Detection of Low Levels of Brain Galactitol in Galactosemia Using ^{1}H 2D Double-Quantum Spectroscopy

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Introduction

Classic galactosemia is caused by galactose-1-phosphate uridyltransferase deficiency, and galactitol becomes an end product of galactose metabolism accumulating in the brain and body. Under galactose-restricted diets, patients usually lead a normal and healthy live. However, they function generally within the low average IQ range [1]. Patients have elevated urine galactitol even under the dietary restrictions, due to endogenous production of galactose [2]. It has been hypothesized that mildly elevated galactitol in the brain could cause neuro-cognitive impairment. However, in conventional proton MRS a low level galactitol (below 0.5 mM) cannot be resolved from glutamine, glutamate and myoinositol signals [3]. We have optimized a 2 dimensional double quantum (2DDQ) ^{1}H spectroscopy technique for detecting low levels of galactitol in the brains of galactosemics.

Materials and Methods

Studies were carried out on a Philips 3.0 T Gyroscan Achieva whole body clinical scanner. A 2DDQ spectroscopy patch was generated by modification of a double quantum filtered (DQF) spectroscopy pulse sequence [4]. The spoiling of z-magnetization immediately after each signal acquisition was implemented [5] to remove the two-shot stimulated echo artifact [6].

The 2DDQ pulse sequence was optimized for the detection of galactitol, based on previously determined chemical shifts and J-coupling constants [7]. Briefly, this symmetric molecule consists of two identical halves that are decoupled from each other. Each half has 4 non-exchange protons. One proton is uncoupled, and the other three can be approximated as A_2X system at 3T. The X and A_2 spins resonate at 3.962 and 3.682 ppm, respectively, and the J-coupling constant between the A_2 and X spins is 6.4 Hz. The pulse sequence timing parameters were first optimized through computer simulation and then tested on phantom solutions. The pulse sequence has 4 parts: (i) double quantum (DQ) preparation; (ii) DQ evolution; (iii) converting DQ to single quantum (SQ); (iv) detection of SQ signal. An echo time of 46 ms was used for optimal preparation of the double quantum interference. The evolution time t1 ranged from 0 to 31.75 ms with increment of 0.25 ms (total 128 time points). A selective "45°–-45°" binomial pulse was used to selectively flip and X spin and convert the DQ interference into anti-phase SQ signal. An echo time of 71 ms was used in the detection block to obtain in-phase SQ signal. Other parameters in human studies were NSA = 4, TR = 2000 ms, VOI = 6x6x6 to 7x7x7 cm^3. Computer simulation showed that the A_2 spins can be detected with 58% efficiency with the technique. The actual detection efficiency was approximately 52% in phantom tests, yielding to 2 full proton signals per molecule. On the other hand, myoinositol signal was attenuated by 10 folds.

Results

Four control subjects and two galactosemia patients were studied successfully with the pulse sequence. Galactitol signal was identified in one patient and not from the rest of the subjects. Patients had elevated urine galactitol (see Figure, reference range was 3-81 mmol/mol creatinine). The figure shows a stack plot of the 2DDQ spectra acquired from 0.3 mM galactitol solution and two patients.

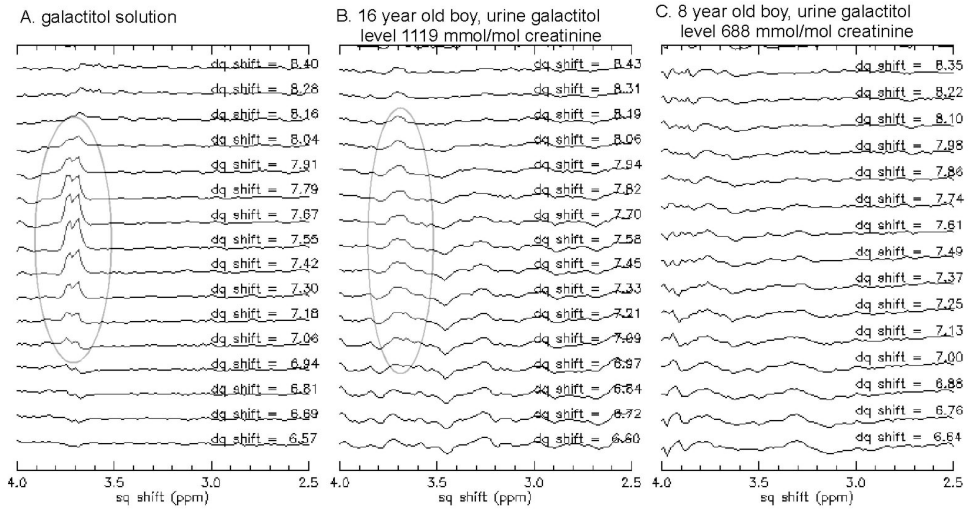

Fig. Stack-plot of 2DDQ spectra, where SQ spectra are plotted for different DQ frequencies. Galactitol peaks are indicated with ellipses. (A) Galactitol solution (0.3 mM galactitol, VOI = 125 cm^3). (B) *In vivo* brain spectrum from a patient (VOI = 343cm^3) where galactitol is present. (C) *In vivo* brain spectrum from another patient (VOI = 294 cm^3), where galactitol is not detected. All signals are plotted on the same absolute scale. Using water signal for calibration (PRESS, TR/TE =2000/92 ms in phantom and brain) without correcting the effects of relaxation and assuming brain water content is 70%, the galactitol signal in (B) corresponds to a concentration of 0.16 mM.

Discussion and Conclusions

Presence of galactitol in the brain of galactosemia patients on a galactose-restricted diet has not been demonstrated with MRS previously, due to its low level and overlapping with other metabolites. With the 2DDQ technique at 3T, these difficulties can be overcome. It is necessary to work at 3T because selectively exciting the X spin is difficult at 1.5T due to the small chemical shift difference between the A_2 and X spins. A quantification procedure will be implemented in the future to obtain absolute galactitol concentration. This work opens the possibility for further investigations of the role of residual brain galactitol in the well-being of galactosemia patients.

References : **1.** Antshel KM et al., Neuropsychology 2004, 18: p658-64. **2.** Berry GT et al., J Inherit Metab Dis 1993, 16:p91-100. **3**. Mueller SG, et al., Neurology 2001, 57: p1422-7. **4**. Trabesinger AH et al., MRM 1999, 42: p283-9. **5**. Wang ZJ et al., *ISMRM 15th scientific meeting*. 2007, p2935. **6**. Pictet J et al., MAGMA 2004, 17: p74-9. **7**. Wang ZJ et al., *ISMRM 13th Scientific Meeting*, 2005, p 2488.

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