 ms with $\gamma B1 = 250$ Hz ensuring $(\gamma B1)^2 > (J_{PH})^2$, TR = 2000 ms, FOV 260 × 260 × 260 mm; matrix size = 10 × 10 × 10, acquisition time 13:08 min). Prior to acquisition, an automatic procedure was applied to optimize the magnetic field homogeneity of a rectangular shim volume maximizing brain coverage while bound by the skull. Subsequently, if necessary, the field homogeneity was further adjusted manually until a value of < 25 Hz was obtained for the full width at half maximum of the absolute-value ^{1}H MR water signal. K-space was sampled with a weighted elliptical phase-encoding scheme with four averages. The volume of interest was centered on the midline and parallel to the line from the anterior commissure to the posterior commissure. Spatial post-processing consisted of zerofilling to a matrix size of 16 × 16 × 16. The nominal volume of the measured voxels is about 17.5 cm^3, the effective voxel at 64% of the spatial response function has a spherical shape with a volume of about 40 cm^3 (Pohmann and von Kienlin, 2001).

2.3. MRS and MRI data analyses

Four regions of interest (ROI) were selected for analysis from the 3D ^{31}P–MRSI data: ACC, RSC, and left and right hippocampus (HL and HR). Guided by the T1-weighted images, the MRSI grid was shifted in the x, y and z dimension to position voxels in the ROI's (by AR; Fig. 1). For the ACC, a voxel was selected anterior to the genu of the corpus callosum, with the inferior border aligned with the line from the anterior commissure to the posterior commissure (AC-PC line), and on the midsagittal plane. For the RSC, a voxel on the midsagittal plane was selected posterior to the splenium of the corpus callosum, with the inferior border aligned with the AC-PC line. For the HL and HR, a voxel was selected at the anterior end of each hippocampus, with the inferior and lateral border of the voxel aligned with the inferior and lateral side of the hippocampus.

The software package Metabolite Report (Siemens Healthcare, Erlangen, Germany) was used for post-processing (i.e. 100 ms exponential filter, zero-filling, phase correction, baseline correction) and for automatic fitting of the spectra in the time-domain using prior knowledge appropriate for ^{31}P MR spectra (own spectral data and from de Graaf (2008)). Eleven well-resolved resonance peaks were fitted: the phospholipid metabolites phosphoethanolamine (PEth), phosphocholine (PCh), glycerophosphoethanolamine (GPEth) and glycerophosphocholine (GPCh), the high-energy phosphorus molecules PCr, ATP (α-ATP, β-ATP and γ-ATP), nicotinamide adenine dinucleotide (NAD(H)) and inorganic phosphate (Pi), and membrane-bound phospholipid (details of this procedure are described in the Appendix).

Both a quantitative evaluation of the fitting results and a visual quality control were performed. Quantitatively, only metabolite fits