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Assessment of underlying neurocircuitry in dysregulation of the Hypothalamic Pituitary Adrenal Stress Axis in HIV-1 Tat Male Mice

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Project Summary

Overview

My name is Salahuddin Mohammed, a 2nd year PhD graduate student from Dr. Jason Paris' Lab. My research dissertation focuses on investigating the neuroendocrine underpinnings of HIV- and opioid-mediated anxiety-/depression-like behavior and cognitive impairment via experiments utilizing humans and animal models. Through this work I strive to delineate the underlying mechanism for the neuroHIV symptomology and develop novel therapeutic agents which can ameliorate HIV-1 mediated Tat-neurotoxicity. Approximately 50% of the HIV infected patients suffer from HIV associated neurocognitive disorders (HAND) which can be exacerbated by drug use/abuse. Some neuroHIV symptoms include anxiety, major depressive disorder, neurocognitive impairment, and additional psychiatric comorbidities that impair the quality of life (QOL) like and increased abuse risk for opioids, alcohol, psychostimulants, etc. One protein, the HIV-1 regulatory protein, trans-activator of transcription (Tat), may contribute to neuropathology by promoting neuroinflammation and neurotoxicity which may be exacerbated by opioids like oxycodone. The underlying mechanisms for the neuroHIV symptomology are unknown. Moreover, the HIV⁺ population is commonly prescribed opioids like oxycodone (Merlin et al., 2016) which may further raise concerns about HIV-1 Tat and oxycodone interactions. Evidence shows that 20-80% of HIV⁺ patients may have a dysregulated hypothalamic-pituitary-adrenal (HPA) stress axis (usually characterized by high basal stress hormones with a lack of appropriate hormonal response to additional stressors). Preliminary findings from our lab use a mouse model of HIV-1 Tat exposure. These mice demonstrate higher circulating stress hormone (i.e. corticosterone) when exposed to the HIV-1 Tat protein and appear to recapitulate the human phenotype. These mice may be used to assess the underlying mechanisms within the brain that cause HPA dysregulation associated with HIV and, thus, may be used as a model with which to screen treatments for this disorder.

Intellectual Merit

The present project will delineate the neurocircuitry involved in HIV-protein-mediated dysregulation of the stress axis. This work will further provide sites to be targeted to restore HPA stress axis homeostasis and reduce the overall burden of present and future neurological sequela in HIV⁺ patients.

External Opportunity

The findings will be presented at the Society for Neuroscience (SfN) conference scheduled for this year November 13– 21, 2021 at Chicago, IL, U.S.A. The conference is expected to be attended by approximately 30,000 scientists from over 80 countries. My attendance at this conference would greatly help me to garner structured feedback and insights from experts in this domain. Attending this meeting would also provide opportunities to learn relevant cellular and molecular advancements in the fields of neuroscience. Moreover, I would be enthusiastic to meet leaders in fields of sex differences and opioids/HIV research such as Drs. Pamela Knapp, Margaret McCarthy, Georgia Hodes, Oliver Hobert, Wendy Macklin, and others. I believe attendance at this conference will have a formative impact on my career. Additionally, this grant may also help me to apply for extramural Sigma Xi society funding which provides fellowship of \$1000 to graduate students with application deadline of October 1 every year. This grant will advance my scientific fluency, professional development, and capacity for building my CV.