Neurogenetics in the Pediatric Brain: A ^{1}H MRS Study of Brain Development

J. Knight-Scott[1], and S. A. Wijtenburg[1]
[1]Radiology, CHOA, Atlanta, Georgia, United States

Introduction

In short TE ^{1}H spectra from healthy human brains, the region between 0-1.9 ppm is dominated by resonances from macromolecules (1). These resonances are thought to arise from amino acids in flexible polypeptides chains of microtubule associated proteins (1, 2). Given the intrinsic catalytic function of proteins, these macromolecules are more likely intimately involved in processes related to brain function and its development than the standard low molecular weight metabolites that dominate human brain spectra. To test this hypothesis, we characterized age-related differences in macromolecule resonances between healthy adults and children. We specifically targeted Broca's area under the hypothesis that the obvious differences in language skills between children and adults generate significant spectral differences between these two populations.

Methods

Very-short TE spectra (STEAM: 10-ms TM, 3-s TR, 6.5-ms TE; voxels: 5-6 cm^3; 180-200 averages; SW: 2500 Hz; and Pts: 2048) were acquired from Broca's area in nine sedated pediatric patients (range: 9 months-5 yrs; mean = 2.4±1.5 yrs) and fourteen healthy adults (range: 21-46 yrs; mean = 33.2±8.5 yrs) on a 3.0 T MRI system. All studies were approved by the IRB. Each acquisition also included the collection of a water spectrum for phase correction. Data processing was limited to phase correction, apodization, and normalization to respective water signals. All the adult spectra were averaged and all the pediatric spectra were averaged. These averaged spectra were quantified in LCModel with concentrations reported as ratios relative to total creatine (3).

Results and Discussion

The table to the right lists all metabolites with Cramer-Rao Lower Bounds, i.e., standard deviations (std), of 20% or less as well as all 5 macromolecule resonances. Chemicals that exhibit a difference of 10% or more are bold and italicized, and chemicals with a difference of 20% or more are also in red. Using the std values, we calculated the z-score and p-value for each metabolite to test the hypothesis that the means of the groups were different. As evidenced by the large number and degree of significance, the young pediatric brain is obviously neurochemically distinct from that of an adult. While overall the spectral patterns are similar, the higher concentrations in the pediatric group suggest a greater level of chemical activity than that of the adult. The relative difference is normalized to the adult concentration, thus positive values indicate concentrations that are currently elevated in children and expected to decrease with development. Negative differences represent concentrations that are expected to increase with development.

Metabolite	Concentration (relative to /tCr)		Relative Difference
	Adults (n=14)	Children (n=9)	
Asp†	***0.382 ± 0.050***	***0.329 ± 0.059***	***-14%***
Cr	0.407 ± 0.049	0.390 ± 0.055	-4%
GABA‡	***0.258 ± 0.049***	***0.381 ± 0.057***	***48%***
Gln†	***0.325 ± 0.052***	***0.380 ± 0.061***	***17%***
Glu‡	***1.149 ± 0.058***	***1.350 ± 0.068***	***17%***
GSH‡	***0.234 ± 0.021***	***0.277 ± 0.028***	***18%***
mI‡	0.854 ± 0.034	0.916 ± 0.046	7%
NAA‡	1.323 ± 0.040	1.204 ± 0.048	-9%
PCr	0.593 ± 0.053	0.610 ± 0.055	3%
PE‡	***0.313 ± 0.053***	***0.628 ± 0.063***	***101%***
sI§	***0.052 ± 0.010***	***0.065 ± 0.012***	***25%***
tCho¥	0.214 ± 0.011	0.205 ± 0.012	-4%
tNAA‡	1.323 ± 0.040	1.234 ± 0.049	-7%
Glx‡	***1.474 ± 0.074***	***1.730 ± 0.104***	***17%***
Macromolecules			
M1	1.424 ± 0.171	1.516 ± 0.197	6%
M2	0.741 ± 0.163	0.775 ± 0.178	5%
M3	1.059 ± 0.117	1.134 ± 0.306	7%
M4¥	***0.823 ± 0.230***	***0.635 ± 0.260***	***-23%***
M5	1.084 ± 0.325	1.107 ± 0.376	2%

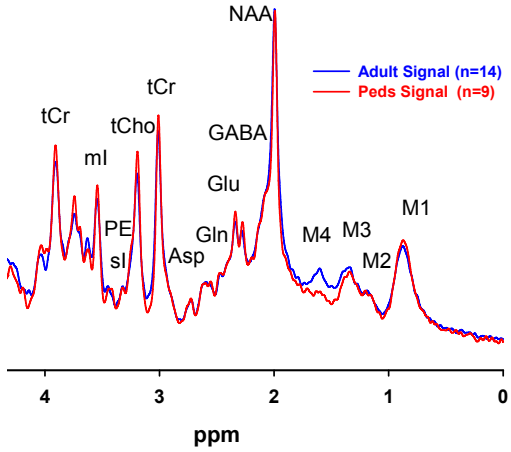
‡p < 0.001, §p < 0.01, †p < 0.05, ¥ p < 0.1

Tracking Neurodevelopment

Based on p-values, phosphorylethanolamine (PE), N-acetylaspartate (NAA), glutathione (GSH), glutamate (Glu), and γ-aminobutyric acid (GABA) will exhibit the most easily measurable developmentally sensitive spectral changes. PE and GABA are particularly interesting as they exhibit the largest differences of all the metabolites. PE is known to be elevated during early development and decreased in adults (4, 5). Recent work by Wang and Kriegstein indicates that in addition to GABA's normal role as the primary inhibitory neurotransmitter in the central nervous system, GABA is also involved in regulating cortical development in the immature brain (6). This could account for its elevation in children.

Macromolecules

The M4 resonance at 1.63 ppm appears to be the only macromolecule resonance sensitive to brain development. According to Behar and Ogino, M4 has major contributions from the amino acids leucine, arginine, and lysine (1,2). In spite of its higher p-value, compared to the major metabolites, M4 exhibits the most visually conspicuous difference between the two groups. The fact that this obvious difference is only a very weak trend suggests that our identification and quantification of the M4 resonance is inaccurate. Improvements in modeling of the M4 could improve the precision and thus improve the sensitivity of age-related concentration changes. Of all the chemicals that show large appreciable differences between children and adults (PE, GABA, sI), all decrease with age, suggesting reduced neurogenetic activity in adults. In comparison, M4 is increased in adults, possibly indicating an association with brain processes related to aging or even tissue maturation.



Conclusions

We have identified several resonances within ^{1}H-MRS brain spectra that could potentially serve as markers of development and tissue maturation, these include: Asp, GABA, Gln, Glu, GSH, mI, NAA, PE, and sI. The most conspicuous difference between the adult and pediatric brain occurred for the 1.63 ppm M4 resonance. Poor sensitivity to this resonance suggests needed improvement in modeling the macromolecule background in LCModel.

References

(1) Behar and Ogino, MRM, 1993; 30: 38-44.
(2) Behar et al., MRM, 1994; 32: 294-302.
(3) Provencher, MRM, 1993; 30: 672-679.
(4) Cady et al., Lancet, 1983; 14: 1059-1062.
(5) Gyulai et al., FEBS, 1984; 178: 137-142.
(6) Wang and Kriegstein, J Physiology, 2009; 587: 1873-1879.