R01. 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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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 neuro-HIV-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 MSM; Tat+) mice expressed a Tat−; protein that became transcriptionally-active in the presence of doxycycline induction. Fifty-eight for 5d, Tat+ mice were exposed to the transcription factor necessary to activate transgene induction, but did not express the transgene itself. Antagonistic effects of Tat induction have been previously observed using these mice. Mice were kept in a temperature- and humidity-controlled environment on a 12:12 h light-dark cycle (lights off at 00:00 h) with ad libitum access to food and water.

Behavioral Assay. Mice were behaviorally tested in open field and light-dark transition task. All tests were completed within 5 days of doxycycline induction and occurred 2-3 h into the dark phase of the light cycle. Data were encoded by an AVENues 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 at constant temperature (12-22 °C) and allowed to swim for 15 min followed by injection with saline/oxycodone and behavior assessment.

Chemicals. Tat was induced in transgenic mice (Tat+ or Tat−) via doxycycline injection (30 mg/kg, ip; 7 days). Cyclic AMP, Antalarmin (20 mg/kg, ip; 5 days), CA-4616, Oxycodone (3 mg/kg, ip), and salin (0.9%) was administered 15 min prior to testing.

Gene/linked immune-suppressed mice (GSIS). Circulating corticosterone was assessed via ELISA kit per manufacturer instructions (Shinon Life Sciences). Plots were read on a CLARIOstar microplate reader (BMG Labtech, Inc. Cary, NC).

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