Increased Glucose Concentration in the Hippocampus in Early Alzheimer's Disease Following Oral Glucose Ingestion

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Abstract

Glucose is the primary source of energy for brain cells. Because energy storage in the brain is limited, an uninterrupted supply of glucose and its rapid metabolism are essential for normal cognitive function. This study examined the utility of oral glucose loading and ^{1}H MRS for studying glucose metabolism in early Alzheimer's disease (AD). In a ^{1}H MRS study of 8 patients with probable AD and 28 healthy adults, AD patients exhibited elevated hippocampal glucose concentrations post-glucose ingestion ($p<0.01$). These results suggest that AD leads to an increased steady-state concentration of cerebral glucose due to glucose hypometabolism.

Introduction

Progressive cognitive decline and cerebral glucose hypometabolism are hallmark symptoms of Alzheimer's disease (AD), the most common form of dementia in the elderly (1,2). AD currently has no cure, but disturbances in glucose regulation are a potential treatment target. Our ability to study cerebral glucose metabolism is limited by problems detecting and quantifying cerebral glucose *in vivo.* The use of ionizing radiation in PET limits its use in repeated studies for short-term monitoring of cerebral metabolism. In this study, we examined the feasibility of using ^{1}H MRS to study cerebral glucose regulation in AD through oral glucose loading.

Method

Participants were 8 patients fulfilling the NINCDS-ADRDA criteria for probable AD (mean age 75±8 yrs) and 28 healthy volunteers separated into two age groups: young (mean age 21±3 yrs, N=14), and elderly (mean age 70±9 yrs, N=14). All spectroscopy data were collected from the right hippocampal region at 1.5T, using a STEAM sequence (TE/TM/TR = 20/10/4000 ms, 128 excitations, mean VOI ~ 6 cm^3). ^{1}H MRS data were collected twice from each participant: after an 8-hr fast, and following the ingestion of an 8 oz lemon flavored beverage sweetened with 75 g of glucose. Glucose was quantified from the 3.44 ppm resonance after correcting for overlap from *myo*-inositol, taurine and choline (3). Concentrations were reported in millimoles per kilogram of brain water (4).

Results and Discussion

AD patients, but not healthy adults, exhibited a significant increase in their hippocampal glucose concentration following oral glucose loading ($p<0.01$, Figs. 1 & 2). Our data show that AD leads to an increased steady-state cerebral glucose concentration due to glucose hypometabolism. This elevation of cerebral tissue glucose indicates a problem early in the glycolytic chain, since glucose and fructose are the only constituents in the chain that would contribute to the 3.44 ppm resonance. Our results could be accounted for by a reduction in the activity of any of the enzymes that catalyze the first steps of glycolysis (i.e. hexokinase (HK), phosphohexose isomerase, and phosphofructokinase (PFK)). Impaired HK and PFK activity have been reported in AD, though the findings have not been consistent (5). Regardless of the cellular mechanisms responsible for the observed glucose concentrations, our study demonstrates the feasibility of studying cerebral response to glucose loading in AD with ^{1}H MRS.

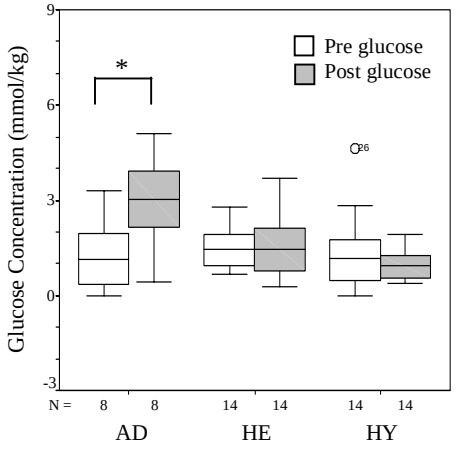

Figure 1. Box plot showing significantly increased hippocampal glucose concentration in the AD patients post glucose loading. AD=Alzheimer's disease; HE=healthy elderly; HY=healthy young.

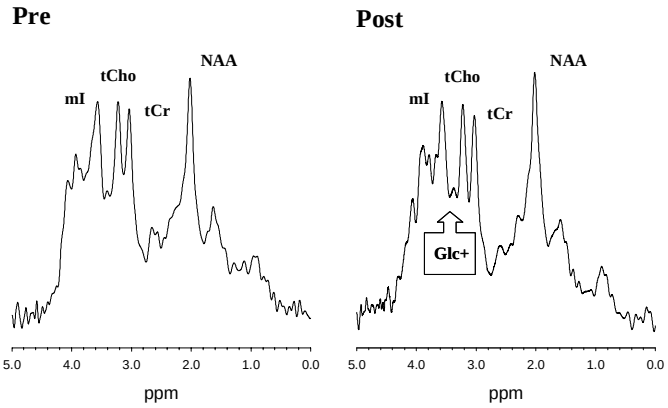

Figure 2. Spectral averages: AD group pre and post glucose loading. mI=*myo*-inositol; tCho=total choline; tCr=total creatine; NAA=N-acetyl-aspartate; Glc$^+$=glucose+*myo*-inositol+choline+taurine.

References

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