An Investigation of Resting State NAA and NAAG Fluctuations in Rat Brain at 21.1 T

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Introduction

The exact cellular mechanisms involved in the signaling between neurons and the vascular system, known as neurovascular coupling (NVC) is poorly understood. Based on several recent studies, there is now a consensus that NVC in brain is bimodal. There is a fast-phasic component associated with synaptic firing, resulting in an increase focal blood flow within 2-3 seconds. Second, there a slow tonic component that is not associated with synaptic firing and results in an increase in focal blood flow in 10's of seconds. The exact mechanism responsible for this slow modulation remains unknown. However, in some of our recent publications, we have proposed and presented preliminary evidence [1] that suggests the brain metabolite N-acetylaspartylglutamate (NAAG) plays a key role in the mechanism of slow tonic signaling. The main goal of this proposal is to measure resting state changes in NAAG concentration with sufficient temporal resolution to test the hypothesis that NAAG is the neurotransmitter responsible for the slow tonic component of NVC operating via the astrocyte mGluR3 receptor.

Experimental

The first goal of this project and subject to this report was to establish the best localization and acquisition technique. The options being, ISIS, RE-MRS, STEAM and MEGA PRESS, all localized MRS sequences with different approaches for spectral acquisition and voxel localization. Suitable NAAG and NAA phantoms with 140mM NaCl were made to optimized coil loading. These phantoms were used for sequence evaluation and to assess the system stability. As a first *in vivo* test we used the STEAM sequence to measure NAAG in the medial prefrontal cortex of a naïve rat brain with a voxel size of 2x2x2 mm^3. All experiments were performed on the 21.1 T system at the NHMFL.

Results and Discussion

Using an ISIS sequence modified for spectral selectivity, we demonstrated that the system stability was on the order of 2% and signal to noise ratio, temporal resolution suitable for *in vivo* experiments. The expected changes in NAA and NAAG are on the order of 15% and 60% respectively (2). The ISIS sequence had however localization errors and would not allow the use of high RF bandwidth pulses, which are needed particularly at 21.1 T to minimize chemical shift displacement errors. **Fig 1** shows an *in vivo* spectrum of the NAA and NAAG methyl resonances from a 2x2x2 mm^3 voxel placed in the medial prefrontal cortex of rat brain. The acquisition used here was a STEAM sequence with a TR = 2.5 s and NEX = 728. The FWHM of the voxel was 30 Hz. The NAAG resonance is highlighted in the figure. This results show that we can get a FWHM of 30 Hz, required to resolve NAAG from NAA. Further experiments are underway to optimize the detection of NAAG and NAA with higher sensitivity and better time resolution.

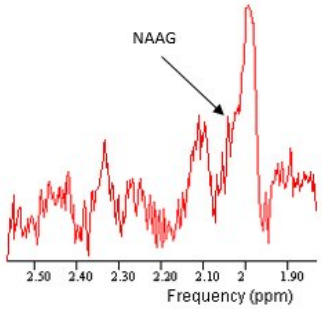

Fig.1 *In vivo* spectrum of the medial prefrontal cortex from a 2x2x2 mm^3 voxel.

Conclusions

We demonstrated that the level of system stability using localized spectroscopy is more than adequate for our needs. Further *in vivo* experiments are required to evaluate the quality of the spectra. In order to achieve reasonable SNR within a 2-minute time fame a larger voxel may be required. Larger voxels may result in higher FWHM values and if that is the case then direct excitation experiments may not be feasible and a MEGA-PRESS spectral editing approach may be a more appropriate choice.

Acknowledgements

The National High Magnetic Field Laboratory is supported by the National Science Foundation through NSF/DMR-1157490/1644779 and the State of Florida. D. Guilfoyle would like to acknowledge funding from the office of Mental Health, New York State.

References

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[2] Baslow, M.H., *et al.*, NMR Biomed., **29(12)**, 1678-1687 (2016).