Clinical Application of Low-Power 13C MRS Suited to Neuropsychiatric and Frontal Brain Disorders

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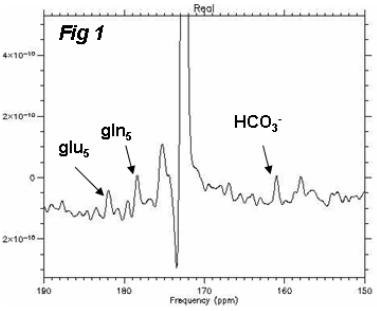
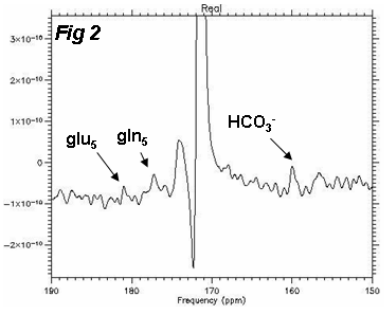
Aim: A feasible and safe ^{13}C MRS for the human frontal lobe.

Background: In vivo ^{13}C spectroscopy provides an incisive means to detect enzyme deficiencies due to genetic mutations. However, when a clinical manifestation is a cognitive deficit that points to pathology of the frontal lobe, the proton decoupling required for well resolved ^{13}C spectra is a potential source of excess heating of the eye. The purpose of this abstract is to demonstrate the diagnostic efficacy of heat-mitigating, low power proton excitation in subjects with ornithine transcarbamylase deficiency (OTCD). OTCD is an X linked inborn error of metabolism and the most common urea cycle disorder. It leads to hyperammonemia resulting in substantial cognitive and motor deficits. Previous work has delineated a specific cognitive profile with deficits in executive function, implicating pathology in frontal lobe and underlying white matter tracts (1, 2). ^{13}C MRS is especially useful in OTCD because it allows the detection of the enzyme deficiency. However, the use of waltz 4 at 8 watts for decoupling the coupled ^{13}C resonances of Glu and Gln, i.e., C_2, C_3 and C_4 which works well in the occipital cortex, is prohibited for studying the frontal lobe because of its potential to cause eye damage. On the other hand, the $^{13}C_5$ spins of Glu and Gln are not directly bonded to a proton and for these carbons decoupling is not an issue, but they still provide a window on metabolic integrity. In contrast to some other schemes, the data acquisition scheme used here renders all the carbon sites in Glu and Gln, including C_5, visible when labeled with ^{13}C. Notwithstanding the absence of ^{1}H-^{13}C splittings, the $^{13}C_5$ resonance can still benefit from proton excitation through the NOE enhancement. The strategy outlined below, is suitable for evaluating the frontal cortex, because it employs such low power ^{1}H excitation.

Methods: Proton enhanced ^{13}C MRS was performed on a 1.5T Signa GE scanner equipped with a stand-alone proton channel, controlled from a vector signal generator (Agilent 4438C). Using a simple pulse-acquire data acquisition sequence, together with low power pulses of 0.9 watt, applied from the proton channel for generation of the nuclear Overhauser effect, an acquisition of 200 msec gave rise to an enhanced $^{13}C_5$ resonance. The carbon spectra were recorded for a further ~120 min after start of $^{13}C_1$ Glc infusion.

Results: Enrichment of all of the isotopomers of glutamate in the brain of a patient with OTCD was readily achieved by





administration of 1-13C glucose over 10 minutes. Figure 1 shows a representative 13C brain spectrum acquired in 20 minutes, of the C5 carbon and bicarbonate resonances in a fully decoupled 13C spectrum from posterior brain regions. Figure 2 shows the same spectral region, from the same brain region in the same subject, but using low power proton excitation (Sailasuta and Robertson), with a SNR sufficient to provide diagnostic metabolic information from that brain region. Because the power deposited in the second sequence falls within FDA guidelines for SAR in optic lens (4), we anticipate that this tehcnique can now be routinely applied to the frontal lobe, not only to patients with OTCD, but also in much commoner neuropsychiatric disorders, including schizophrenia, HIV and drug abuse, known to impact higher executive functions of the frontal lobe.

Discussion: This study demonstrates the feasibility of using low power proton excitation with ^{13}C MRS to interrogate occipital brain. The low power employed permits identical studies (in progress) of the frontal lobe with resultant adequate spectral resolution and signal to noise. This is expected to be a safe alternative to PET, currently the only metabolic imaging sequence applicable in all brain regions. Because of radioactivity concerns however, PET has no role in longitudinal studies of children. Furthermore, the isotopomer and specific metabolic information contained in ^{13}C brain spectra, MRS promises a much richer reward in these critical treatable inborn errors to study a more clinically relevant brain region implicated in damage in OTCD.

Conclusion: 1. A scheme is described whereby in vivo 13C MRS can safely be performed in human brain regions hitherto precluded on grounds of SAR. 2. Demonstrated efficacy for measurement of glutamate, glutamine and bicarbonate in 20 minute MR scans. 3. Identification of clinically useful biomarkers of neuropsychiatry and genetics. 4. Ready transferability of 13C MRS to frontal lobe.

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