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"Peripheral immune cell pro- and anti-nociceptive gene expression in chronic binge alcohol administered SIV-infected rhesus macaques"

People living with HIV (PLWH) have a 2-fold higher prevalence of chronic pain compared to the general population. Reports in the literature indicate that alcohol consumption to self-medicate pain may increase the incidence of at-risk alcohol use. Chronic alcohol use, HIV infection, and anti-retroviral therapy (ART) all independently lead to altered pain states, yet the underlying pathophysiology is poorly understood. The aim of this study was to explore the utility of peripheral blood mono nuclear cells (PBMCs) as indicators of alcohol-, ART-, and HIV-associated alterations in pro and anti- nociceptive pathways in a relevant preclinical model of HIV-infection. Four- to six-year-old male rhesus macaques *(Macaca mulatta)* were administered chronic binge alcohol (CBA) daily through an intragastric catheter (13–14 g of ethanol/kg body weight/week; 30% w/v water) or vehicle (VEH) starting three months prior to intrarectal simian immunodeficiency virus ($SIVmac_{251}$) infection and continued for the duration of the study. After 2.5 mo of SIV infection (viral set point), macaques were randomized to receive ART (provided by Gilead Sciences, Inc.) consisting of daily subcutaneous injections of 20 mg/kg of Tenofovir (TFV, 9-[R-2-(phosphonomethoxy) propyl] adenine, PMPA) and 30 mg/kg of Emtricitabine (FTC). Four experimental groups were studied; VEH/SIV/ART-; VEH/SIV/ART+; CBA/SIV/ART-; and CBA/SIV/ART+ (N=5-7/group). mRNA was isolated from PBMCs collected at 4 timepoints: baseline, 3 months of CBA/VEH administration, viral setpoint, and at study end point (11.5 months post-SIV infection). RT-qPCR was used to determine the expression of ORMu, ORD, ORK, POMC, PENK, PDYN, SubP, NK1R, TRPV1, CBR1, CBR2, FAAH, MAGL, DAGLa, DAGLb, and RPS13 as control. Expression of ORD, SubP, PDYN and CB1R was below the limit of detection in these samples. At viral set point, expression of CB2R in CBA/SIV macaques was significantly decreased compared to baseline. At study endpoint, CB2R and ORMu expression was significantly decreased from baseline in all four treatment groups. These results indicate that alcohol, and SIV infection result in marked modulation of components of anti-nociceptive and immunomodulatory (CBR2) pathways in PBMCs. We speculate that decreased CBR2 expression may contribute to CBA- and SIV-associated pro-inflammatory milieu. The possible role of decreased PBMC ORMu expression to pain states remains to be elucidated. Future studies will test the prediction that these alterations in PBMC gene expression parallel those seen in specific brain regions involved in modulation of algesia-hyperalgesia.