Quantification of Frontal Glutamate Neurotranmission in human HIV

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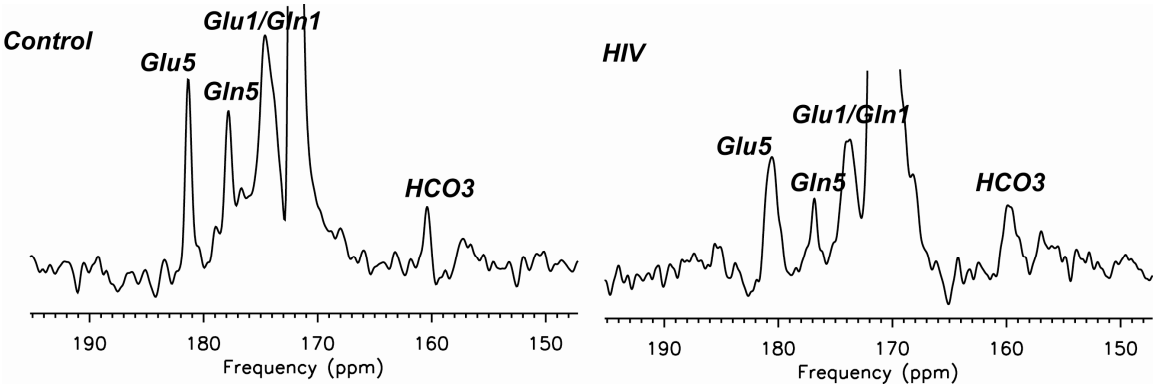
Purpose: Cognitive deficits in HIV infected individuals are common even when MRI is normal. Recent studies detected significant reduction in frontal brain glutamate concentration. It is hypothesized that cognitive deficits result from reduction in the local rate(s) of glutamate neurotransmission confined to the frontal lobe.

Background: Abnormalities in cerebral glutamate homeostasis, manifesting as changes in steady state concentration measured with proton MRS has now been identified in otherwise 'normal' subjects with HIV (1). This observation most likely results from altered flux in cerebral glutamine glutamate and TCA-cycles in the frontal white matter. Localized 13C MRS assays have been developed which, by avoiding high-power proton decoupling and reducing heat deposition below FDA –SAR guideline ((International standrad, medical equipment part 2: Pratical requirement for the safty of magnetic resonance equipment for medical diagnostic, 2002; Shellock 2000)2) permit such abnormalities to be directly imaged. For assay of frontal brain, specifically neuronal metabolic rates, the starting substrate 2-13C glucose is infused and the weakly coupled products C-5 and C1 glutamate and glutamine, and the oxidation product 13C bicarbonate are determined over a 2 hour time course.

Patients and Methods: Seven HIV positive subjects and 7 age-matched normal controls were recruited from the Phil Simon Clinic of Huntington Hospital (Director: Dr. Kimberly Shriner). With IRB approval and patient consent cerebral MRI and quantitative 1H MRS, including TE Average for accurate assay of brain glutamate in two locations; frontal white matter and posterior cingulate gyrus grey matter was performed. In HIV subjects who showed significantly reduced steady state brain glutamate in FWM we then performed 2-13C glucose infusion followed by frontal brain low power 13C MRS examination over a period of 120 minutes. Metabolic rates, including neuronal TCA-cycle rate, were calculated and compared with controls.

Results: C2 glucose enters the frontal brain of HIV as it does in the normal control. Thereafter, activity in the glutamine glutamate cycle and TCA cycle of neurons of the frontal brain is demonstrate in the HIV-brain by the sequential enrichmentof C5 Glu, Gln and C1 Glu/Gln with progressively increasing intensity over time. 13C bicarbonate enrichment (proof of complete oxidation of glucose in the third turn of TCA of frontal lobe neurons and axons) is also evident in HIV (Figure below). In this preliminary study, the enrichment of the (smaller) pools of glutamate is apparent when peak areas of C5 of HIV (figure right) and Control (figure left) are compared. The overall rate of neuronal TCA and neuronal glutamate glutamine cycle will be presented.



Discussion and Conclusion: This is a feasibility study, the first to explore 13C MRS of HIV neurochemical pathology. Two advances in particular open the way for a systematic examination of the long-term impact of HIV on human glutamate neurotransmitter function. The successful application, for the first time in HIV, of safe 2- 13C assays of frontal neuronal function, when coupled with analogous development of a 1-13C acetate assay of frontal glial function should provide a complete picture of glutamate neurotransmission in recovering HIV encephalopathy.

References: (1). Sailasuta et al. *NMR Biomed* 22:326-331 2009 (2) International standrad, medical equipment part 2: Pratical requirement for the safty of magnetic resonance equipment for medical diagnostic. (2002) 2nd revision, Geneva:29-31.

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