Brain GABA and Glutathione in People with HIV

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Combination antiretroviral therapy (cART) has greatly reduced morbidity and mortality in people with HIV (PWH). However, HIV-associated neurocognitive disorders (HAND) persist among PWH, likely due to ongoing neuroinflammation, oxidative stress, and neuronal loss. A post-mortem study found lower γ-aminobutyric acid (GABA)ergic markers in PWH, suggesting abnormal GABAergic transmission *pre*mortem.[1] In preclinical studies, HIV-mediated generation of reactive oxygen species (ROS) in brain cells increased oxidative stress, contributing to neuronal damage.[2,3] In this study, we examined the effects of HIV on the neurochemistry of PWH using advanced edited magnetic resonance spectroscopy, HERMES,[4] to simultaneously measure brain GABA and GSH, providing insights into neurotransmission integrity and antioxidant levels in PWH. Two groups were enrolled – PWH (sex=19/9 M/F; age:51.49±14.50 years) and PWoH (people without HIV; sex=8/18 M/F; age:39.70±13.39 years). HERMES was performed on a 3T Siemens MRI scanner in the predominantly white-matter motor cortices to understand the underlying mechanism of HAND-related impairment. In both cortices, unsuppressed water reference data were also acquired for each subject to allow quantification in absolute concentrations. Spectra were processed and modeled in LCModel to estimate metabolite concentrations, which were corrected for tissue/relaxation effects.[5] Metabolite levels from the regions were analyzed using ANOVA to determine differences between groups. Age was added as an interaction in the model. 53 participants were included, 27 of whom were PWH and 26 PWoH. GABA was lower in PWH than in PWoH (PWH: 8.95±0.89; PWoH: 8.40±1.15; 6% lower in PWH; $p < 0.09$). Regarding GSH, differences between PWH and PWoH differed by age (p for interaction = 0.048). In PWoH, GSH increased with age (Pearson $r=0.47$, $p<0.01$), whereas PWH showed no change ($r=0.06$, $p=0.66$). Our findings suggest GABA abnormalities in PWH, which may relate to a disrupted inhibitory mechanism related to HIV. PWoH showed an increase in GSH with aging, suggesting a compensatory mechanism for age-related oxidative stress, but this compensation is absent in PWH (possibly HIV-related protection against oxidative stress). Future (and longitudinal) studies with larger sample sizes may resolve these differences, ultimately direct the targeting and timing of therapeutic strategies, and provide biological assays of treatment response.