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Calorie-Dense Diet, Alcohol and Simian Immunodeficiency Virus Infection Alter Skeletal Muscle Proteome and Metabolic Pathways

People with HIV (PWH) have a higher prevalence and progression of sarcopenia, and this increases the risk for morbidity and all-cause mortality. The maintenance of muscle mass is essential for energy metabolism, protein synthesis and storage. Among PWH, a higher prevalence of alcohol use disorder (AUD) is observed. Binge and heavy drinking predict higher caloric and fat intake, which increase the risk of comorbidities for PWH. A non-human primate model was used to mechanistically understand the interaction of calorie-dense diet, alcohol and SIV-infection on skeletal muscle protein regulation and metabolic pathways. We examined proteomic alterations in the vastus lateralis in a male rhesus macaque model of high-fat, high-sucrose diet (HFSD), chronic binge alcohol (CBA) and SIV infection. Twenty adult male rhesus macaques were placed on a HFSD (Fat 42%, Protein 16%, Carbohydrate 42%; 27% of carbohydrate is Sucrose). After three months, animals were assigned to CBA (13-14g/kg/week) or isovolumetric water (VEH) groups. CBA or VEH were administered via gastric catheter. Following a four-month period, a subset of animals in the CBA group and in the VEH group were intravenously infected with SIV (mac251+17E). Animals were treated daily with antiretroviral therapy (ART) beginning 2.5 months after infection. The five treatment groups were VEH /SIV-/HFSD (n = 4), CBA/SIV-/HFSD (n = 4), VEH/SIV+/HFSD (n = 5), CBA/SIV+/HFSD (n = 4) and CTRL (n = 3). At study endpoint, muscle samples were collected and processed for proteomic analysis by the Metabolomics Core of LSUHSC. A total of 4,120 unique proteins were detected across the five treatment groups. Of those, 908 unique proteins were significantly differentially expressed across all treatment groups compared to control. One-hundred and forty-seven unique proteins were downregulated and 761 were upregulated. Ingenuity Pathway Analysis was performed to analyze metabolic pathway activation. CBA/SIV+/HFSD significantly altered 135 canonical pathways compared with the control group and 62 canonical pathways compared to VEH/SIV+/HFSD. The most common canonical pathways altered by CBA/HFSD in SIV- and SIV+ groups are largely involved in mitochondrial metabolic activity, including oxidative phosphorylation, respiratory electron transport, mitochondrial dysfunction, mitochondrial protein import and degradation, Complex I biogenesis, Complex IV assembly and sirtuin signaling. These findings provide evidence that alcohol alters proteins that are essential for maintaining mitochondrial function in skeletal muscle.