Apparent NAA Synthesis Rate and NAA/Cr are Normal in Schizophrenia

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Introduction: N-acetyl aspartate (NAA) is an important amino acid derivative synthesized in the vertebrate brain by neurons and transported along the axon. Steady-state NAA can be assayed in vivo, using proton magnetic resonance spectroscopy (^{1}H MRS) where its concentration has been shown to be directly correlated with neuronal density[1]. ^{1}H MRS study results of NAA/Cr in Schizophrenia are mixed[2,3] and in a meta-analysis show no significant differences. A possible explanation is that NAA-turnover in schizophrenics is modified by disease, medication or other factors which were not controlled for between different study Groups. However, NAA synthesis rates have not been determined in schizophrenia.

Aims: Measure NAA synthesis rates[4] in schizophrenic and control subjects, using proton-decoupled ^{13}C (dc13C) MRS with infusion of 1-^{13}C labeled glucose (Glc).

Methods: Four patients diagnosed with schizophrenia and five age-matched neurologically normal controls were examined with both ^{1}H and dc^{13}C MRS. ^{1}H MRS was acquired using single voxel short-echo PRESS (TE=35ms, TR=1500ms) in the posterior cingulate gyrus and 5 other brain locations. A low dose 1-^{13}C labeled glucose protocol was given to both groups and non-localized dc^{13}C MR spectra acquired as previously described[5]. Formal determination of NAA-synthesis rate requires 'high-dose' 1-13C glucose infusion to achieve steady-state 13C enrichment of aspartate. In this pilot study we used the less costly 'low-dose' protocol and measured apparent NAA synthesis rate[6]. In this variant, NAA-synthesis 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, without the use metabolic modeling. Neuronal density was determined by NAA/Cr ratio from ^{1}H MRS.

Results: Cerebral glutamate C2, glutamine C2, aspartate C2 and NAA C2 were rapidly enriched in schizophrenics and control subjects (Fig 1 A, B). NAA C3 and Aspartate C3 were also readily identified in non-localized 13C spectral acquisitions (not shown). Time courses of summed enrichments of NAA C2 + 3 for representative Sz and control are shown (Fig 2 left). Significant 13C NAA synthesis was noted in all study participants. Apparent NAA synthesis rate in Sz was not different from control (Mann-Whitney ranked test U=8.0, p=.62). NAA/Cr ratios was not different (P=0.12) in Sz when compared to controls. A measure NAA synthesis per neuron can be achieved with a ratio of the two measures. When plotted for this correlation, NAA synthesis rate per neuron (NAA/Cr) varied widely and Sz and Controls were similar (Fig. 2 right). Noted however, is the spread of the schizophrenia data and possible differences within a subgroup of patients.

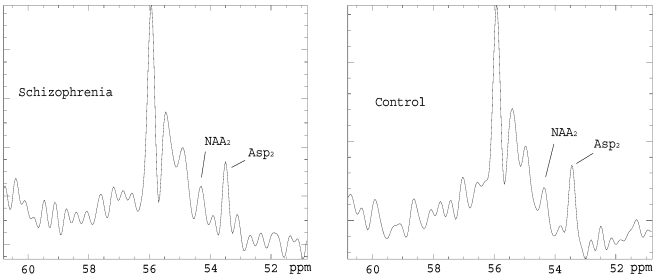

Figure 1. Representative spectra Sz patient (left) control (right)

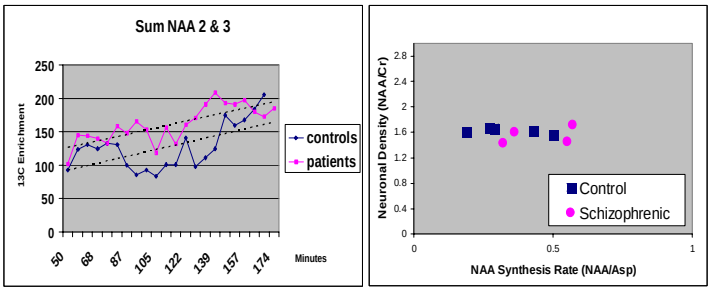

Figure 2. NAA enrichment (left) NAA Synthesis per Neuron (right)

Discussion: Apparent NAA-synthesis rate was not different between Sz and Control. Short-comings remain the small patient-number of treated rather than drug-naïve SZ and that the 'apparent' rather than the actual NAA-synthesis rate was determined, decisions made largely on grounds of 13C-glucose cost ($1500 vs $400 per patient). In this pilot study, the hypothesis that altered NAA synthesis rate might explain alterations in NAA/Cr ratio in various groups of Schizophrenic subjects was not confirmed. A high-dose 1-13C glucose study to determine actual NAA-synthesis rates in a larger and better defined group of SZ is in progress.

Conclusions: a) Neuronal density observed as NAA/Cr is not different between schizophrenics and controls. b) NAA synthesis (NAA^{13}C/Asp^{13}C) is unchanged. We propose to perform high dose studies in SZ to determine the absolute rate of NAA-synthesis. ^{13}C MRS measurements of NAA synthesis provide a unique window into the metabolism of neurodegenerative diseases.

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