Alterations of Brain Metabolites during Normal Aging: Correlation with Altered Energy Metabolism

F. Boumezbeur[1], R. A. de Graaf[1], G. F. Mason[1], G. W. Cline[2], K. L. Behar[1], G. I. Shulman[2,3], D. L. Rothman[1], and K. Falk Petersen[2]

[1]Diagnostic Radiology, Magnetic Resonance Research Center, Yale University, New Haven, Connecticut, United States, [2]Internal Medicine, Yale School of Medicine, New Haven, Connecticut, United States, [3]Cellular and Molecular Physiology, Howard Hughes Medical Institute, Yale School of Medicine, New Haven, Connecticut, United States

Introduction

For the past few years, many metabolite abnormalities in age-related brain diseases have been reported. However, there is little information on how metabolite levels change in healthy volunteers [1]. We used short TE ^{1}H MR spectroscopy at 4 Tesla in healthy elderly and young volunteers to measure age-related changes in Creatine (Cr), Choline (Cho), N-acetyl-aspartate (NAA), Glutamate (Glu), myo-inositol (Ins) and Glutamine (Gln). Further, we correlated the metabolite concentrations with glutamate-glutamine cycle rate (V_{NT}) and neuronal and astrocytic TCA cycle rates (V_{TCAn} and V_{TCAa}) measured in the same subjects using separate infusions of [1-^{13}C]glucose and [2-^{13}C]acetate and ^{13}C MRS. Altogether, the results suggest a major evolution of the neuronal-astrocytic metabolic unit with normal aging and support the further use of combined ^{1}H and ^{13}C MRS to study the role of brain metabolism in normal aging and the etiology of neurodegenerative diseases.

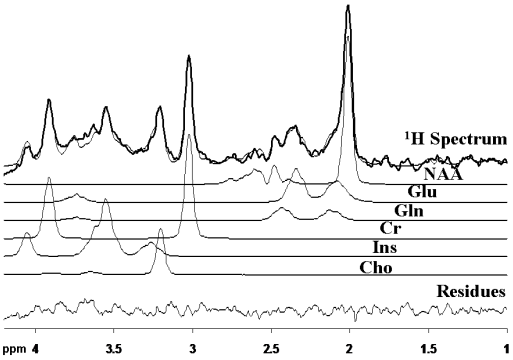

Fig. 1. Localized ^{1}H neurochemical profile acquired from the occipital lobe of an elderly (thick line) and best fit by linear combination of spectra (thin line).

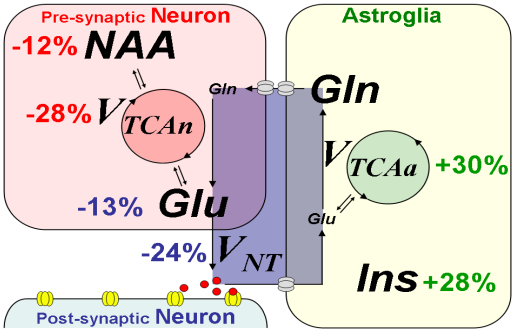

Fig. 2. Neuronal and astrocytic metabolites concentrations and fluxes alterations with normal brain aging.

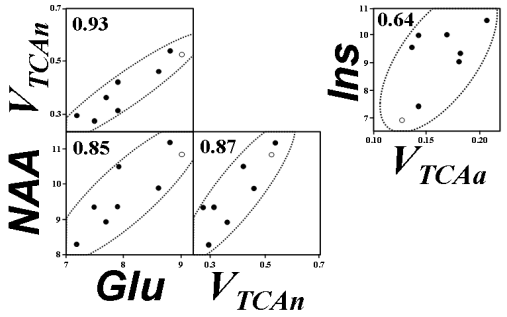

Fig. 3. Pearson correlation matrixes. Left: between neuronal metabolites NAA and Glu and V_{TCAn}; Right: between astrocytic metabolite Ins and V_{TCAa}. ●: individual values measured for Elderly (n=7). ○: average values for Young. Fluxes as µmol.g^{-1}.min^{-1} and metabolites levels as µmol.g^{-1}.

Materials and Methods

MRS acquisition. Short-TE ^{1}H spectra were acquired from ten healthy volunteers, three young (three males; aged 26±7 years, BMI 24±4 kg/m^2; mean ± SD) and seven elderly (two females and five males; aged 76±8 years, BMI 24±3 kg/m^2; mean ± SD) using a LASER-POCE sequence [2]. Subjects lay supine in a 4.0 T whole-body magnet (Bruker Instruments, Billerica, MA) with the head lying on top of a 7-cm-diameter ^{1}H circular coil. After tuning, acquisition of scout images, shimming with the FASTERMAP procedure [3], spectra were acquired from a 50x25x20 mm^3 volume located in the occipital-parietal lobe (16 transients, TR=3.5s, TE=42ms). Water reference spectra and double-inversion metabolite-nulling spectra (TI_1=1.7s, TI_2=0.54s) were also acquired from the same volume of interest for respectively absolute quantification [4] and subtraction of the MM baseline [5]. At another session, ^{13}C spectra were acquired with polarization transfer [6] in the exact same conditions from a 50x40x45 mm^3 volume before and during infusions of [1-^{13}C]glucose or [2-^{13}C]acetate (TR=2500ms, 128 transients) [16].

MRI segmentation. The tissue composition of each volume of interest was determined from T_1-based image segmentation maps according to a previously described protocol [7].

MRS spectral analysis. After averaged MM baseline subtraction and application of a 1-Hz-gaussian apodization, ^{1}H neurochemical profile were analyzed using LCModel 6.1 [8] (Stephen Provencher Inc., Oakville, Ontario, Canada) with a simulated basis set using Matlab 7.0 (The MathWorks Inc., Natick, MA) and published values of ^{1}H chemical shifts and coupling constants [9]. Absolute concentrations were derived by refereeing to the water signal taken as an internal reference of concentration [10].

Metabolic modeling analysis. More details in abstract at this meeting [16].

Results and Discussion

The proportion of gray and white matter in our volumes of interest were similar in both groups (Young: %GM=51±4% vs. Elderly: %GM=50±2%, mean±SD). As shown on Fig. 1, Cr, Cho, NAA, Glu, Ins and Gln were detected consistently from the ^{1}H neurochemical profiles, with Cramer-Rao lower bounds (CRLB) being systematically below 5% (except for Gln, CRLB<15%). In spite of the limited number of young subjects so far, significant age-related differences were seen: a 12% decrease in NAA (9.7±0.4 vs. 10.9±0.3 µmol.g^{-1}, p=0.13), a 13% decrease in Glu (7.9±0.3 vs. 9.0±0.2 µmol.g^{-1}, p=0.05) and a 28% increase of Ins (9.4±0.3 vs. 6.9±0.6 µmol.g^{-1}, p=0.03) (mean±SD, non-parametric Kruskal-Wallis analysis). The concentrations measured were consistent with previous reports for young and old healthy volunteers [11, 12]. More interestingly, as shown by Fig. 2, these changes can be related to the 30% increase of V_{TCAa} (p=0.002), 28% decrease of V_{TCAn} (p=0.013) and 24% decrease of V_{NT} (p=0.03) observed in the same elderly group [16]. Indeed, Pearson correlation matrixes can be calculated among the mostly neuronal parameters NAA, Glu and V_{TCAn} and between the mostly astrocytic parameters Ins and V_{TCAa} (Fig.3). The results show strong correlations between all parameters (Fig.3: R values at the top-left corner of each plot). Altogether, our results depict a global alteration of neuronal and astrocytic metabolism, consistent with (1) decreased neuronal activity due to either mitochondrial dysfunction [13] or changes of neuronal spines and synapses morphology and density [14]; and (2) increased astrocytic volume and metabolism with age, perhaps linked to age-related reactive astrocytosis or microgliosis [15].

Conclusion

In this study, we used MRI, and ^{1}H and ^{13}C MRS for quantitative characterization of changes in brain metabolite levels and their relationships to metabolic rates in the aging brain. Our data support the theory that alterations in NAA, Glu and Ins concentrations occur in normal aging even in very healthy people. These observations include correlations of major changes in the neuron-astrocyte relationship. These data support the further use of combined ^{1}H and ^{13}C MRS to study the role of brain metabolism in the etiology of neurodegenerative diseases.

Acknowledgments This work was supported by R01-NS037527 (DLR), K02-AA13430 (GFM), R01-AG23686 (KFP) and P01-DK68229 (GIS, KFP, DLR), Howard Hughes Medical Institute (GIS), The Keck Foundation and NIH/NCRR/GCRC/M01-RR00125.

References

1. Haga et al., Neurobiol Aging *in press*, 2007; 2. Marjanska et al., 12th ISMRM (Kyoto):p 679, 2004; 3. Shen et al., MRM. 38:834, 1997; 4. Barker et al., MRM 32(2):157, 1994; 5. Behar et al., MRM. 38:832(3):294, 1994; 6. Shen et al., PNAS. 96:8235, 1999; 7. Hetherington et al., MRM. 36:21, 1996 ; 8. Provencher, MRM. 30:672, 1993; 9. Govindaraju et al., NMR Biomed 13(3):129, 2000; 10. Lentner C. Geigy scientific tables. p 222, 1981; 11. Mangia et al., MRI 24:343, 2006; 12. Kaiser et al., Neurobiol Aging 26:665, 2007; 13. Reddy PH, Antioxid Redox Signal 9(10):1, 2007; 14. Duan et al., Cereb Cortex. 13(9):950, 2003; 15. Finch CE, Neurobiol Aging 24(s1):S123, 2003; 16. Boumezbeur et al., *Increased Glial Energy Metabolism during Normal Brain Aging assessed by Dynamic ^{13}C NMR Spectroscopy*, this meeting.