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R02. HIV-1 Tat Promotes Age-Related Anxiety-like, Antinociceptive, and Neuromuscular Impairments in Aged Male Mice

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HIV-1 Tat Promotes Age-Related Anxiety-like, Antinociceptive, and Neuromuscular Impairments in Aged Male Mice

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NIH National Institute on Drug Abuse

National Institute of General Medical Sciences

Background

- Combination antiretroviral therapy (cART) has significantly reduced the incidence of HIV-1 associated dementia and increased life expectancy among infected patients. However, ~50% of the HIV$^+$ population still suffers from neurological and psychological symptoms, including increased incidence of cognitive deficits, anxiety/depression, and neuropathic pain, collectively called neuroHIV [1,3].
- HIV-1 proteins, such as the trans-activator of transcription (Tat), are neurotoxic, remain present in the central nervous system despite combined antiretroviral therapy, and are thought to contribute to neuroHIV [2, 4].
- The U.S. HIV$^+$ population is aging with over 60% of individuals 45 years or older. These individuals experience accelerated aging and characterized by vulnerability to numerous age-related comorbidities, including endocrine and immune dysfunction, neurocognitive deficits, vascular and metabolic disorders [4-6].
- HIV-1 Tat protein, cART, and chronological aging can disrupt endocrine function, dysregulate the hypothalamic-pituitary-adrenal and -gonadal axes, and impair steroidogenesis. [4-7].

Hypotheses

HIV-1 Tat expression will interact with aging as assessed by affective, antinociceptive, and neuromuscular comorbidities. Tat may accelerate Age-related comorbidities.

Methods

Animal Housing

HIV-1 Tat transgenic mice were generated in the vivarium at the University of Mississippi (University, MS). HIV-1 Tat_{1-86} protein is expressed via a glial fibrillary acidic protein (GFAP)-driven, tetracycline (Tet)-on promoter activated by doxycycline (30 mg/kg, i.p.). Middle-aged (6-8 mons) and Aged (11-13 mos), male (n=43) that expressed Tat (Tat+) and their non-Tat-expressing counterparts (Tat-) were housed (4-5/cage) in a temperature- and humidity-controlled room on a reversed 12:12 h light/dark cycle (lights off at 20:00 h).

Elevated Plus Maze (EPM)

Mice were placed in the center of an elevated plus maxe (5× 5 cm) and allowed to explore the maze for 5 min. Animals were tracked digitally using Noldus Ethovision tracking software. The latency to enter, and time spent on, the open arms of the maze were considered an index of anti-anxiety-like behavior.

Grip Strength

The apparatus consisted of a wire bar grid connected to a force transducer that recorded the maximal force (*g*) created by gently pulling mice from the bar by the base of the tail until the grip was released. Grip strength was assessed independently for the forelimbs vs. all four limbs.

Electronic Von Frey (eVF) Mechanical Allodynia

The eVF probe was applied to the middle plantar surface of the hind paw and force was incrementally increased until paw withdrawal. The required force (g) to produce the withdrawal was recorded. Each mouse was tested in eight trials (4: right and 4: left) alternating between right and left paws with a 3-min interval break between trials.

Thermal Hyperalgesia

A radiant heat source was applied to the middle plantar surface of the hind paw (2.5℃/sec) until paw withdrawal. Each mouse underwent 4 trials (2: right and 2: left) with a 3 -5 min interval break between trials.

HIV-1 Tat Expression and Aging Exacerbates Anxiety-like Behavior in an Elevated Plus Maze

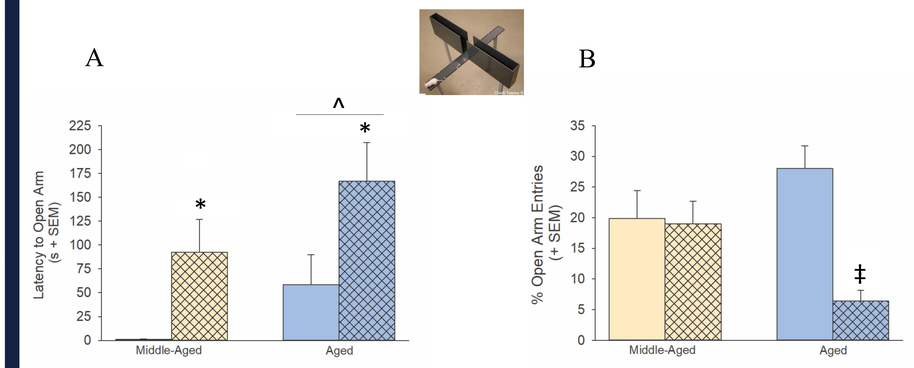

Figure 1: (A) Tat exposure and aging increased anxiety-like behavior. (D) Aged Tat + male showed a lower % open arm entries. * indicates Tat+ significantly differs from respective Tat- control group. ^ indicates aged male significantly differs from respective middle-aged group. ‡ indicates significant difference from all other groups (2-way ANOVA, $p < 0.05$).

Aging Potentiates Mechanical Allodynia Neither Tat nor Aging Produce Thermal Hyperalgesia

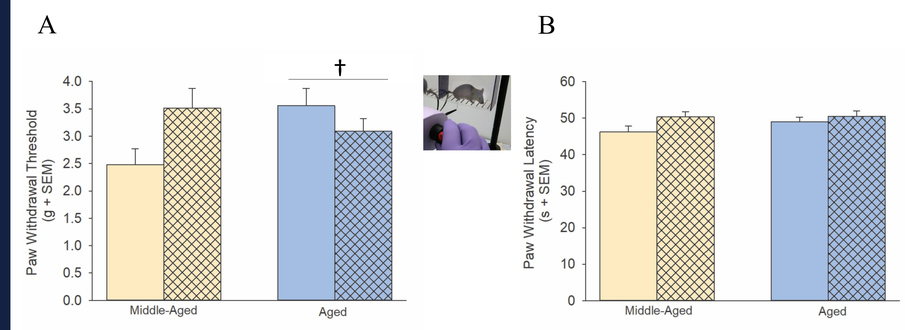

Figure 2: (A) Irrespective of Tat exposure, aged mice demonstrated increased mechanical allodynia. (B) Neither Tat nor aging influenced thermal hyperalgesia. † indicates Tat- control group significantly differs from all other groups (2-way ANOVA , $p < 0.05$).

HIV-1 Tat or Aging Influences Neuromuscular Function

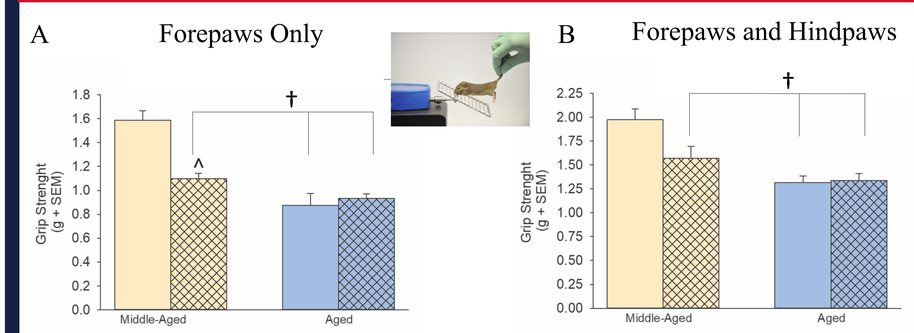

Figure 3: Tat exposure or aging influenced muscle strength normalized to body weight (A) in forelimbs (B) in all four limbs exposure. † indicates Tat- control group significantly differs from all other groups . ^ indicates significant difference from aged Tat – group (2-way ANOVA, $p < 0.05$).

HIV-1 Tat or Aging Alters Organ Weight (Proportional to Body Weight)

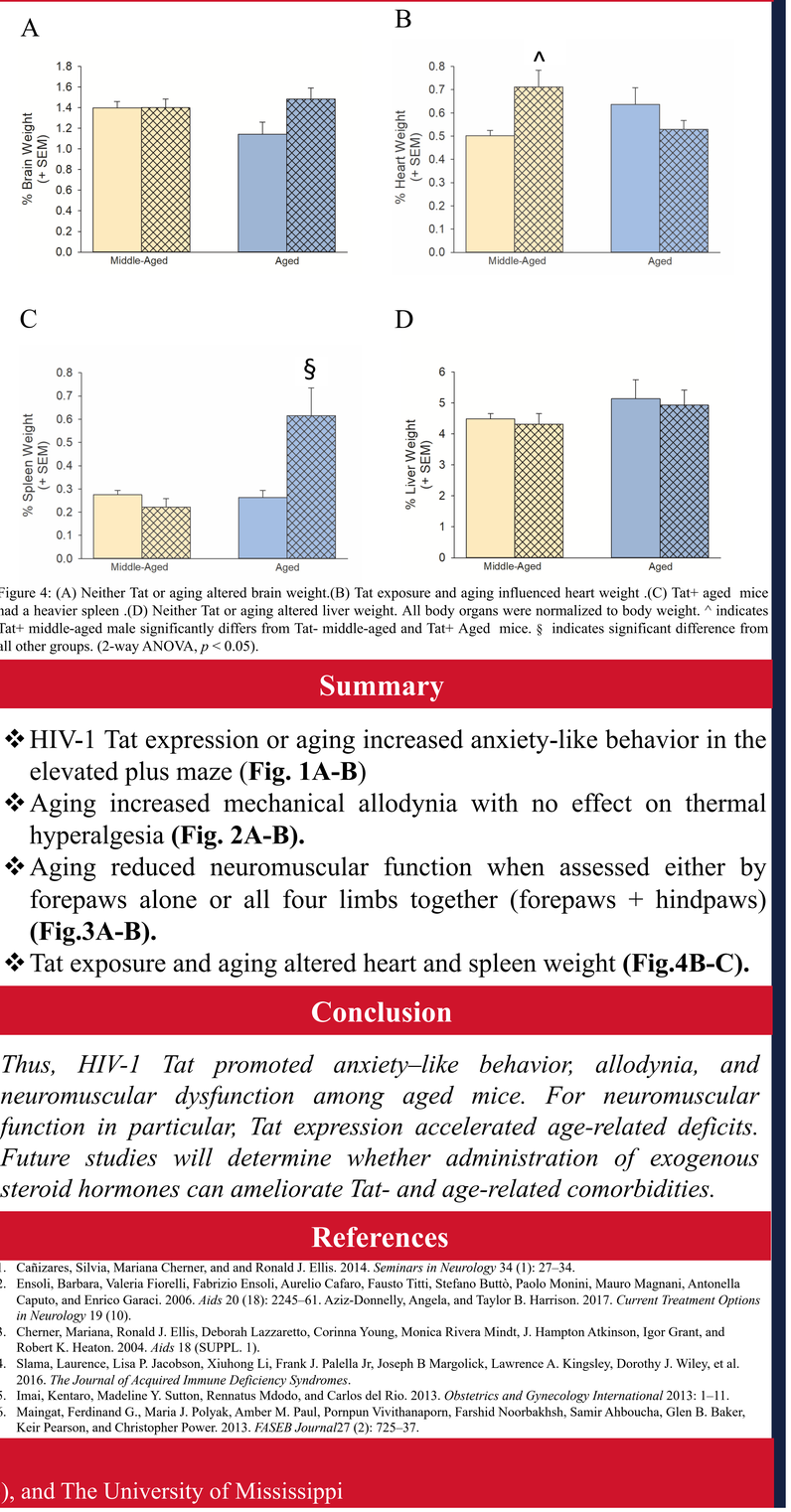

Figure 4: (A) Neither Tat or aging altered brain weight.(B) Tat exposure and aging influenced heart weight .(C) Tat+ aged mice had a heavier spleen .(D) Neither Tat or aging altered liver weight. All body organs were normalized to body weight. ^ indicates Tat+ middle-aged male significantly differs from Tat- middle-aged and Tat+ Aged mice. § indicates significant difference from all other groups. (2-way ANOVA, $p < 0.05$).

Summary

- HIV-1 Tat expression or aging increased anxiety-like behavior in the elevated plus maze (**Fig. 1A-B**)
- Aging increased mechanical allodynia with no effect on thermal hyperalgesia **(Fig. 2A-B).**
- Aging reduced neuromuscular function when assessed either by forepaws alone or all four limbs together (forepaws + hindpaws) **(Fig.3A-B).**
- Tat exposure and aging altered heart and spleen weight **(Fig.4B-C).**

Conclusion

Thus, HIV-1 Tat promoted anxiety–like behavior, allodynia, and neuromuscular dysfunction among aged mice. For neuromuscular function in particular, Tat expression accelerated age-related deficits. Future studies will determine whether administration of exogenous steroid hormones can ameliorate Tat- and age-related comorbidities.

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