Increased GABA in Basal Ganglia of HIV-Infected Adults Measured by ^{1}H MRS

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Introduction

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain [1], and altered GABA levels and/or GABA turnover rates have been implicated in a range of neurological and psychiatric disorders [2]. Human immunodeficiency virus (HIV) infection can cause a spectrum of primary neurological deficits ranging from mild neurocognitive impairments to HIV dementia, and several clinical features are consistent with altered BG function. The basal ganglia (BG), which are rich in GABA innervations, show evidence of (HIV) within days to weeks of infection and bear a high viral burden. We therefore hypothesized that altered BG GABA metabolism may be an early consequence of HIV infection, and used a robust and reproducible GABA editing protocol [3] to compare BG GABA levels in chronically infected, relatively immunocompetent, neurocognitively intact HIV+ patients who were not receiving antiretroviral treatment, with those of presumed non-infected control subjects.

Methods

5 HIV+ and 5 healthy controls (the latter presumed uninfected) were studied. The former were relatively immunocompetent without HIV therapy (>500 CD4 cells/mm^3 with low plasma HIV-1 RNA concentrations) and had normal neuropsychometric tests. Two were being prescribed gabapentin for chronic neuropathic pain. All experiments were performed on a 3 Tesla Philips Achieva spectrometer. We acquired 256 transients from 7.32 mL voxels using the MEGA-PRESS pulse sequence [4] from mostly gray matter voxels located in the putamen with 2.5 second recycle delays. We sampled 2048 complex points with 2 kHz receiver bandwidth and apodized with a 2 Hz exponential function prior to FFT. The carrier frequency was maintained within ~2 Hz using the manufacturer ^1H_2O navigator-based frequency drift compensation and free-induction decays were retrospectively corrected for frequency and phase variations [3]. Concentration ratios were obtained using LCModel [5] with basis sets generated from full density matrix simulations employing ideal and real slice-selective and editing pulses, respectively, and 10^4 gradient points. A well known confound of GABA measurements made using spectral editing techniques is that metabolites with similar chemical shifts and coupling networks, such as homocarnosine and macromolecules (MM), co-edit with GABA. Differences in T1 between MM and smaller metabolite molecules could be exploited as an additional filter [6] with the caveat that the dependence of such relaxation times as a function of region or pathology are generally unknown. Given these concerns, we report the GABA* concentration, recognizing that any observed variations in GABA* levels may reflect variations in these co-edited components.

Results and Discussion

A representative spectrum is shown in Figure 1. In all cases, the edited GABA peak at 3.01 ppm was consistent with the pseudo-doublet lineshape as predicted from theory and baselines were flat. [GABA]/[tCr] ratios among HIV+ patients and controls were 0.66 ± 0.14 and 0.41 ± 0.10, respectively (P = 0.005). The corresponding values for the Cramer-Rao lower bounds (CRLB's) are 4.4 ± 1.6 and 3.4 ± 0.6, respectively, and for all data the CRLB's were below 10%. These differences remained significant after excluding the two individuals being prescribed gabapentin (P = 0.02). These initial findings from a small cohort suggest that BG GABA concentrations are increased among neurocognitively intact HIV+ individuals for whom antiretroviral therapy is not otherwise indicated (treatment guidelines based on peripheral blood immunologic and viral parameters). Better understanding of pathogenic events in the brain during untreated HIV infection may influence treatment guidelines. Extending similar analyses to a larger sample size should provide greater insight into this issue.

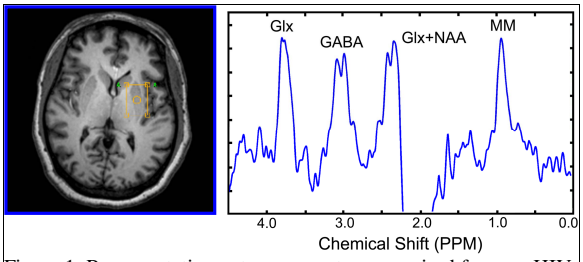

Figure 1. Representative putamen spectrum acquired from an HIV-infected patient. Glx: glutamate + glutamine.

References

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