New Window on Human Cognition: 13C Assays of Glutamate Neurotransmission in Frontal Brain

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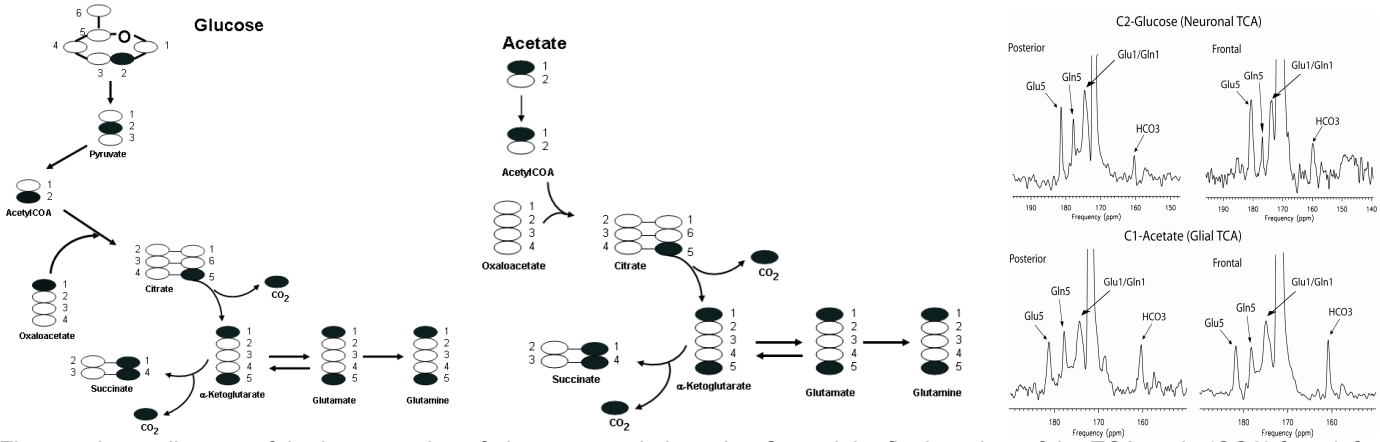
Purpose: Purpose is to obtain normative human brain data for 13C MRS in frontal brain. Current theory ascribes most human cognitive functions to frontal brain structures, previously inaccessible to 13C MRS. Accordingly almost nothing is known of glutamate neurotransmitter function, believed by many to be responsible for more than 80% of all neuronal messaging. SAR limitations which confined human 13C MRS studies to the 'back of the brain' have been overcome in this Laboratory. We compare frontal and posterior brain to obtain vital normative data on several aspects of 13C glutamate neurotransmitter rate.

Theory: Crucial to the task of safely examining human frontal lobe is that the observed cerebral metabolic products of a loading chemical must be those resonating in the 'upfield' region of the spectrum where weakly attached protons allow direct detection of cerebral 13C pools with minimum or absent proton decoupling. For the metabolic biochemist that is a simple matter (Figure). C2 glucose generates C5 and then C1 glutamate and glutamine within the neuronal TCA and glutamine-glutamate cycles, with the end product of complete glucose oxidation, CO2 appearing almost exclusively as 13C HCO3-. C1 acetate generates C5 and the C1 glutamate and glutamine with the astrocytic (glial) TCA and glutamine-glutamate cycles, again providing end-product 13CO2 and C13 HCO3. The obverse metabolic processes (not shown) previously widely exploited generate C2-3-4 glutamate and glutamine (as well as 13C HCO3) from C1 glucose and C2 acetate respectively, with the disadvantage that all of the metabolic products, except C13 HCO3, require high decoupling power for their direct or indirect observation in the brain. The power deposition for these latter approaches precludes application to frontal brain (SAR exceeds limits for optic lens).

Methods: GE 1.5 Tesla broad band clinical MR scanner was adapted for 13C with a programmable decoupler unit; two similar and symmetrical surface coils for proton and 13C acquisition from the hind brain and fore brain respectively. A variety of pulse sequences which develop low power NOE for observation of weakly coupled cerebral 13C metabolites (1-2). Standardized, FDA and IRB approved infusion protocols for intravenous delivery of 1-13C or 2-13C glucose or 1-13C acetate were then applied to normal human volunteers. In general, periods of supervised 13C infusion were 90 – 120 min, and the continuous acquisition of cerebral 13C spectra in 6 min blocks was performed over 120 – 180 min. Blood samples, for plasma 13C enrichment calculations were taken at intervals of 30 min.

Results: The theoretically expected results were found (Figure right) with excellent temporal and chemical shift resolution of the substrate from its metabolic products – confirming that in practice cerebral glial metabolism and neuronal metabolism can be separately observed in either hind brain (as previously known: (3-5)) or forebrain (6).



Figures shows diagram of the incorporation of glutamate and glutamine C5 and the final product of the TCA cycle (CO2) from infusion of C2-glucose (left) and C1-acetate (middle). Filled circle represents the labeled carbon atom. Two turns of the TCA cycle is drawn where glutamate and glutamine C5 were incorporated in the first turn and C1 in the second turn. Comparison of post infusion 13C MRS spectra (150-190ppm) from frontal and parietal brain regions after infusion of C2-glucose (right top) and C1-acetate (right bottom) from human subjects.

Conclusions: Feasibility is demonstrated for fore brain 13C MRS studies of either neuronal or glial metabolic rate, TCA and glutamine-glutamate cycle rates. Calculations (not shown) of in vivo metabolic rates are generally simplified, compared with earlier protocols due to the short (one or two steps only) of metabolic transfer which need to be modeled.

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