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Recommended Citation
Salahuddin, Mohammed; Mahdi, Fakhri; and Paris, Jason J., "R01. HIV-1 Tat Dysregulates the Hypothalamic-Pituitary-Adrenal Stress Axis and Potentiates Oxycodone-mediated Psychomotor and Anxiety-like Behavior of Male Mice" (2020). Annual Poster Session. 1.
https://egrove.olemiss.edu/pharm_annual_posters/1
HIV-1 Tat Dysregulates the Hypothalamic-Pituitary-Adrenal Stress Axis and Potentiates Oxycodone-mediated Psychomotor and Anxiety-like Behavior of Male Mice

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Abstract

Human immunodeficiency virus (HIV) is associated with co-morbid affective and stress-sensitive neuropsychiatric disorders that may be related to dysfunction of the hypothalamic-pituitary-adrenal (HPA) stress axis. The HPA axis is perturbed in up to 46% of HIV patients, but the mechanisms are not known. The neurotoxic HIV-1 regulatory protein, trans-activator of transcription (Tat), may contribute. Tat promotes neuroHIV-like behavior in mice, elevates circulating corticosterone and central corticotrophin-releasing factor (CRF), both of which can be exacerbated by opioids. We hypothesized that HIV dysregulation may contribute to Tat-mediated interactions with oxycodone, a clinically-used opioid often prescribed to HIV patients. In transgenic male mice, exposure to Tat produced significantly higher basal corticosterone levels with adrenal insufficiency in response to a natural stressor or pharmacological blockade of HPA feedback, recapitulating the clinical phenotype. HIV-1 Tat interacted with acute exposure to oxycodone (3 mg/kg) to potentiate psychomotor behavior in an open field and also increased anxiety-like behavior in a light-dark transition test. Pharmacological blockade of glucocorticoid receptors (GR) partially restored the HPA response and decreased oxycodone-mediated psychomotor behavior in Tat-expressing mice, implicating GR in these effects. Together, these effects support the notion that Tat exposure can dysregulate the HPA axis, potentially raising vulnerability to stress-related substance use and affective disorders.

Hypotheses

• In vivo, HIV-1 Tat and oxycodone will interact to potentiate psychomotor and anxiety-like behavior involving hypothalamic-pituitary-adrenal (HPA) axis activation.
• Antalarmin and/or RU-486 may attenuate combined Tat and oxycodone psychomotor behavior.

Methods

Animal Subjects: Transgenic mice were bred in the vivarium at the University of Mississippi (University, MS). Tat+ mice expressed a Tat+ protein that became transcriptionally-active in the presence of doxycycline injection. Mice were housed per cage with ad libitum access to food and water. Behavioral Assessment: Mice were behaviorally tested in open field and light-dark transition task. All tests were completed within 3 days of doxycycline injection and occurred 2-3 h into the dark phase of the light cycle. Data were encoded by an AVIncus behavioral tracking system (Stoelting Co., Wood Dale, IL).

Forced Swim Test: The Porsolt forced swim test was used to activate the HPA stress axis. In brief, mice were placed in a room without access to food or water and allowed to swim for 15 min followed by injection with adrenocorticotropin and behavior assessment.

Chemicals: Tat (15 mg/kg) was induced in transgenic mice (Tat+) or Tat− mice via doxycycline injection (30 mg/kg, i.p., 4 times). Antalarmin (20 mg/kg, i.p.) 4 days Ceusin Chemical, Ann Arbor, MI) and RU-486 (20 mg/kg, i.p.) 8 days Ceusin Chemical, Ann Arbor, MI) Oxycodone (3 mg/kg, i.p.) was administered 15 min prior to testing.

Source-linked immunassay assay (SLIA): Circulating corticosterone was assessed via ELISA kit per manufacturer instructions (Shengen Life Sciences). Plate wells were run on a CLARIOstar microplate reader (BMG Labtech, Cary, NC).

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Acknowledgment

This work was supported by funds from NIH R00 DA039791, R01 DA052851 (to JJP), F30 GM122733 (to Dr. Soumyajit Majumdar), GSC intramural research grant (to MS), The University of Mississippi, School of Pharmacy

Figure 1: Tat was induced in Tat+ and not induced in Tat− mice via doxycycline injection (30 mg/kg for 5 d). Saline or oxycodone (3 mg/kg) were administered 15 minutes prior to behavior testing and assessed in an open field (n = 8-12) and a light/dark transition task (n = 7-12). (A-C) Non-Stressed paradigm. (A) Distance (m) traveled in an open field (n=6-12). (B) The time spent in light chamber of light-dark transition task (n=7-12). (C) Circulating corticosterone (ng/mL, n=8-10). (D-F) Stressed paradigm. Force swim for 15 min. (D) Distance (m) traveled in an open field (n=8-9). (E) The time spent in light chamber of light-dark transition task (n=8-9). (F) Circulating corticosterone (ng/mL, n=8-9). * indicates a main effect of genotype wherein Tat+ mice differ from Tat− mouse controls in panel A, B and F; † indicates a main effect for oxycodone to differ from saline administered mice in panel A and D; * indicates an interaction wherein saline-administered Tat+ mice differ from respective Tat− controls in panel C, p < 0.05.

Figure 2: (A) The HPA Axis. (B) Tat− and Tat+ mice were administered antalarmin (CRF-R antagonist; 20 mg/kg, i.p. for 6 d) and/or RU-486 (GR antagonist; 20 mg/kg, i.p. for 7 d) concurrent with the injection of HIV-1 Tat via doxycycline (30 mg/kg, i.p., once daily for 5 d). (C) Distance (m) traveled in an open field among Tat− and Tat+ mice acutely-administered saline (0.9%) or oxycodone 3 mg/kg (n=8-10). (D) Circulating corticosterone (ng/mL, n=8-10). * indicates an interaction wherein Tat− mice differ from respective Tat− controls in panel B, C and D; † indicates an interaction wherein oxycodone- administered mice differ from respective saline-administered controls in panel B and C; † indicates an interaction wherein the group differs from their respective vehicle controls in panels B and C, p < 0.05.

Conclusions

HIV Tat and clinical opioids can interact to activate stress pathways, influencing psychomotor and affective behavior which may be correlated with HPA axis dysregulation. Antalarmin and RU-486 were able to attenuate the psychomotor behavior indicating the involvement of CRF and GR receptor as potential targets for neuroHIV behavior in HIV infected population.