Assessment of Macromolecular and Metabolic Alterations during Normal Brain Aging in the Dark Agouti Rat using 1H MRS at 17.2 Tesla

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Introduction

Normal brain aging is usually associated with a decline in brain function. Yet, the neural basis of age-related cognitive dysfunction in normal brain aging remains to be entirely elucidated. Recently, we established several metabolic alterations that occur during normal human aging using by *in vivo* ^{1}H and ^{13}C MRS[1]. In this study, we sought to explore further these metabolic alterations in the brain of healthy rats with *in vivo* short echo time ^{1}H MRS at 17.2 T.

Methods

MRS Acquisitions. For this study, we chose to use Dark Agouti (DA) rats because of their small weight at advanced age. Two cohorts were examined: "Young" rats (n=6, 1 month old, weight 220±20 g) and "Elderly" rats (n=4, 16 months old, weight 330±30g). Animals were anesthetized using isoflurane (1-2% in pure O_2). Body temperature was monitored and maintained at 37° ± 0.5°. All Experiments were performed on a 17.2 T/26 cm Bruker BioSpec MRI scanner (Ettlingen, Germany) using a home-made 20 mm diameter single-loop surface coil. Anatomical images were acquired for positioning using a RARE sequence. ^{1}H MR Spectra were acquired with a LASER[2] sequence (TE/TR=28/5000ms, 128 averages, 2048 points) from a 50 µL (5x5x2mm^3) volume containing mostly cerebral cortex and contributions from the corpus callosum and the hippocampus. For local B_0 field homogenization mapshim and local shim Bruker routines were employed. Typical water linewidth for Young rats was 21 ± 3 Hz and for Elderly rats 24 ± 3 Hz. Water suppression was done using a WET module[3] with numerically optimized flip angles and delays. Metabolite-nulled spectra were acquired at TE=16.5 ms using a double-inversion scheme (TI1/TI2/TR= 2600/600/5000ms).

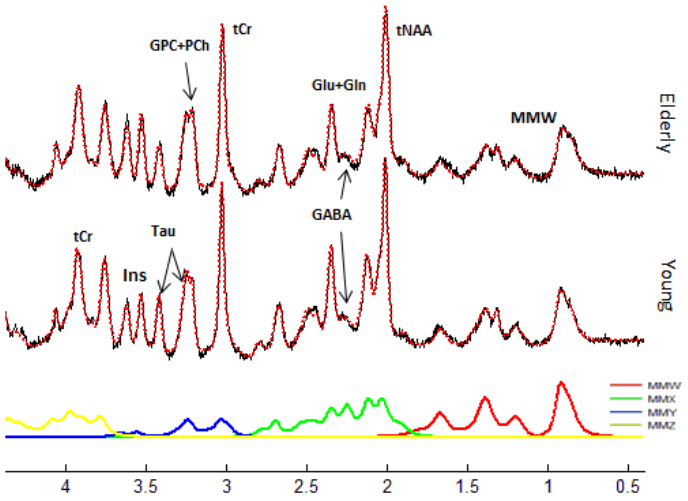

Fig.1 Metabolic profile of Elderly (top) and Young (middle) DA rats. The 4 groups of MM resonances are presented (bottom). LCModel fits are in red.

Data Analysis. After removal of the residual water signal using the HLSVD[3] algorithm, MR spectra were analyzed using LCModel[5] and a set of simulated spectra. The signal of macromolecules (MM) was parameterized[6] and implemented in LCModel as 4 groups of MM resonances in order to fit the experimental metabolite-nulled spectra (Fig.1). Absolute concentrations were derived by using the non-suppressed water signal as an internal reference of concentration and by correcting for T_1 and T_2 relaxation effects. Statistical significance between Young and Elderly rats was established using a bilateral Welch's t-test.

Results and Discussion

Figure 1 shows examples of ^{1}H MR spectra acquired in Young and Elderly rats. Figure 2 illustrates the difference in concentrations calculated for the major brain metabolites and MM resonance groups in Young and Elderly rats. Notably, one can observe a significant decrease in Glu+Gln (-6%) and GABA (-23%) levels as well as an increase of glial marker Ins (+24%) and tCho levels (+30%). Also, an increase of MM concentrations is detected in Elderly (from + 8 to 16 %). Considering that a LASER sequence was used for localization, it is unlikely that these differences in MM levels are due to contamination from extracranial lipids.

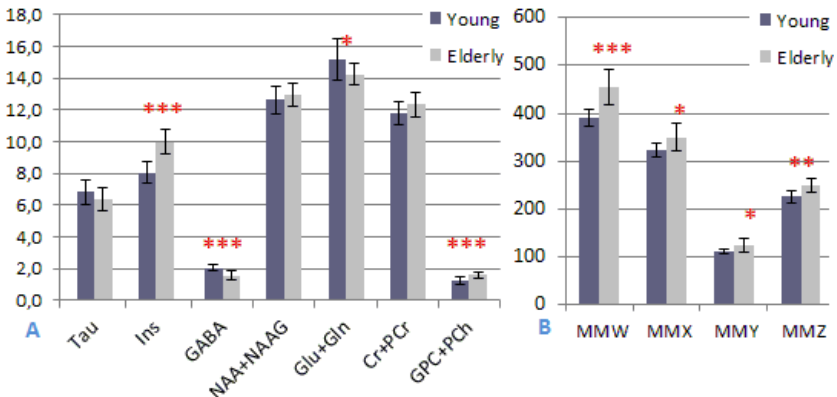

Fig.2.A Concentrations of major brain metabolites and **B** MMs for Young and Elderly rats. Metabolic and MM concentrations are expressed respectively in mmol/L and mmol/L of ^{1}H. Statistical significance is indicated using * P<.05 , ** P<.005 and *** P<.0005.

Conclusion

The decrease of neurotransmitter levels is consistent with a moderate decline in the neuronal function during normal brain aging. Whereas, the increase of Ins and tCho levels in addition to the macromolecule signals indicate a chronic low-level glial activation and neuroinflammation consistent with our previous observations in humans[1].

References

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