Assessment of Cerebral Acetate Oxidation and Glial Metabolism in Human Brain by ^{13}C MRS

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Introduction
In normal adult humans the brain derives most of its energy from the aerobic oxidation of glucose. Acetate (Ac) is an alternative fuel, metabolized to acetyl-CoA only in the glial compartment (1).
Aim: Feasibility of ^{13}C MRS after [1-^{13}C] Ac infusion for investigation of glial metabolism in humans.

Material and Methods
Three controls (3m, 39±20 yrs, fasted > 10 h) and one patient (f, 20 yrs, fasted 5 h) were studied with natural abundance and with ^{13}C MRS after intra-venous (i.v.) 99% [1-^{13}C] Ac infusion. The patient was on a ketogenic diet for seizure control and received tegretol (0.3 g/day) and valproate (2 g/day). 2 mg/min/kg body weight of Ac was infused in 60 min in each subject. Experiments were carried out on a GE, Signa 1.5 T system. Spectra before, during and after infusion were acquired from the occipital brain region with a FID sequence, TR = 2s, 1024 pts, 4 kHz excitation bandwidth and quantified (2). Blood samples were collected every 10-20 min and Ac conc. and ^{13}C enrichment of plasma Ac (E_{Ac}) was determined (3,4). To determine the rate of Ac oxidation (V_{Ac}) relative to the total neuronal/glial TCA-cycle rate (V_{Tot}), the time course of fractional ^{13}C enrichment of HCO_3^- (E_{HCO3}) was fitted to a model shown in Fig. 1 for $30 < t < 80$ min and the steady state enrichment of HCO_3^- was obtained. Resonances of Glu_5/Ac_1 and Gln_5 were ~ constant and E_{Ac} was ~ 95% during that interval.

Results
In all subjects, ^{13}C enriched resonances of Ac_1/Glu_5, Gln_5, were observed within 20 min. Evidence of ^{13}C enriched HCO_3^- was observed within 30 min. ^{13}C accumulation in Gln_5 was notably increased in the patient 55-80 min after infusion start (Fig. 2). The mean rate of Ac oxidation, V_{Ac}, was 8% (±3%, N=4) of V_{Tot}. With V_{Tot} in adult mammalian brain ranging from 0.6 - 1.5 μmol/min/g (5), we estimate V_{Ac} ~ 0.04 - 0.11 μmol/min/g in fasted adult human brain.

Discussion
In earlier studies it was demonstrated that after i.v. [1-^{13}C] glucose infusion, labeling of $Glu_{1,2,3,4}$, $Gln_{1,2,3,4}$, $Asp_{2,3}$, $NAA_{2,3}$, $lactate_3$, $alanine_3$, and HCO_3^- can be observed (2). Using the same MR technique we are now able to investigate glial acetate metabolism in normal and diseased brain. A strikingly altered pattern of ^{13}C accumulation in Gln_5 was observed in a single patient. The rate of Ac oxidation in human brain was estimated. These results indicate that ^{13}C MRS is an appropriate tool to investigate diseases which are believed to originate in glial cells.

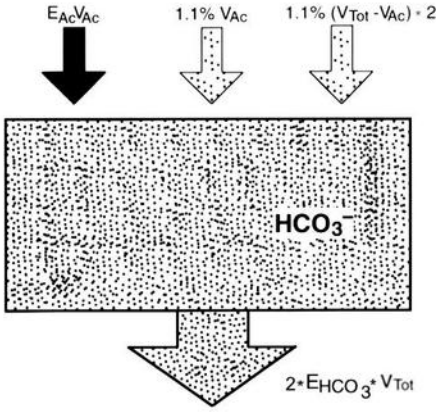

Fig. 1: Model of ^{13}C flux into/out of the HCO_3^- pool. At steady state $V_{Ac}/V_{Tot} = 2*(E_{HCO3}-1.1\%)/(E_{Ac}-1.1\%)$.

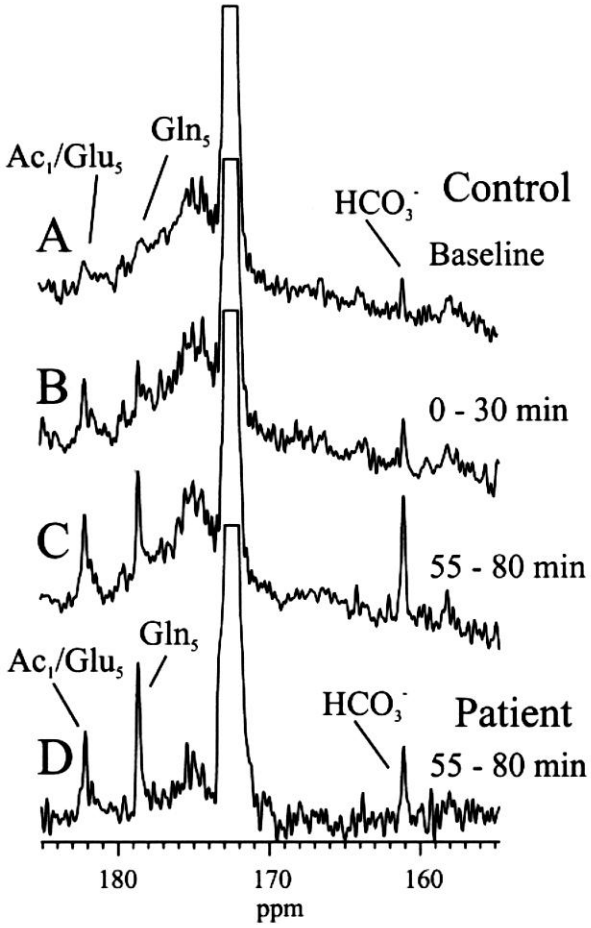

Fig. 2: Spectra obtained from one of the normal subjects before (A) and 30-55 min (B) and 55-80 min (C) after i.v. Ac infusion. In controls, the signal intensity of Gln_5 in the spectra acquired 55 - 80 min is ~ 0.7 times that of HCO_3. In an equivalent spectrum from the patient, the Gln_5 amplitude is twice as intense as HCO_3^- (D). Ac_1 and Glu_5 resonances cannot be separated; the term Ac_1/Glu_5 refers to the combined signal.

References
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