Gender, Age and Regional Differences of Brain Glutamate Concentration in Healthy Subjects

N. Sailasuta[1], T. Ernst[1], L. Chang[1]

[1]Department of Medicine, John A, Burns School of Medicine, University of Hawaii, Honolulu, HI, United States

Introduction

Single-voxel MRS methods with short (TE=30 to 45ms) and long (TE=135 to 270ms) echo times have been used to measure on overlapping single resonances of N-acetylarpartate (NAA, 2.02ppm), Creatine (3.03ppm), Choline (3.22ppm) and myo-inositol (3.7ppm). However, direct detection of the resonances of strongly coupled spin systems of glutamine and glutamate without contamination by nearby resonances is problematic. The majority of short echo time proton MRS studies reported the combined resonances of glutamine and glutamate between 2 and 3 ppm. The direct detection of glutamate without contamination by glutamine or the aspartyl group of NAA resonances is important because of its important role in neurotransmission in the central nervous system. Excess brain glutamate is toxic and can lead to cell death. In this study, we employed a more reliable method, TE-averaged PRESS, to measure the uncontaminated glutamate resonance at 2.35 ppm (1).

Methods

Twenty-four healthy subjects (16 men and 8 women) were recruited from the local community. Subjects were 21-71 years of age (39.4 ±15.5) and had 15.5±2.3 years of education. They were in good health, as indicated by stable vital signs and a normal general physical exam, and were on no medications (except vitamins and birth control). These subjects all had normal cognitive function with Mini Mental State Exam scores (29.3±0.6). Eleven subjects were scanned twice within a six month-period to evaluate the reproducibility of the measurements. MRS was performed on a Siemens 3T Trio scanner, with an eight-channel head coil. A single voxel TE-averaged PRESS pulse sequence was used to acquire multiple TE spectra in one scan, with TR 2sec, TE starting at 30ms and ending at 195ms with 32 increments of 5ms. Four brain regions were measured; the voxel size was 8cc for frontal white, frontal gray and parietal gray matter and 12cc for basal ganglia. The number of averages for each TE step was set to 8 for frontal white, frontal gray and parietal gray and 12 for basal ganglia, resulting in total acquisition times of 8 or 12 min per region. Metabolite concentrations were obtained from the LCModel fitting routine using the basis set spectra acquired with data acquisition parameters identical to those used *in vivo*.

Result and Discussion

TE-averaged PRESS allows the glutamate concentration to be measured unambiguously, and NAA, Cr and Cho resonances can also be measured with relatively low coefficients of variation (%CV) compared to short echo time PRESS. We consistently found 2-4 % smaller %CV using TE-averaged PRESS compared to PRESS for all metabolite concentrations. The %CV for the repeated scans of eleven subjects was on average 8% for all metabolite and all regions, indicating that our measurements were highly reproducible. A similar observation was reported in the study of Alzheimer patients (2). As expected, we found that the concentrations of the metabolites varied significantly between the brain regions. NAA and Cr were higher in parietal gray matter than in frontal white matter, frontal gray matter and basal ganglia. Cho was higher in frontal white matter and glutamate was higher in frontal gray matter. This is consistent with previous findings of regional differences of metabolite concentrations (3).

Analyses of covariance (ANCOVA) with gender as a factor and age as a covariate were used to evaluate the effects of age and gender on the metabolite concentrations in each brain region. In this model, we found no significant interaction between gender and metabolite concentrations. Table 1 lists the combined results. The glutamate concentration was higher in gray matter than in white matter for all age groups, which is very similar to recent MRS studies (4-6).

An age-related decline in glutamate concentration was observed in three brain regions: frontal white matter (p=0.036), parietal gray matter (p=0.001) and basal ganglia (p=0.019) (Figure 1). The decrease in glutamate concentrations were 0.31mM (frontal white), 0.57mM (parietal gray) and 0.35mM (basal ganglia) per decade. Several MRS studies have found age-related changes and regional differences for NAA, Cr and Cho concentrations in elderly subjects (7-8). Therefore, one possible interpretation of the observed age-related decrease in glutamate concentration, especially in the parietal gray matter, is that it might reflect a decrease in neuronal density in the aging population which is supported by our observation of age-related decrease in neuronal marker, NAA (p=0.07). However, no significant age-related decrease in NAA in frontal white and basal ganglia was observed.

Our study also highlights the importance of regional and age-matched controls for studies of brain neurochemistry, given that different brain regions and age can show marked differences in brain metabolism.

ACKNOWLEDGEMENTS: The authors thank C. Cloak, T. Chahil, D. Ramones, R. Yakupov, K. Yue and L Girton for subjects recruitment and scanning. Studies were supported by NIDA (K24-DA16170; K02-DA16991)

Table 1. Effect of age on metabolite concentrations in four difference brain regions of healthy subjects.

	Concentrations (Institutional Units)				
Age(years)	20-30(n=9)	30-40(n=5)	40-50(n=3)	50-60(n=4)	60-70(n=3)
Frontal White					
N-acetylaspartate	8.17(0.56)	7.98(0.61)	7.89(0.39)	7.26(2.0)	8.41(0.22)
Choline-containing compound	2.0(0.25)	2.18(0.23)	2.12(0.32)	1.98(0.75)	2.06(0.22)
Creatine plus phosphocreatine	4.96(0.18)	5.02(0.21)	4.74(0.17)	4.41(1.32)	5.61(0.69)
Glutamate	5.891(1.11)	5.47(0.54)	5.16(0.75)	4.50(1.80)	5.27(0.55)
Frontal Gray					
N-acetylaspartate	7.74(0.64)	7.66(0.49)	7.47(0.74)	7.36(1.27)	8.93(0.77)
Choline-containing compound	1.96(0.44)	2.01(0.35)	2.10(0.21)	1.92(0.36)	1.82(0.21)
Creatine plus phosphocreatine	5.93(0.90)	5.78(0.98)	6.03(0.49)	6.03(1.14)	6.61(0.86)
Glutamate	7.55(1.80)	7.39(0.35)	7.14(1.22)	7.34(0.78)	7.68(0.83)
Parietal Gray					
N-acetylaspartate	8.48(0.89)	8.13(0.29)	7.90(0.65)	8.30(1.32)	8.46(0.06)
Choline-containing compound	1.44(0.21)	1.49(0.12)	1.41(0.05)	1.27(0.12)	1.10(0.07)
Creatine plus phosphocreatine	6.54(0.81)	6.28(0.59)	5.89(0.62)	6.05(0.23)	6.67(0.52)
Glutamate	7.64(0.92)	7.82(1.38)	6.67(0.94)	6.26(0.93)	5.45(0.43)
Basal Ganglia					
N-acetylaspartate	8.08(0.98)	7.63(0.30)	7.82(0.27)	7.69(0.78)	8.12(0.26)
Choline-containing compound	1.48(0.40)	1.43(1.4)	1.22(0.16)	1.44(0.19)	1.35(0.10)
Creatine plus phosphocreatine	4.90(0.57)	4.62(0.65)	4.18(0.63)	4.45(0.25)	4.70(0.79)
Glutamate	4.25(0.93)	3.80(1.15)	2.93(0.12)	3.02(0.22)	3.22(0.40)

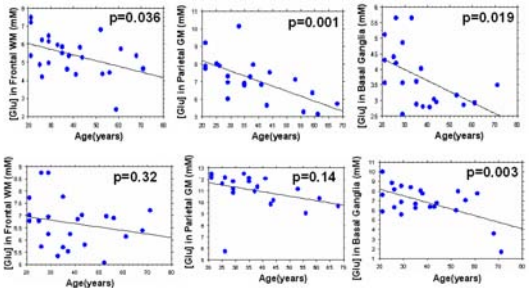

Figure 1. Plots showing age-related decreases in frontal white, parietal gray and basal ganglia glutamate concentrations in healthy subjects using TE-averaged PRESS (upper row) and short echo time PRESS (lower row).

Reference:

1. Hurd R. et.al MRM 2004; 51:435-440.
2. Hancu I, el.al MRM 2005; 53:777-782.
3. Komoroski R. et.al. MRI 1999;17:427-433.
4. Knorle et al. Neuroscience Lett 1997; 221: 169-172.
5. Pan J. et al. MRM 1996;36:7-12.
6. Auer DP et al. Biol Psy 2000;47:305-313.
7. Pouwels P. et al MRM 1998; 39:53-60.
8. Sijens PE et.al Invest. Radio. 2001;36:597-603.