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REVIEW ARTICLE

Allopregnanolone and neuroHIV: Potential benefits of neuroendocrine modulation in the era of antiretroviral therapy

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Abstract

Forty years into the HIV pandemic, approximately 50% of infected individuals still suffer from a constellation of neurological disorders collectively known as 'neuroHIV.' Although combination antiretroviral therapy (cART) has been a tremendous success, in its present form, it cannot eradicate HIV. Reservoirs of virus reside within the central nervous system, serving as sources of HIV virotoxins that damage mitochondria and promote neurotoxicity. Although understudied, there is evidence that HIV or the HIV regulatory protein, trans-activator of transcription (Tat), can dysregulate neurosteroid formation potentially contributing to endocrine dysfunction. People living with HIV commonly suffer from endocrine disorders, including hypercortisolemia accompanied by paradoxical adrenal insufficiency upon stress. Age-related comorbidities often onset sooner and with greater magnitude among people living with HIV and are commonly accompanied by hypogonadism. In the post-cART era, these derangements of the hypothalamic-pituitary-adrenal and -gonadal axes are secondary (i.e., relegated to the brain) and indicative of neuroendocrine dysfunction. We review the clinical and preclinical evidence for neuroendocrine dysfunction in HIV, the capacity for hormone therapeutics to play an ameliorative role and the future steroid-based therapeutics that may have efficacy as novel adjunctives to cART.

KEYWORDS

HIV-associated neurocognitive disorder, hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-gonadal axis, mitochondria, neurosteroids

1 | INTRODUCTION

It has been 40 years since the beginning of the HIV pandemic and an estimated 37.6 million people continue to live with the virus worldwide.[1] The tremendous success of combination antiretroviral therapy (cART) has increased the life expectancies of people living with HIV (PLWH) and has greatly improved morbidity. However, the transformation of HIV to a chronic care illness has also revealed the long-term consequences of living with infection. Even in the post-cART era, many individuals continue to suffer from neurological symptoms including an increased prevalence of cognitive impairment, major depression, generalized anxiety disorder, neuropathic pain and motor dysfunction, collectively referred to as "neuroHIV".[2] Identifying and treating the mechanisms of these neurological deficits

is the subject of intense investigation. To this end, the influence of neuroHIV on the neuroendocrine system has become increasingly apparent. In this review, we summarize the recent advances made in our understanding of HIV effects on neuroendocrine function and the potential benefits of steroid-based therapeutics, including the progesterone metabolite, 5α-pregnan-3α-ol-20-one (3α,5α-THP or allopregnanolone), on neuroHIV and HIV viremia. Taken together, the data support a reciprocal relationship between HIV and neuroendocrine status, in which HIV dysregulates the neuroendocrine axes, facilitating stress- and age-related comorbidities that neuroendocrine-based therapeutics may help ameliorate.

2 | HIV-MEDIATED NEUROLOGICAL DYSFUNCTION

In the post-cART era, approximately 50% of PLWH suffer from neuroHIV.[3] Although cART has reduced the incidence of the most severe form of neurocognitive impairment, HIV-associated dementia (present in ~20% of HIV patients in the pre-cART era vs. ~2% in the post-cART era),[3] the proportion of individuals that continue to express any cognitive impairment has remained stable, albeit the symptoms are markedly milder.

2.1 | The HIV central nervous system reservoir

HIV enters the central nervous system (CNS) early in infection, likely by the crossing of infected monocytes and monocyte-derived macrophages through the blood–brain barrier.[4] Within the CNS, microglia (the macrophages of the brain) are thought to be the first cells to contact the virus. Microglia and astrocytes largely comprise the central HIV reservoir (albeit, astrocytes do not infect productively), capable of harboring proviral HIV in a latent state.[5,6] There is a paucity of therapeutic treatments for HIV within the CNS. cART does not accumulate well within this compartment, which may partly be a result of active efflux[7] and its accumulation in endothelial cells,[8] nor can cART target the latent reservoirs that harbor virus.[9,10] As such, a functional cure for HIV is priority.

2.2 | Mechanisms of neuroHIV

There are multiple mechanisms by which HIV can promote CNS damage and dysfunction (Figure 1).[4,11-13] In brief, neuronal damage is largely promoted by both indirect inflammatory mediators and by direct excitotoxic challenges from HIV proteins. The most well-characterized of these virotoxic proteins are the trans-activator of transcription (Tat) and glycoprotein (gp120). Tat is an important regulatory protein that drives HIV transcription. It is present in post-mortem HIV$^+$ brain tissues[14,15] and in the cerebrospinal fluid of HIV$^+$ patients, even when virally-suppressed,[16-19] supporting its presence within the CNS despite cART treatment. Tat can produce neurotoxicity through a variety of mechanisms including the direct activation of L-type calcium channels,[20,21] direct or low density lipoprotein receptor-related protein 1-mediated activation of NMDA receptors,[22-24] and imbalance of intracellular sodium and potassium.[25,26] Tat-mediated cellular pathogenesis is also demonstrated to involve many additional divalent cations beyond Ca^{2+},[27] as well as via the activation of pro-apoptotic activator protein 1 and nuclear

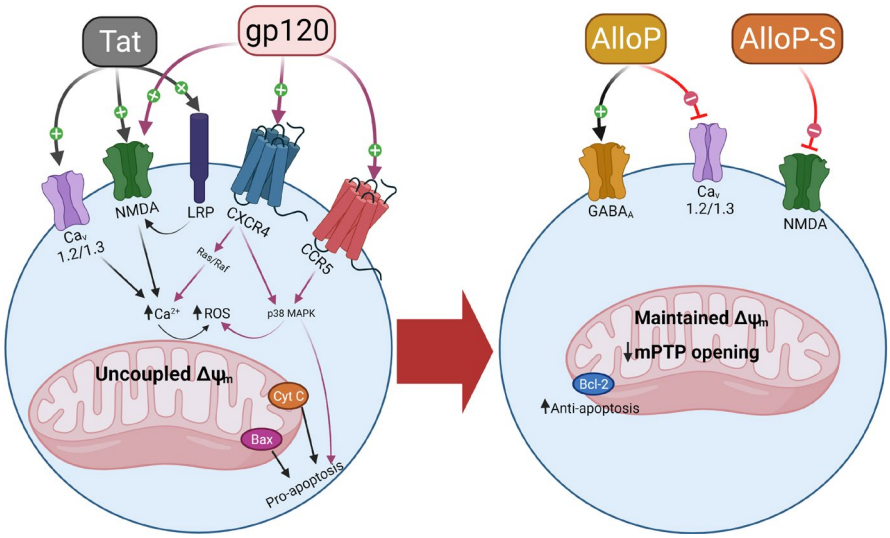


FIGURE 1 Mechanisms of direct neuronal damage for the HIV proteins, trans-activator of transcription (Tat) and glycoprotein 120 (gp120). HIV proteins can directly drive intracellular Ca^{2+} (partly by activation of NMDA receptors, L-type Ca^{2+} channels or activation of chemokine receptor-mediated signaling) or can indirectly activate NMDA receptors via activation of low density lipoprotein receptor-related protein (LRP). The downstream effects of HIV proteins dysregulate mitochondrial membrane potential, drive the formation of reactive oxygen species (ROS), and promote cell injury and death (left). Allopregnanolone is a potent positive allosteric modulator of $GABA_A$ receptors that can antagonize L-type Ca^{2+} channels and restore mitochondrial homeostasis, potentially off-setting the excitotoxic actions of HIV proteins. Allopregnanolone-sulfate is an antagonist of NMDA receptors (right)

factor-kappa B (NF-κB) signaling, thereby promoting downstream inflammatory cytokine production.[13] These effects may occur alone or in synergy with other HIV proteins including gp120. As a non-covalently bound glycoprotein comprising the outer HIV envelope, gp120 can be shed to act at chemokine receptors (largely CXCR4 or CCR5, among other HIV co-receptors), thereby promoting intracellular Ca^{2+} accumulation and neuroinflammatory cytokine release.[28,29] Of great importance when considering HIV virotoxicity in light of endocrine function, Tat, gp120 and additional HIV proteins (Nef, viral protein R) can alter mitochondrial dynamics, biogenesis and membrane potential, as well as glycolytic pathways and ATP production, to promote oxidative stress, mitophagy and apoptosis.[30-32] Thus, there are multiple pathways by which HIV virotoxic proteins can exert neuronal damage or death.

In addition to the use of infectious animal models, the functional effects of single or multiple HIV proteins to promote a neuroHIV-like phenotype have been elucidated via the use of transgenic rodent models. Understanding the singular or synergistic effects of HIV proteins to promote neuroHIV pathology is an important step in identifying therapeutic targets and testing novel therapeutic strategies. To this end, a Tet-on transgenic mouse model has been widely used to conditionally-express Tat from astrocytic sources. Using Tat-transgenic mice, the functional effects of Tat have been identified to be sufficient to produce cognitive impairment on spatial learning tasks,[33-35] executive learning tasks[34,36,37] and fear conditioning,[38] as well as to impair sensorimotor gating.[39] Tat is also sufficient to promote affective-like disturbances in mice, increasing anxiety- and depression-like behavior.[40-48] Both of these affective phenotypes were associated with increased reactive oxygen species in the CNS of mice[42,45] which correlated with anxiety-like behavior.[45] Peripheral neuropathy is also indicated in this model with allodynia observed in response to mechanical stimuli[49,50] and CNS increases in cytokine production.[51,52] Notably, sex differences are seen with females demonstrating antinociceptive thresholds that are intractable to morphine.[53] Conversely, greater durations of Tat exposure impair learned motor performance and grip strength among males, but not females, in this model.[54] These findings implicate Tat as an important therapeutic target within the HIV genome.

Although there are limitations to the use of transgenic models, they are an improvement over direct pharmacological manipulations. In particular, accurate i.c.v. infusion of Tat is challenging given that it is a highly basic peptide (pI = ~9 at physiological pH) that readily adsorbs to surfaces, including glass. Nonetheless, i.c.v. infusion of Tat is found to increase depression-like behavior of Balb/c or C57BL/6J mice.[55] Despite positive findings, this approach suffers from additional drawbacks including the acute nature of the i.c.v. bolus which is unlikely to mimic the virotoxin exposure associated with HIV and the disruption of the blood–brain barrier which produces additional neuroinflammatory confounds.

Constitutive expression of an astrocytic gp120 transgene has also been observed to impair spatial cognitive performance[56,57] and increase anxiety-like behavior.[58] Similarly, transgenic gp120 expression or intrathecal infusion recapitulates peripheral neuropathy in rodents[59,60] with mechanical allodynia and cold sensitivity found to be greater in female mice.[61] These data support findings in HIV transgenic rats (which express all HIV proteins with the exception of Gag and Pol) wherein cognitive deficits and increased anxiety- and depression-like behavior have been reported.[62-64] Thus, secreted HIV proteins are likely contributors to the etiology of neuroHIV and may exert separate or interacting effects.

3 | STEROIDOGENIC DYSREGULATION BY HIV

The endocrine system has long been known to be perturbed by HIV infection with patients presenting with dysfunction of the adrenals, gonads, pituitary and thyroid.[65] However, it is becoming apparent that the interactions between HIV and the endocrine system are dynamic. Endogenous steroids influence HIV replication and neuropathology and, conversely, HIV virotoxins can influence steroid formation. As such, the relationship between neuroendocrine function and neuroHIV symptomatology is reciprocal.

3.1 | Steroid hormones modulate HIV replication

Gonadal steroids have long been proposed to be ameliorative to HIV viremia. 17β-estradiol attenuates HIV replication in cultured peripheral blood mononuclear cells (PBMCs) or human fetal astrocytes in an estrogen receptor α-dependent manner[66,67] and inhibits HIV infection of $CD4^+$ T-cells or monocyte-derived macrophages (MDMs).[68] Moreover, estradiol was observed to decrease Tat-driven activation of the HIV long terminal repeat (LTR; essential for efficient HIV replication), but exerted no effects on basal HIV LTR activity,[69] supporting the notion that these effects were relegated to a direct inhibition of Tat peptide or of the Tat-trans-activation response element (TAR) complex within the LTR. However, large variability in the capacity for estrogens to alter HIV replication has been observed across donors, HIV clades[70] and the menstrual cycle.[71] Similarly, progesterone has been reported to improve antiretroviral potency in cell culture,[72] as well as to attenuate HIV replication at high concentrations in PBMCs,[73] monocytes and MDMs.[74] These effects may be concentration-dependent with low concentrations of estradiol or progesterone being permissive of HIV replication in cultured MDMs, and greater concentrations attenuating HIV replication.[75]

3.2 | Steroid hormones ameliorate HIV-related neuropathology

Given the critical role that Tat plays in HIV replication and its potent neurotoxic effects, it has been recognized as an important therapeutic target, particularly given that current cART does not target Tat. Several studies report that estradiol ameliorates Tat and/or

gp120-induced oxidative stress in human neuroblastoma cells or rat striatal synaptosomes,[76] as well as Tat-induced expression of pro-apoptotic Bax, caspases related to mitochondrial-driven apoptosis and cell death in human fetal neurons[77,78] or neuroblastoma cells.[46] Estradiol was also observed to attenuate Tat-induced activation of a microglial cell line and the subsequent release of proinflammatory cytokines in these[79] and human endothelial cells.[80] Progesterone also exerts protection against Tat-mediated cell death in human fetal neurons[78] or neuroblastoma cells,[46] albeit to a lesser extent than estradiol. Rather, we have observed greater neuroprotective capacity exerted by the 3α-hydroxy/5α-reduced metabolite of progesterone, allopregnanolone (AlloP). We have observed AlloP (up to 100 nM) to partially attenuate microgliosis and neuronal or microglial influx of intracellular Ca^{2+}, to fully-attenuate Tat-mediated depolarization of mitochondrial membranes and to protect human neuroblastoma cells or primary murine neuron/glial co-cultures against Tat-mediated cell death (Figure 2).[45,81] It is likely that steroid hormones also exert beneficial effects over Tat-mediated insults given their pleiotropic capacity to attenuate cytokine production. In particular, AlloP is recently observed to attenuate toll-like receptor signal activation.[82] Thus, estradiol and AlloP exert marked protection against several mechanisms of Tat-mediated cellular dysfunction and death.

3.3 | Pregnane steroids ameliorate HIV Tat-induced behavioral pathology

The functional effects of pregnane steroids to ameliorate neuroHIV-like behavior have been demonstrated using Tat-transgenic mice. High dose progesterone (4 mg kg^{-1} per day for 7 days)[44] or a physiological progesterone schedule (4 mg kg^{-1} once every 5 days for 15 days)[45] rescued the anxiety-like profile induced by Tat expression in ovariectomized mice. However, the protective effects of progesterone were attenuated when the 5α-reductase inhibitor, finasteride (50 mg kg^{-1}), was co-administered, implicating metabolism to AlloP as underlying these beneficial effects.[45] We later observed Tat expression to potentiate the psychomotor effects of opioids and found AlloP to dose-dependently attenuate this.[81] Notably, estradiol did not significantly improve anxiety-like performance following Tat exposure in our hands and rather antagonized the beneficial effects of progesterone when co-administered.[44] However, these studies utilized high, pharmacological estradiol dosing and should be reassessed with physiological concentrations. Thus, AlloP ameliorates neuroHIV-like behavior in a mouse model, consistent with its anti-Tat activities observed *in vitro*.

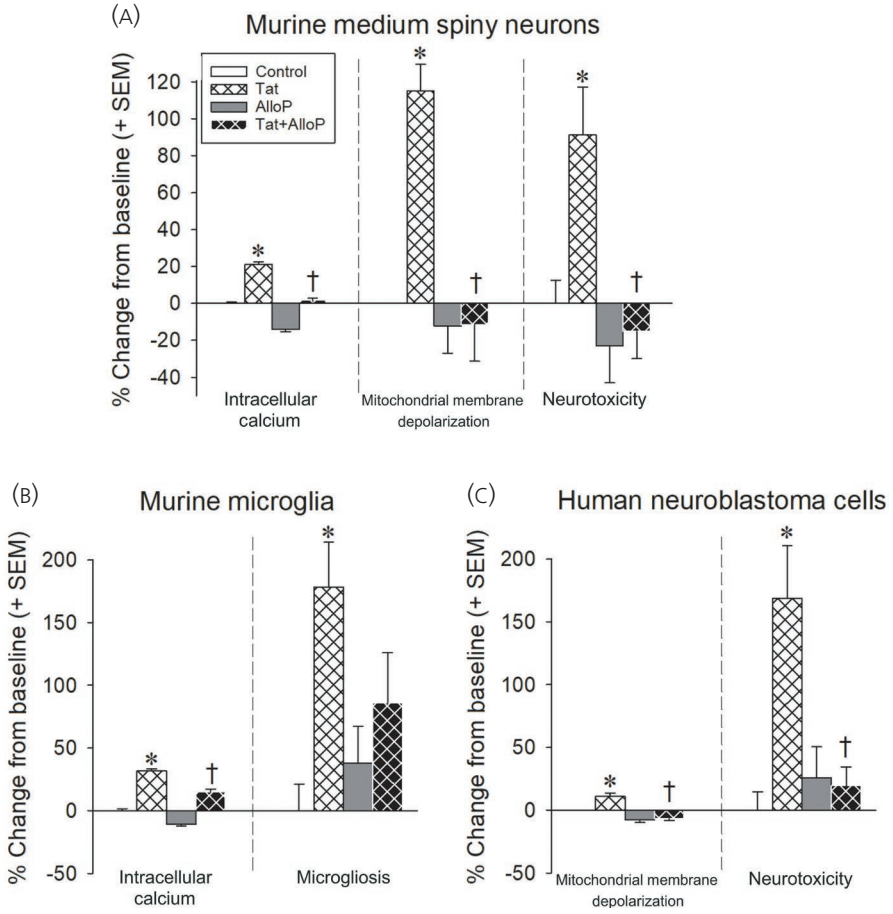


FIGURE 2 HIV Tat (50–100 nM) increases intracellular calcium, depolarizes mitochondria, and promotes microgliosis and/or neurotoxicity in murine striatal medium spiny neurons (A), murine microglia (B) or differentiated human SH-SY5Y neuroblastoma cells (C). Pretreatment with allopregnanolone (AlloP; 100 nM) attenuates Tat-mediated effects. *Significant increase from control following Tat exposure. †Significant AlloP-mediated rescue from Tat exposure

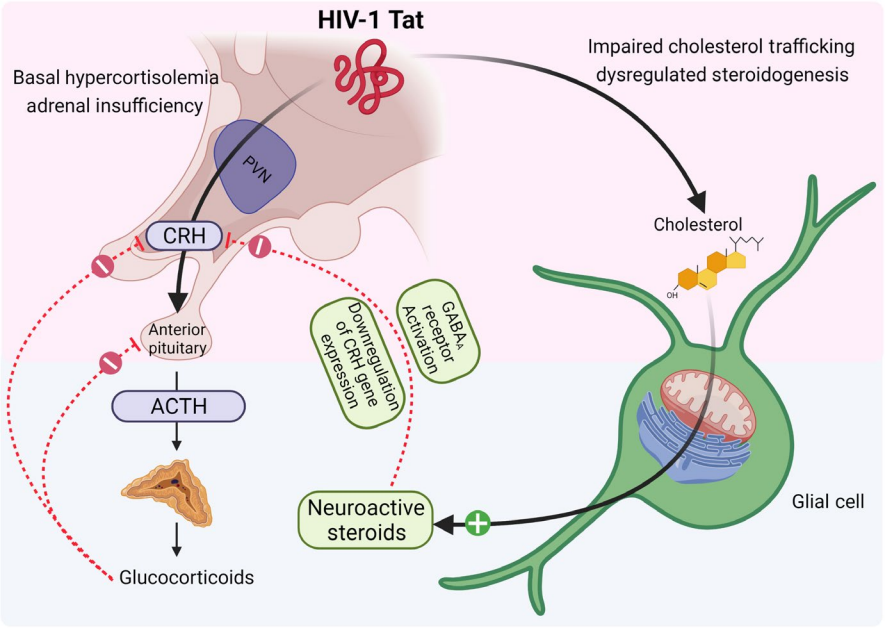


FIGURE 3 Expression of HIV Tat protein in mice increases basal corticotropin releasing hormone (CRH) and corticosterone. Upon stress, male (but not female) mice demonstrate adrenal insufficiency. The effects of Tat to dysregulate cholesterol homeostasis and alter steroidogenesis may contribute to the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. In normative systems, neuroactive steroids such as allopregnanolone restore HPA axis homeostasis, downregulating CRH, adrenocorticotropic hormone (ACTH) and glucocorticoid production

3.4 | HIV disrupts central and circulating steroidogenesis

Given the mitotoxic capacity of HIV virotoxins (Tat, gp120, Nef, viral protein R), it is perhaps not surprising that HIV infection can be associated with perturbations in CNS steroid formation. Tat is also found to alter homeostasis and bioavailability of the steroid precursor, cholesterol (Figure 3),[83,84] and to upregulate ceramides that can inhibit steroid-synthesizing CYP enzymes.[85] However, this has been the subject of surprisingly little investigation. Immunohistochemical observations of post-mortem brains from PLWH indicated a reduction in P450scc, 5α-reductase and 3α-hydroxysteroid dehydrogenase compared to seronegative controls.[86] These findings are intriguing and were supported by parallel studies in human fetal astrocytes that revealed downregulated protein expression of 5α-reductase and 3α-hydroxysteroid dehydrogenase following exposure to HIV-infected supernatants.[86] Changes in neuroactive steroid formation may be particularly important for neuroHIV status. A recent investigation profiled circulating neuroactive steroids in 99 PLWH and found that eight steroids were downregulated in those individuals with high depressive symptoms, including pregnenolone sulfate, dehydroepiandrosterone-sulfate (DHEA-S) and 5α-androstane-3β,17β-diol monosulfate.[87] However, a comprehensive profile of CNS steroids in human patients is lacking.

We have begun to address these questions using a mouse model of neuroHIV. We assessed a panel of 23 pregnane steroids in male HIV Tat-transgenic mice and unexpectedly found Tat to upregulate CNS pregnenolone, AlloP and its 3β isomer (3β,5α-THP), as well as their 20α-hydroxylated metabolites.[81] The only steroid found to be downregulated was deoxycorticosterone and no differences were observed in plasma, supporting the notion that Tat may influence neurosteroidogenesis.[81] Although we had anticipated neurosteroidogenesis to be reduced given the clinical observations in post-mortem brains, the upregulation of 5α-reduced CNS steroids observed is consistent with findings in models of traumatic brain injury and ischemic stroke, which may indicate a neuroadaptive response to challenge.[88-90] It is also important to note that the HIV$^+$ post-mortem brains assessed had HIV encephalitis and were compared with seronegative brains of individuals who suffered from stroke, sepsis and leukemia, which may have promoted a high neurosteroid baseline in the control group. Irrespective of changes within the CNS, the capacity for HIV to disrupt circulating steroids is well-documented in the post-cART era and may contribute to HIV comorbidities.

4 | HIV EFFECTS ON HYPOTHALAMIC-PITUITARY-ADRENAL AND -GONADAL AXES

HIV can exert profound influence on circulating steroid hormone production. These effects can reduce circulating steroid content via actions at endocrine glands, such as the adrenals or gonads (i.e. primary insufficiency), or via actions targeted to the source of steroid-promoting corticotropins and gonadotropins in the hypothalamus and anterior pituitary (i.e. secondary insufficiency). The latter is far more common in the post-cART era, emphasizing the need for HIV therapeutics with efficacy in the CNS. As a result, PLWH are commonly affected by disruptions to the hypothalamic-pituitary-adrenal (HPA) and –gonadal (HPG) axes.[91,92] Such dysfunction likely contributes to the neuropsychiatric components of neuroHIV and the age-related comorbidities that are observed earlier in life and to a greater magnitude among PLWH.

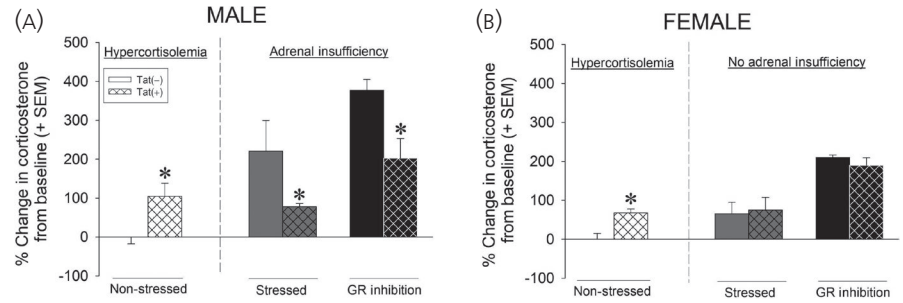


FIGURE 4 Compared to Tat(−) controls, male Tat(+) mice demonstrate greater corticosterone at baseline with paradoxical adrenal insufficiency in response to a stressor (15-min forced swim) or pharmacological inhibition of the glucocorticoid receptor (GR) via RU-486 (A). Compared to controls, female Tat(+) mice also demonstrate increased corticosterone at baseline; however, no differences are observed following a 15-min forced swim stress or administration of RU-486 (B). *Significant difference from Tat(−) control[46-48]

4.1 | HPA stress axis dysregulation in people living with HIV

In the pre-cART era, HIV-related pathogenesis of the HPA axis was largely primary and associated with direct invasion of opportunistic infections, neoplasms or infiltrative diseases that promoted adrenal atrophy.[65] In the post-cART era, HPA axis dysfunction is considered to be secondary (mediated at the level of the hypothalamus or pituitary).[93] Estimates vary, but approximately 14–46% of HIV patients demonstrate HPA axis dysfunction.[94-99] This is characterized by elevated basal serum cortisol levels (hypercortisolemia), yet a paradoxical adrenal insufficiency when exposed to a stressor (Figure 3).[95] PLWH already experience a variety of stigma-related psychosocial stressors that reduce medication adherence, increase the difficulty of receiving a diagnosis and treatment, reduce accessibility to financial aid programs and exacerbate HIV-related psychological symptomatology.[100-104] Although the focus of the current review is on the molecular mechanisms of neuroHIV, it should be appreciated that a number of socioeconomic and environmental stressors may also contribute. Given the importance of glucocorticoids in re-establishing organismal homeostasis following a stressor, the incapacity to mount a sufficient response further predisposes an individual to a plethora of psychological and physiological disorders.[105]

4.2 | Potential mechanisms involved in HIV dysregulation of the HPA axis

Hypercortisolemia is observed in many PLWH during both early and late stages of HIV infection.[106,107] Potential mechanisms may include a chronic enzymatic shift in the production of adrenal androgens to cortisol,[108] a compensatory increase in response to the decline of other steroids, such as DHEA,[87,109] a compensatory response to elevated corticosteroid-binding globulin as has been noted in the transition to AIDS[110] and/or a reduction in the sensitivity of glucocorticoid receptors in response to their cognate ligands.[111] In support of the latter point, elevated basal glucocorticoid receptor (GR) density has been observed,[111] which may be the product of a glucocorticoid resistant state. Increases in proinflammatory cytokines are found to promote a shift in the GRα to GRβ ratio (GRβ is a dominant negative inhibitor of the bioactive GRα), thus reducing GR mediated inhibition of the negative feedback loop.[112] Moreover, PBMCs collected from women living with HIV demonstrated increased gene expression of *FKBP5*, a negative regulator of the gene encoding GR, compared to seronegative PBMCs.[113] The phenotypical adrenal insufficiency that is concurrently observed may be indicative of a depletion in the "adrenal reserve" and/or a consequence of the mitotoxic effects promoted by HIV proteins.

There are several virotoxic proteins secreted by HIV-infected cells that may be involved in HPA dysregulation. Viral protein R is an HIV accessory protein that serves important regulatory functions including viral incorporation, transcription and nuclear translocation of the HIV complex.[114,115] However, viral protein R can also act as a co-activator of the GR and potentiate glucocorticoid actions, perhaps promoting a glucocorticoid resistant state.[116,117] In addition, the HIV envelope protein, gp120, is seen to increase plasma adrenocorticotropic hormone (ACTH) and corticosterone levels, with an analogous increase in pituitary ACTH content, when expressed in a transgenic mouse model.[118] Furthermore, gp120 increases CRH mRNA expression and CRH release in *ex vivo* mouse or rat hypothalamic explants.[119,120] Tat may also act in concert with these virotoxins to influence HPA function and has apparent effects to recapitulate the clinical phenotype when expressed in mice.

As described, Tat-transgenic mice demonstrate several behavioral aspects of neuroHIV (e.g., impairments in cognition and sensorimotor gating, increased anxiety- and depression-like behavior). Our group has assessed HPA function in these mice and found Tat expression to be sufficient in recapitulating the clinical endophenotype. Compared to controls, Tat-expressing male or female mice demonstrate basal hypercortisolemia (Figure 4).[46-48] We have also observed increased hypothalamic CRF protein expression in females (males have not been assessed).[46] Of interest, males also demonstrate adrenal insufficiency in response to a stressor (15-min forced swim) or when adrenal corticosterone production is stimulated by pharmacologically-blocking GRs (Figure 4A); however, females appear to be protected from these effects (Figure 4B).[48] Although the mechanisms by which Tat may induce hypercortisolemia or a sex-specific adrenal insufficiency are not yet understood, several avenues have potential. Expressing Tat

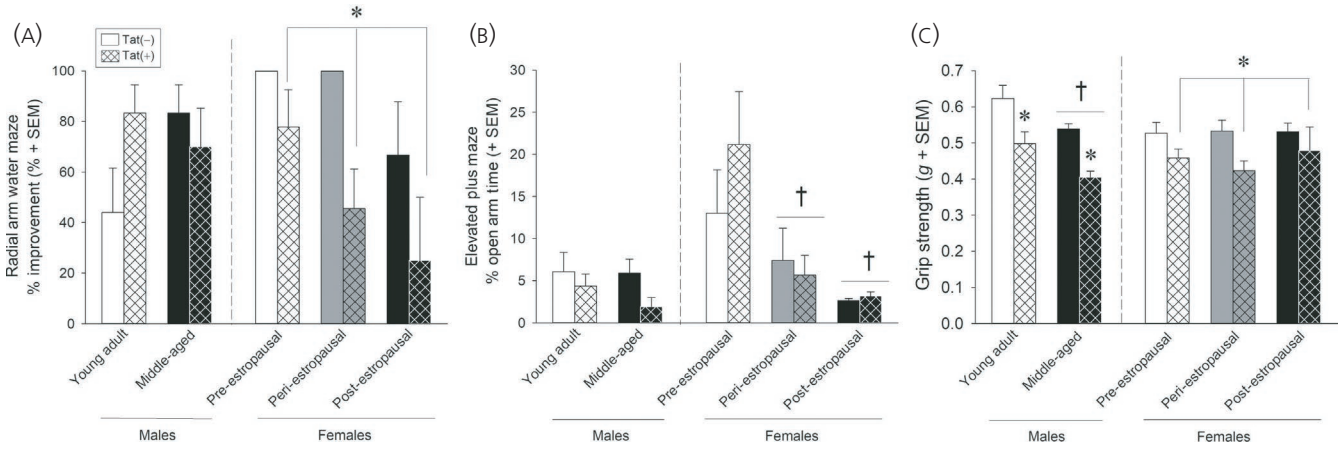


FIGURE 5 Middle-aged (16–19 months old) female Tat(+) mice had greater learning deficits on a radial arm water maze than their Tat(−) counterparts, irrespective of estropausal status (A). Anxiety-like behavior on an elevated plus maze was greater among peri- and post-estropausal mice compared to those that were pre-estropausal, irrespective of Tat exposure (B). Male or female Tat(+) mice had reduced grip strength compared to Tat(−) controls. Middle-aged males (11–13 months old) had reduced grip strength compared to young adult males (6–8 months old) (C). *Significant difference from Tat(−) control. †Significant difference from young adult male or pre-estropausal female group[177]

protein in this model promotes the production of cytokines within the CNS.[51,52] Several second messengers and transcription factors associated with cytokine production, such as signal transducer and activator of transcription (STAT) 5, p38 mitogen-activated protein kinase (MAPK) and NF-κB, inhibit GR signaling.[121] Interleukin (IL)-1α, IL-2, IL-4, or STAT5 phosphorylation are reported to inhibit nuclear translocation of the GR.[122-124] In particular, IL-2 and IL-4 can phosphorylate the GR via p38 MAPK signaling, thereby reducing affinity for its cognate ligands.[125,126] Together, these actions may contribute to a GR-insensitive state. In support, we have found Tat to induce glucocorticoid resistance in primary mouse splenocytes *in vitro*.[81] Thus, Tat, gp120 and/or viral protein R may act alone or in concert to promote glucocorticoid resistance. Given the importance of the stress response in overcoming psychological and physiological challenges, disruption of the HPA axis may be an important contributor to the neuroHIV-like phenotype observed.

4.3 | HPG stress axis dysregulation in people living with HIV

Consistent with central neuroendocrine dysfunction in the post-cART era, approximately 10–50% of PLWH present with hypogonadism (defined by low testosterone levels in men and dysregulated estradiol/progestogen levels in women).[127-131] The consequences of this phenotype are particularly evident among PLWH that are ≥ 50 years of age, which now comprise the majority of all HIV cases in the US.[132] People living with HIV experience an early occurrence of age-related complications, including frailty, cardiovascular diseases, renal diseases that are co-morbid with diabetes and hypertension, cognitive deficits, endocrine disorders, and bone diseases including osteoporosis.[133-143] Animal models of some of these disorders, such as diabetes, are associated with a downregulation of steroid-synthesizing enzymes and dysregulated formation of androstane/pregnane steroids, including AlloP.[144-147] Both men and women living with HIV experience an earlier onset of the climacteric, concurrent with hormonal deficiencies. As such, early hormone therapeutic intervention may provide a particularly salient benefit to this population.

In men living with HIV, modern-day hypogonadism is mainly secondary and occurs in both young or middle-aged cART-treated men (approximately 12–28%).[127,130,148-150] The incidence of hypogonadism increases with age, HIV duration and lower $CD4^+$ T-cell counts.[150-153] Men living with HIV experience a premature transition to andropause associated with a lower level of circulating testosterone,[127,131,154-158] normal or low levels of luteinizing hormone,[127,131,159] a greater level of sex hormone binding globulin[150,155,160] and a greater estradiol-to-testosterone ratio.[159] Androgen deficiency increases the risk for central fat accumulation, cardiovascular diseases and frailty among HIV-infected men.[155,161]

Similarly, women living with HIV display accelerated ovarian aging (transition to peri- and post-menopause) sooner than seronegative women,[162-164] lower circulating androgens[165,166] and 17β-estradiol,[165] and a greater frequency of vasomotor/climacteric symptoms, including hot flashes, depression/anxiety and bone degeneration.[164,167-173] Hormonal replacement therapy may be particularly effective in attenuating these HIV-associated co-morbidities. Taken together, the aging HIV^+ population faces a myriad of premature and/or accentuated co-morbidities that are likely to influence the pathogenesis of neuroHIV and age-related complications.[139,142,174]

4.4 | Potential mechanisms involved in HIV dysregulation of the HPG axis

Although the mechanisms of HIV-mediated neuroendocrine dysfunction are not known, animal models have begun to provide some

insights. Recent work has established a link between HIV Tat expression and some age-related comorbidities. Long-term Tat expression in middle-aged mice impaired both short- and long-term memory of males, although only short-term memory of female mice; motor coordination and balance were impaired in both sexes.[175] Nuanced sex differences in neuropathology were observed, with Tat inducing greater pre- and post-synaptic marker density in the female cortex and lower pre-synaptic marker density in the cerebellum of males.[175] In addition, global DNA methylation was greater in Tat-exposed females.[175] These plastic and epigenetic changes may occur in response to CNS challenge. Magnetic resonance imaging reveals increased ventricular volume and decreased motor cortex gray matter volume in Tat-exposed middle-aged male mice, concurrent with astrogliosis and elevated proinflammatory cytokines.[85] When aged males and females were directly compared, magnetic resonance spectroscopy revealed Tat exposure to reduce the antioxidants, glutathione and taurine, in aged female mice, but not aged males.[176] However, it is also important to parse the influence of aging and HIV Tat exposure to better understand the source of such sex differences. When stratified by estropause status (pre-, peri- or post-estropausal), Tat-exposure and aging were found to exert largely independent effects on behavioral pathology.

Irrespective of Tat exposure, peri- and post-estropausal mice demonstrated greater anxiety-like behavior and cognitive impairment than pre-estropausal mice (Figure 5A,5B).[177] Tat exposure independently reduced learning in a radial arm water maze (Figure 5A), as well as grip strength (Figure 5C) and mechanical nociceptive thresholds.[177] Males appeared more resilient to Tat's age-related effects; however, Tat-impairment of grip strength was exacerbated with aging (Figure 5C). When endocrine function was assessed, estropausal status and Tat exposure interacted, such that pre-estropausal Tat(+) mice had a greater estradiol-to-testosterone ratio (largely driven by reduced testosterone levels) and post-estropausal Tat(+) mice had an estradiol reduction not observed in any other group.[177] Similar endocrine interactions were observed when comparing young and middle-aged male mice exposed to Tat. Tat greatly reduced circulating total testosterone and increased corticosterone in middle-aged males. Regressions revealed increased corticosterone to be associated with greater anxiety-like behavior, greater swim speed in a radial arm water maze and poorer grip strength. Among young adult males, Tat increased circulating 17β-estradiol, the estradiol-to-testosterone ratio and progesterone, a profile consistent with an early andropausal transition. AlloP was significantly elevated in the hippocampus of young adult and middle-aged males and the midbrain of middle-aged males (with no changes seen in the frontal cortex). Together, these data reveal the separate and interactive constructs on which the aging endocrine system interacts with Tat exposure.

The capacity of Tat to promote circulating steroid deficits may partly involve its toxic actions at mitochondria, the rate-limiting organelle required for steroid synthesis,[25,178,179] and may also involve its capacity to alter lipid substrate bioavailability.[83,84] Pharmacological maintenance of steroid concentrations may be beneficial. In support, testosterone replacement therapy among men living with HIV improved depression inventory scores,[180,181] increased muscle and lean body mass,[181,182] and improved sexual function by restoring libido.[182] Administration of testosterone to women living with HIV also improved body weight and quality-of-life.[183] Similar benefits for reduced depressive symptomatology have been observed in response to DHEA administration.[184] Thus, steroid intervention may provide a benefit to aged PLWH and the timing for optimal implementation may differ from seronegative aged individuals.

5 | STEROID-BASED THERAPEUTICS FOR THE TREATMENT OF HIV

5.1 | Novel adjunct therapeutics for HIV suppression

Antiretroviral therapeutics have dramatically increased the life expectancy of PLWH. However, these drugs are not able to eradicate the virus, nor neuroHIV, given that they cannot target reservoirs such as those within the CNS and do not target certain virotoxins such as Tat. It is notable that several promising leads are based on a steroid-scaffold. Most notably, didehydro-cortistatin A (dCA), an analogue of a steroid-like alkaloid obtained from marine sponge, is demonstrated *in vitro* to bind to the Tat-TAR complex, blocking HIV replication without producing cellular toxicity, to attenuate HIV-mediated cytokine expression and to inhibit behavioral effects promoted by Tat *in vivo*.[185,186] dCA was found to selectively bind the unstructured basic region of Tat.[187] A combination of dCA and cART suppressed active HIV viral replication, reactivation and rebound of the latent viral reservoir.[188] Additional chemical derivatives of dCA were sought to rationalize their ability to dock at specific binding sites of the Tat protein.[187] Given the ability of dCA to inhibit Tat expression during early viral replication and penetrate latent viral reservoirs in the brain with good bioavailability, dCA and its novel steroidal-based analogs hold potential as future cART adjuncts.[187-189]

Additional estrogen-based therapeutics have also been identified, including selective estrogen receptor β agonists, such as (*S*)-equol and several phytoestrogens. (*S*)-equol improved sensorimotor gating and motivational deficits in HIV transgenic rats[190-192] and prevented combined cocaine and HIV-mediated synaptopathy.[193] The phytoestrogens, daidzein and liquiritigenin, restored Tat-mediated synaptodendritic recovery.[194] Our own work has focused on the potential therapeutic advantages of neurosteroids.

Neurosteroids are synthesized *de novo* in brain from cholesterol[195] and can also reach the brain from peripheral sources such as the adrenals and gonads.[196] AlloP is perhaps the most well-characterized neurosteroid with a pharmacodynamic profile that is suitable for potentially offsetting the effects of HIV Tat (Figure 1). Given the excitotoxic profile exerted by Tat, the actions of AlloP as a potent positive allosteric modulator of $GABA_A$ receptors are

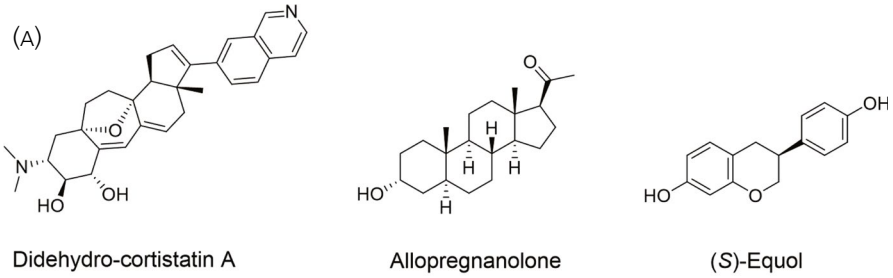
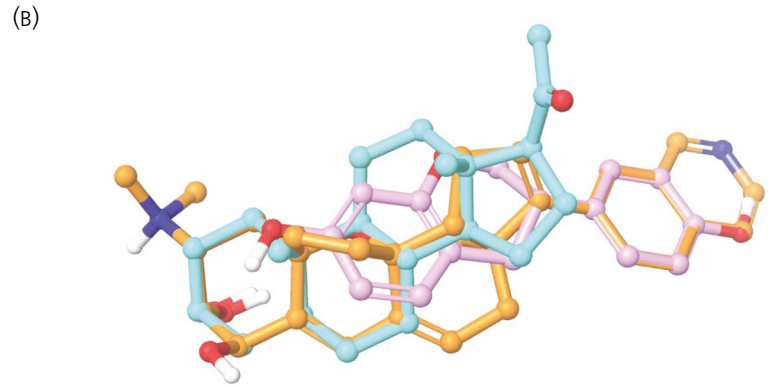


FIGURE 6 Didehydro-cortistatin A (orange), allopregnanolone (cyan) and (*S*)-equol (pink) demonstrate structural similarities (A) that are evidenced in a ligand-structure alignment (B)



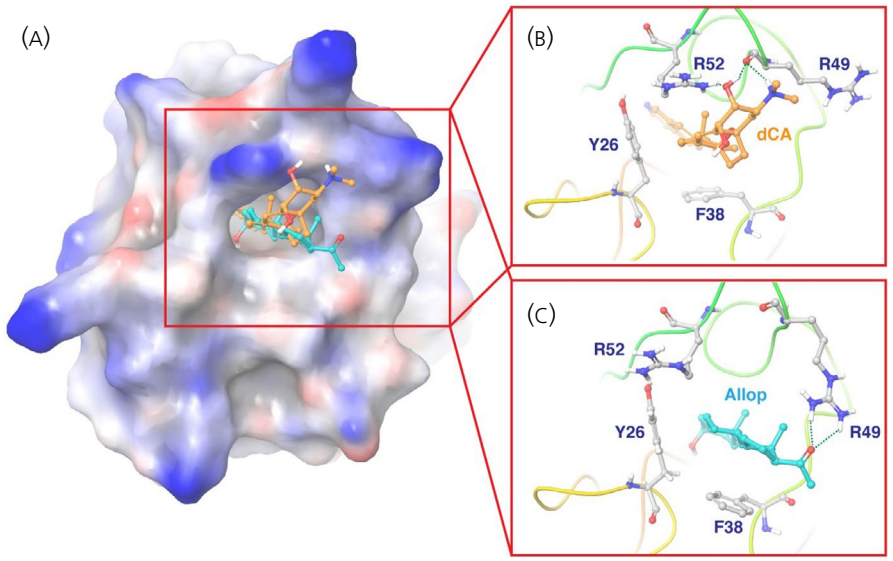


FIGURE 7 Molecular docking of didehydro-cortistatin A (dCA) (orange) and allopregnanolone (cyan) in HIV Tat (Protein Data Bank: 1K5K). Tat is shown in a surface representation in the zoom-out view (A) and in a ribbon representation in the zoom-in view (B, C). Key residues of Tat for ligand binding are shown in stick representation

expected to reinstate excitatory–inhibitory balance via the influx of Cl^-. Moreover, AlloP may act as an antagonist of L-type Ca^{2+} channels,[197,198] further attenuating the excitotoxic actions of Tat. We have seen promising evidence for AlloP to offset Tat-mediated neurotoxicity *in vitro* (Figure 2) and to attenuate Tat-mediated behavioral interactions with opioids *in vivo*.[81] Although AlloP is a small molecule that readily crosses the blood–brain barrier and is well-tolerated,[199] it is also rapidly re-distributed from the brain, accumulates in adipose tissue and has a short elimination half-life.[200,201] As such, we are currently working to synthesize AlloP analogues with anti-Tat and anti-viremic properties. A ligand structural alignment of dCA, (*S*)-Equol and AlloP reveals structural similarities that may help explain their anti-HIV activities (Figure 6). For example, both terminal ends of the molecules contain polar elements (an oxygen or a nitrogen atom). Induced-fit docking of dCA in the NMR-derived structure of Tat (Protein Data Bank: 1K5K) reveals important hydrogen bonding interactions between dCA and the R49 and R52 residues, which are part of the identified motif (the ARM domain) (Figure 7). Induced-fit docking of AlloP in this binding site also reveals important hydrogen bonding interactions between AlloP and the R49 residue, in addition to strong hydrophobic interactions (Figure 7). These preliminary data suggest that dCA and AlloP may target a shared Tat binding site that may partly underlie their potential anti-Tat efficacy. In light of this, the development of novel AlloP analogs may hold promise with respect to potential future cART adjunctive therapeutics.

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Mohammed F. Salahuddin: Conceptualization; data curation; formal analysis; funding acquisition; investigation; writing-original draft; writing-review & editing. **Alaa N. Qrareya:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; writing-original draft; writing-review & editing. **Fakhri Mahdi:** Data curation; formal analysis; methodology. **Emaya Moss:** Data curation; formal analysis; funding acquisition. **Nicholas S. Akins:** Data curation; formal analysis. **Jing Li:** Conceptualization; data curation; formal analysis; methodology; supervision; writing-review & editing. **Hoang V. Le:** Conceptualization; data curation; formal analysis; methodology; supervision; writing-review & editing. **Jason J. Paris:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; writing-original draft; writing-review & editing.

DATA AVAILABILITY STATEMENT

Data are available from the authors upon suitable request.

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