In vivo measurements of brain serine with 1H-MRS

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Introduction

Developing treatments in schizophrenia addressing the glutamatergic component of the pathophysiology have used specific amino acid supplementation to improve the response of negative and cognitive symptoms to antipsychotic treatment (1). These supplements typically act as co-agonists of glutamate neurotransmission via interactions with the glycine site of the NMDA post-synaptic receptor. Glycine and serine are naturally present in the brain and can both bind with the glycine site. Oral supplements of Glycine, D-cycloserine or D-serine can be administered to affect brain levels of glutamatergic co-agonism. A 1H-MRS method to measure brain glycine levels has been reported recently (2), but no 1H-MRS technique has been used to measure brain serine levels. Serine level measurements would be particularly useful in the study of schizophrenia and its treatment with D-serine co-administration. This abstract presents the first attempt to detect brain levels of serine within the anterior cingulate cortex of a healthy volunteer using a single-voxel 1H-MRS technique.

Method

A recent method developed by Choi et al. (3,4) based on the adiabatic PRESS sequence and the addition of triple- or quadruple-DANTE frequency-selective pulses has allowed this group to obtain in vivo spectra uniquely composed of selected metabolites such as Myo-Inositol, glutamate and glutamine. Our attempt to detect brain serine in vivo is based on similar principles but uses a standard PRESS sequence in which the 0^{th} and 1^{st} sideband of a single-DANTE pulse (5) are used to select narrow bands centered on the 3.83ppm resonance of serine (X spin of an ABX system, see figure 1) and the 3.02ppm resonance of creatine methyl-protons. The method is named DANTE-PRESS or D-PRESS. Scans were performed using a Varian Unity Inova 4.0 Tesla system. A single-voxel symmetrical PRESS sequence with long echo time (TE=166ms) was modified to include a frequency-selective 67.24 ms DANTE pulse centered at the time of the first spin echo (figure 2). The DANTE pulse was composed of a train of 0.151 ms square pulses played 7.194 ms apart and was amplitude-modulated by a Gaussian envelope truncated at 20%. This produced a frequency-domain inversion profile with Gaussian passbands (FWHM 20Hz) repeating every ~138Hz. This exact frequency is determined at run time using data from a traditional PRESS acquisition. Creatine is set to 3.02 ppm and the difference between 3.83ppm and 3.02 ppm is converted to hertz. The DANTE-pulse is generated at run-time using this information and the D-PRESS acquisition is immediately started with the same sequence parameters. Since B0-drift can quickly degrade this frequency calibration, the measurement is kept short (64 averages, TR=2.0s, total duration = 2 min 8sec) and therefore the voxel size is kept fairly large (2x2x2cc). Concentration measurements can be obtained by taking into account the signal lost due system and movement-related B0-drift by comparing creatine amplitudes with and without DANTE pulse application. A water-unsuppressed acquisition (1 average) is also obtained with and without the application of a DANTE pulse centered on the water frequency. Calibration of the DANTE pulse is done using water-unsuppressed water-selective D-PRESS. Initial tests of the selectivity of the technique were performed on a phantom solution of creatine (7.5mM) and serine (30mM). Expected in vivo concentrations of total serine (L-Ser + D-Ser + PSer) vary between 0.4-0.7mM in frontal grey matter (6).

Results

Serine-selected phantom spectra show a good suppression of the 3.91ppm creatine singlet and show the reversal of J-evolution for the signal of the X spin of serine (figure 3d). As a proof of concept, D-PRESS was used to obtain the first serine-selected human brain spectrum (figure 3b). A brain region known to be rich in serine was selected (frontal lobe, bi-lateral anterior cingulate gray matter).

Discussion

In vivo human spectra show signals with J-evolved patterns corresponding to serine patterns observed in phantoms (figure 3d). The D-PRESS method shows promising preliminary results and suggests the ability to quantify brain serine levels in vivo. A formal model of the J-evolved spectral components of serine remains to be developed in order to produce concentration estimates.

References

1. Tsai, et al., Biol Psychiatry 44:1081-1089, 1998.
2. Prescot et al., Mag Reson Med 55(3) :681-6, 2006.
3. Choi et al., Mag Reson Med 54(6) :1536-40, 2005.
4. Choi et al., Mag Reson Med 55(5) :997-1005, 2006.
5. Geen et al., J Mag Reson 81:646-52, 1989.
6. Kumashiro, et al., Brain Research 681:117-125, 1995.

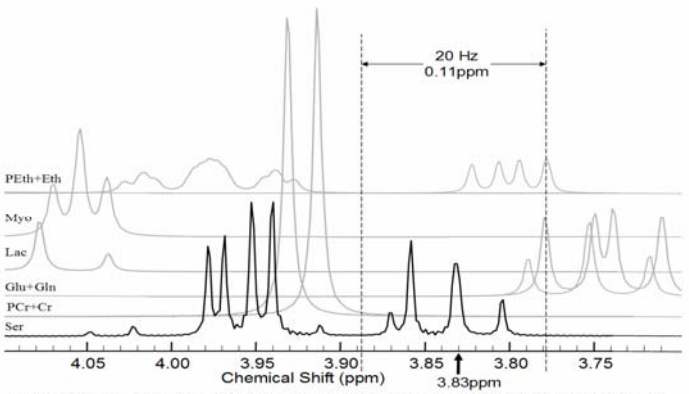

Figure 1. Resonances near the 20 Hz wide region selected by the frequency-selective DANTE RF pulse (from simulated FID).

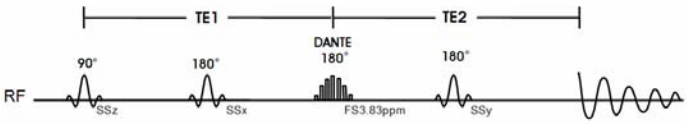

Figure 2. Simplified sequence diagram showing the timing and order of slice-selective (SS) and frequency-selective (FS) pulses. Here TE1 = TE2 = 83ms for a total echo time of 166 ms. Because the DANTE frequency selective pulse only inverts the X spins of the ABX spin system of serine, these spins effectively experience a 83ms total J-evolution time.

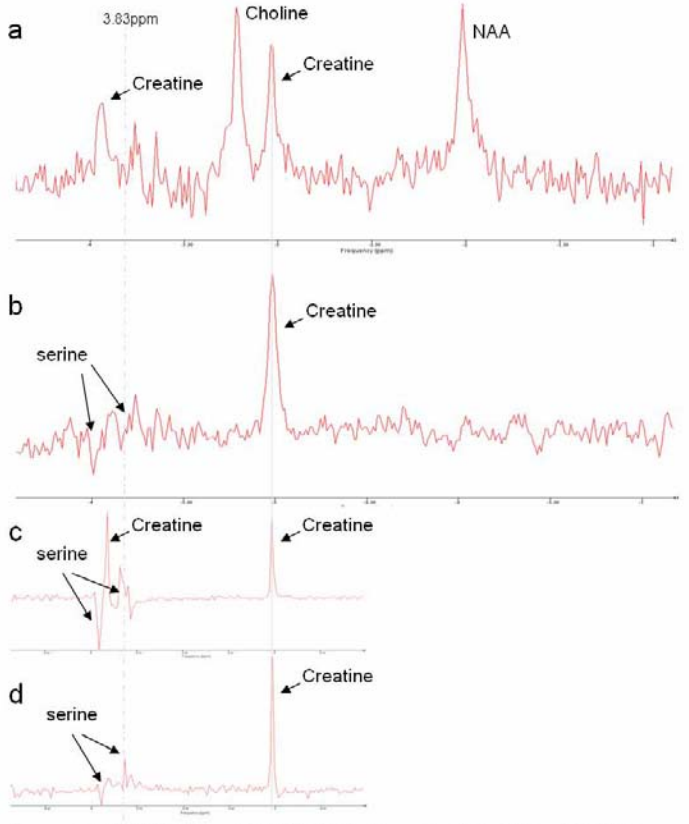

Figure 3. PRESS (a,c) and D-PRESS (b,d) spectra (TE=166ms, TR=2.0s, Navg=64) were collected from the bi-lateral anterior cingulate in vivo (a,b) 4Hz Gaussian filter) and in a phantom composed of a solution of creatine and serine (c,d) (1Hz Gaussian filter).