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High field ^{1}H MRS of the hippocampus after donepezil treatment in Alzheimer disease

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Abstract

The purpose of this study was to measure metabolite level changes in patients with newly diagnosed Alzheimer Disease (AD) following four months of donepezil treatment. A small number of cognitively normal elderly subjects were also scanned longitudinally (twice within one year) to assess the reproducibility. Short echo-time ^{1}H magnetic resonance spectra were acquired at 4.0 T in the right hippocampus. Subjects were scanned at the time of first diagnosis (prior to receiving donepezil) and then following four months of donepezil treatment (5 mg/day for the first month, 10 mg/day thereafter). Changes in absolute metabolite levels and metabolite ratios were quantified and compared. There was no change in measured cognitive function following four months of donepezil treatment in the AD patients. Decreased levels of *N*-acetylaspartate, choline, *N*-acetylaspartate/creatine, choline/creatine, and myo-inositol/creatine were observed in AD patients after four months of treatment. Cognitively normal elderly subjects showed an increase in myo-inositol/choline ratio following one year. The reduced levels of *N*-acetylaspartate in AD patients indicates continued decline in neuronal function and/or integrity. However decreased levels of choline and myo-inositol/creatine ratio may indicate a positive treatment effect.

Keywords: Alzheimer disease; Dementia; Donepezil; Hippocampus; Magnetic resonance spectroscopy

1. Introduction

Alzheimer disease (AD) is clinically characterized by a progressive loss of cognitive abilities including deterioration in memory, language, visuospatial, and executive function. Cognitive assessments have become the predominant outcome measure to monitor progression in clinical trials, primarily, the Mini-Mental Status Exam (MMSE) (Folstein et al., 1975) and the Alzheimer Disease Assessment Scale–cognitive subscale (ADAS-cog) (Rosen et al., 1984). These tools offer modest sensitivity to AD (Rosen et al., 1984), but lack specificity (Anthony et al., 1982; Fox and Freeborough, 1997; Kantarci et al., 2002; Rosen et al., 1984). Recently, studies have shown that non-invasive neuroanatomical and neurochemical measures such as magnetic resonance

Abbreviations: AD, Alzheimer disease; MCI, Mild cognitive impairment; MMSE, Mini-mental status exam; ADAS-cog, Alzheimer disease assessment scale–cognitive subscale; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, *N*-acetylaspartate; Glu, glutamate; Cho, choline; Cr, creatine; Myo, myo-inositol; ChEI, Cholinesterase inhibitors; DRS-2, Dementia Rating Scale-2; FLASH, Fast low angle shot; TI, Inversion time; TE, Echo time; TR, Repetition time; LASER, Localization by adiabatic selective refocusing; HSVD, Hankel singular value decomposition.

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imaging (MRI) and magnetic resonance spectroscopy (MRS) can be used to evaluate disease progression and response to treatment (Dixon et al., 2002; Fox and Freeborough, 1997; Kantarci et al., 2002; Krishnan et al., 2003). Although the pathological, neuroanatomical and neurochemical abnormalities that occur in AD are not completely defined, there is mounting evidence of both progressive anatomical and chemical changes that involve multiple brain regions. The entorhinal cortex and hippocampus have been implicated early in the pathophysiology of AD (Braak and Braak, 1991), supported by the known role of the hippocampus in memory function (Grady et al., 2001). Post-mortem (Stokes and Hawthorne, 1987) and in-vivo imaging studies have also demonstrated decreased entorhinal cortex and hippocampal volume (Fox et al., 1996) and decreased glucose metabolism (De Santi et al., 2001) at various stages of disease. In addition, the rate of *global* atrophy has been estimated at 2–6% (Fox et al., 2000; Fox and Freeborough, 1997) in AD, supporting the notion that the pathophysiology of AD ultimately spreads to many brain regions.

Neurochemical profiles measured by ^{1}H MR spectroscopy (MRS) typically show decreased *N*-acetylaspartate (NAA) increased myo-inositol (Myo) (Miller et al., 1993; Moats et al., 1994), and increased choline (Cho)/creatine (Cr) ratio (Kantarci et al., 2004) in patients with AD. NAA is present primarily in neurons within the CNS and is mostly absent from glial cells or non-neural tissue. Decreased NAA levels may indicate neuronal loss or damage, mitochondrial dysfunction, or decreased hydration, (Baslow, 2003; Chen et al., 2000; Clark, 1998) while elevated Myo levels have been linked to gliosis, membrane dysfunction, and/or cytoskeletal abnormalities (Ross, 1991). Increased choline may reflect increased membrane phosphatidylcholine breakdown to provide the precursors for acetylcholine synthesis (Kantarci et al., 2004; Klein, 2000). Cognitive decline through the spectrum of normal aging, Mild Cognitive Impairment (MCI), and AD, has been associated with decreased NAA/Myo ratio (Kantarci et al., 2003). While a positive correlation between the magnitude of NAA decrease and the severity of neuropathologic findings (i.e. increased counts of amyloid plaques and neurofibrillary tangles) has also been reported (Klunk et al., 1992).

Although there is clearly mounting evidence that non-invasive imaging markers can be used to identify aspects of AD pathophysiology, monitoring response to therapy has been less well studied. Cholinesterase inhibitors (ChEI) (i.e. donepezil, rivastigmine, and galantamine) have been shown to provide symptomatic treatment for mild–moderate AD, by maintaining or improving cognition, behavior, and global function for 6–12 months (Birks, 2006). Of these drugs, donepezil, which may also have disease modifying properties (Ballard et al., 2005), has been most extensively used and studied. Cholinesterase inhibitors have been shown to affect regional cerebral blood flow (Ceravolo et al., 2004; Nobili et al., 2002), increase glucose metabolism (Tune et al., 2003), modify hippocampal volume (Hashimoto et al., 2005; Krishnan et al., 2003), and have a direct affect on β-amyloid and Tau protein (Francis et al., 2005). In one detailed spectroscopy study, levels of NAA were reported to *increase* from baseline in subcortical gray matter following 12 weeks of therapy (Krishnan et al., 2003).

The purpose of the current study was to measure hippocampal metabolite response to donepezil in newly diagnosed AD patients four months post-treatment using 4.0 T ^{1}H MRS. A previous study demonstrated greater NAA changes in the left hippocampus compared to the right hippocampus in Alzheimer patients when compared to controls (Dixon et al., 2002). Therefore, in the current study, the right hippocampus was chosen so that measured metabolite changes could be attributed primarily to the effect of donepezil, rather than disease progression. The combined use of high magnetic field, small voxel size, and short echo-time MRS incorporating macromolecule subtraction (Knight-Scott, 1999) represents a unique opportunity to critically evaluate MRS as a potentially sensitive biomarker. We hypothesized that following treatment with a ChEI the ^{1}H MRS metabolic profile would be altered in the hippocampi of patients with Alzheimer disease; specifically that NAA would be increased, and that Cho and Myo would be decreased.

2. Methods

2.1. Patient population

Consecutive participants were recruited from the outpatient population of the Aging Brain and Memory Clinic in London, Ontario, Canada. Fifteen participants who met the DSM IV ((APA), 1994) and NINCDS-ADRDA (McKhann et al., 1984) criteria for probable AD consented to participate in this study, which was approved by the University of Western Ontario Health Sciences Research Ethics Board. All experiments were conducted in accordance with the Declaration of Helsinki. Alzheimer patients were not eligible for the study if they were currently in a major depressive episode, psychosis, or acute manic or depressive episode of Bipolar Disorder. Five cognitively normal elderly subjects also consented to participate in this study to assess the reproducibility of the measurements over time. The criteria for control subject inclusion were: 1) no history of memory problems; 2) an MMSE score higher than the appropriate cut-off dementia score taking into account age and education level; 3) Dementia Rating Scale-2 (DRS-2, (Jurica et al., 2001)) age and education corrected MOANS scale score of 9 or higher (Lucas et al., 1998); 4) a clock test with a score greater than or equal to 14 (Sunderland et al., 1989); and 5) no impairment of the seven instrumental activities of daily living questions from the Duke Older American Resources and Services Procedures caused by cognitive decline (Fillenbaum and Smyer, 1981). Normal elderly controls were not eligible for inclusion in this study if they were currently in a major depressive episode, psychosis or acute manic or depressive episode of bipolar disorder, had cognitive impairment on testing, or were not ethnically matched to any of the target case cohorts.

The standardized MMSE and ADAS-cog were administered to probable AD patients before and four months after starting donepezil treatment (5 mg/day for the first month, 10 mg/day thereafter). The MMSE was scored using WORLD backwards rather than serial sevens. Two patients were excluded due to motion artifacts in at least one MRS exam, two patients were excluded because they could not tolerate the repeat MRS scan,