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**"Chronic binge alcohol induces hippocampal plasticity in SIV-infected female rhesus macaques"**

**BACKGROUND**: Chronic human immunodeficiency virus (HIV) infection results in diverse comorbidities in people with HIV (PWH), including HIV-associated neurocognitive disorder (HAND) due to its detrimental impact on the central nervous system and cognitive function. Over 50% of PWH suffer from HAND, and it is one of the leading comorbidities of HIV. Cognitive deficits in PWH are further exacerbated by alcohol use disorder (AUD). With the rising prevalence of AUD in females, examining the neurobiological effects of HIV and alcohol in this population is increasingly important. The Comprehensive Alcohol HIV/AIDS Research Center (CARC) has developed a macaque model of the simian immunodeficiency virus (SIV) infection to study the impact of HIV and chronic binge alcohol (CBA) on comorbidities affecting organ systems throughout the body, including the brain. This study examined the hippocampus and the cingulate cortex due to their roles in cognition, learning, and memory. We hypothesized that SIV-infected, ART-treated female rhesus macaques with a history of CBA administration would exhibit increased excitability of brain areas involved in cognition, including the hippocampus and cingulate cortex.

**METHODS**: SIV-infected, ART-treated female rhesus macaques (n=32) were randomized to receive either CBA (13-14 g/kg/week) or water (VEH) for 14.5 months. Ovariectomy (OVX) or sham surgery (SHAM) was performed six and a half months into the experiment, and all animals were euthanized eight months later. Brains were snap-frozen at necropsy and regional brain dissections were taken from 6mm coronal brain slices and guided by the Paxinos Rhesus Macaque Brain Atlas. Regions analyzed include the cingulate cortex (Brodmann area 24) and the whole hippocampus. Western blot protein quantification was used to assess phosphorylation and changes in total protein levels in proteins involved in glutamate and neuroinflammation signaling pathways. Data were analyzed via two-way ANOVA with CBA treatment and OVX factors using GraphPad Prism.

**RESULTS**: Western blot analyses demonstrated that CBA significantly increased phosphorylation of GluR1 ($p=0.0054$), a glutamatergic AMPA receptor subunit, in the hippocampus. In contrast, CBA did not alter GluR1 phosphorylation in the cingulate cortex. Interestingly, CBA did not alter phosphorylation of NR1, a glutamatergic NMDA receptor subunit, in the hippocampus or the cingulate.

**CONCLUSIONS**: Together, this data suggests that CBA differentially alters hippocampal and cingulate glutamatergic signaling and there are regional excitability differences in the brain following CBA exposure. These findings will inform future human and non-human primate studies examining specific cognitive domains associated with these regions.