Apparent Rate of NAA synthesis is Increased in Alzheimer's Disease

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Introduction: N-acetyl aspartate (NAA) is an important amino acid derivative synthesized in the vertebrate brain by neurons and transported down the axon. Steady-state NAA can be assayed in using proton magnetic resonance spectroscopy (^{1}H MRS) where its concentration has been shown to be directly correlated with neuronal density[1]. Furthermore, proton-decoupled ^{13}C (dc13C) MRS with infusion of 1-^{13}C labeled glucose (Glc) can measure NAA synthesis rates[2]. Numerous publications have found NAA to be decreased in patients with Alzheimer's disease (AD)[3] however NAA synthesis rates have never been determined in this disease. It is our hypothesis that with neuronal death there should be an overall reduction of NAA synthesis rates in patients with AD. To do so formally requires expensive "high dose" protocols[2]. In this pilot study, we test the null hypothesis by use of ^{13}C MRS at low dose.

Methods: Three patients with confirmed Alzheimer's disease and three age-matched neurological normal controls were examined with both ^{1}H and dc^{13}C MRS[4]. ^{1}H MRS was acquired using single voxel short-echo PRESS (TE=35ms, TR=1500ms) in the posterior cingulate gyrus. A 1-^{13}C labeled glucose protocol was given to both groups and dc^{13}C MRS was measured as previously described[4]. NAA synthesis rate was determined by measuring the quantity of NAA (NAA_2+NAA_3) enriched per quantity of aspartate enrichment (Asp_2+Asp_3) at t=120min post-infusion when both metabolites reach pseudo-steady state. Since NAA_2 and NAA_3 incorporate ^{13}C label from Asp_2 and Asp_3 with equal probability through NAA synthase, this is a good approximation of NAA synthesis rate. Neuronal density was determined by NAA/Cr ratio from ^{1}H MRS.

Results: NAA/Cr ratio and glutamate neurotransmitter (GNT) rate was significantly decreased ($p<0.05$) in AD when compared to controls. Surprisingly, AD NAA synthesis rate was significantly increased by 46% when compared to control rates. More NAA is synthesized in the AD brain than normal brain as shown by the relatively higher ratio of NAA_2 to Asp_2 as shown in Figure 1. A measure of how much NAA each neuron is synthesizing can be achieved with a ratio of the two measures. When plotted for correlation, a general trend (indicated by the arrow in Figure 2) can be seen that as the number of neuron decreases, the synthesis rate increases.

Discussion: Reduced GNT is supported by post-mortem studies that confirm neuronal loss, however, the increase in NAA synthesis rate was a surprising finding. The increase in NAA synthesis may be the result of a possible compensation mechanism for the loss of neurons. This is supported by hypotheses that NAA acts as an osmoregulatory molecular water pump[5] or modulator of inflammatory diseases[6]. Therefore as neurons are destroyed by AD, NAA synthesis per neuron is increased either to pump more water or respond to the inflammation. The pathway of this compensation is likely to be similar to that in Canavan's disease where end-product inhibition of NAA synthesis is modulated[2].

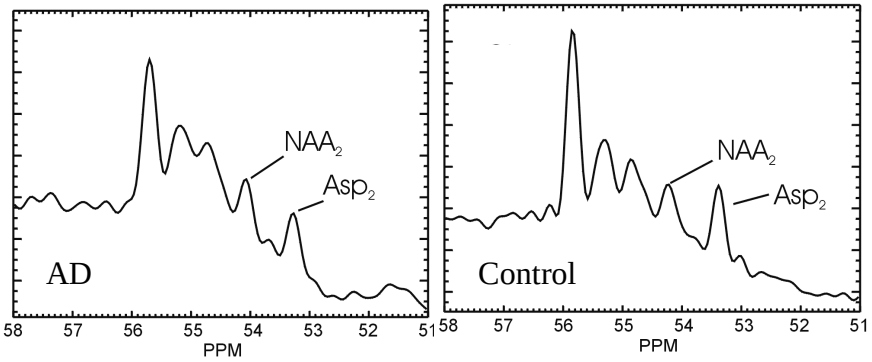

Figure 1. Representative spectra from AD patient (left) and control (right)

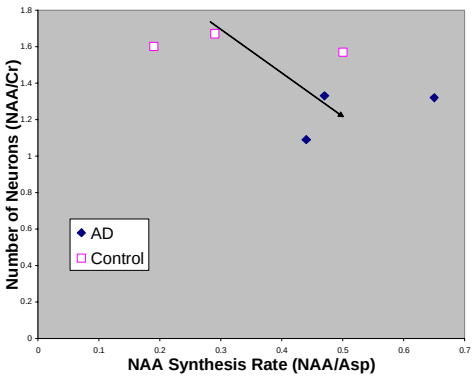

Figure 2. NAA Synthesis per Neuron

Conclusions: a) Neuronal number and NAA/Cr are reduced in AD. b) NAA synthesis (NAA^{13}C/Asp^{13}C) is increased c) "NAA synthesis per neuron" is increased. This implies that the end-product inhibition in AD is lifted as a possible compensatory mechanism for the loss of neurons. To prove these counterintuitive results, requires formal NAA synthesis determined in high-dose glucose infusion to steady-state. ^{13}C MRS measurements of NAA synthesis provide a unique window into the metabolism of neurodegenerative diseases with therapeutic implications.

References: 1) Cheng LL, et al. Magn Reson Imaging. 2002 Sep;20(7):527-33. 2) Moreno A,et al. J Neurochem. 2001 Apr;77(1):347-50. 3) Ross BD, et al. Neuroimaging Clin N Am. 1998 Nov;8(4):809-22. 4) Lin AP, et al. MAGMA. 2003 Feb;16(1):29-42. 5) Baslow MH. J Mol Neurosci. 2003;21(3):185-90. 6) Rael LT, et al. Biochem Biophys Res Commun. 2004 Jul 2;319(3):847-53.