Chronic distress and the vulnerable host: a new target for HIV treatment and prevention?

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Abstract: Pathologic stress (distress) disturbs immune, cardiovascular, metabolic, and behavioral homeostasis. Individuals living with HIV and those at risk are vulnerable to stress disorders. Corticotropin-releasing hormone (CRH) is critical in neuroendocrine immune regulation. CRH, a neuropeptide, is distributed in the central and peripheral nervous systems and acts principally on CRH receptor type 1 (CRHR1). CRH in the brain modulates neuropsychiatric disorders. CRH and stress modulation of immunity is two-pronged; there is a direct action on hypothalamic–pituitary–adrenal secretion of glucocorticoids and through immune organ sympathetic innervation. CRH is a central and systemic proinflammatory cytokine. Glucocorticoids and their receptors have gene regulatory actions on viral replication and cause central and systemic immune suppression. CRH and stress activation contributes to central nervous system (CNS) viral entry important in HIV-associated neurocognitive disorders and HIV-associated dementia. CNS CRH overproduction short-circuits reward, executive, and emotional control, leading to addiction, cognitive impairment, and psychiatric comorbidity. CRHR1 is an important therapeutic target for medication development. CRHR1 antagonist clinical trials have focused on psychiatric disorders with little attention paid to neuroendocrine immune disorders. Studies of those with HIV and those at risk show that concurrent stress-related disorders contribute to higher morbidity and mortality; stress-related conditions, addiction, immune dysfunction, and comorbid psychiatric illness all increase HIV transmission. Neuropsychiatric disease, chronic inflammation, and substance abuse are endemic, and chronic distress is a pathologic factor. It is being understood that stress and CRH are fundamental to neuroendocrine immunity; therapeutic interventions with existing and novel agents hold promise for restoring homeostasis, reducing morbidity and mortality for those with HIV and possibly reducing future disease transmission.

Keywords: corticotropin-releasing hormone, stress, neuroendocrine immunology, hypothalamic–pituitary–adrenal, cytokine, glucocorticoid resistance

Introduction

Individuals who engage in high-risk behaviors remain the principal reservoirs of HIV, allowing continued viral dissemination into the community. Men who have sex with men (MSM) and drug abusers remain the principal pools of HIV, though increasing numbers of women and men contract the disease through heterosexual contacts. Currently, MSM and injection drug users (IDU) represent approximately 55% and 15%, respectively, of people living with HIV/AIDS. Newly infected populations, in 2010, comprised 63% MSM, 8% IDU, approximately 25% heterosexuals, and 3% MSM–IDU. Statistics vary, but injection and non-injection are approximately 30% of those with HIV/AIDS. Thus, MSM, heterosexuals, and IDU remain the pools with the highest
risk of contracting and disseminating HIV.\textsuperscript{1,2} Substance abusers, especially IDU, remain a difficult group to attract to and maintain in effective HIV treatment.\textsuperscript{3}

Although there have been many successes in prevention, education, and screening in some groups and communities, risk behaviors still account for the vast majority of new infections, and reaching these individuals and groups remains a priority to curb spread.\textsuperscript{4} The risks of sexual exposure and drug abuse are not confined to any specific group or behaviors. Finding more effective strategies to connect with and reduce viral transmission is critical at this stage of the epidemic. Neuroendocrine immunity and the study of stress is an evolving discipline seeking to find pathophysiologic commonalities in at-risk populations. How stress contributes to behavioral, neuroendocrine, and immune dysfunction may offer new therapeutic approaches for those with HIV and at high risk. Clinical and preclinical studies show an activated stress system has deleterious effects and increases susceptibility to neurocognitive and psychiatric disease, diminishes immune integrity, and increases metabolic and cardiovascular disease. These contribute to weakened host defenses.\textsuperscript{5–7} Cytokines and stress hormone markers of neuroendocrine immune dysfunction are often present prior to and once HIV infection has occurred.

The central nervous system (CNS) regulates stress through corticotropin-releasing hormone (CRH), as well as through other neurotransmitters and neuromodulators. Stress engages the hypothalamic–pituitary–adrenal (HPA) axis, the extended amygdala (EA), and other limbic structures, as well as neocortical areas responsible for cognition. This also increases vulnerability to infections and weakens immunity directly and indirectly by promoting high-risk behaviors, enhancing susceptibility to cognitive and affective disorders, generating systemic inflammation, and offering a permissive neuroendocrine environment with adverse effects on host defenses.

With HIV infection, the HPA axis is hyperactive, increasing adrenal glucocorticoid (GC)/cortisol secretion and activation of GC receptors (GCrs). At a molecular level, this increases viral replication in lymphocytes and other viral reservoirs. This causes apoptosis of normal lymphocytes, decreases in circulating CD4\textsuperscript{+} cells, adverse shifts in cytokine patterns, and weakening of mucosal defenses, all increasing immune compromise and disease progression.\textsuperscript{8–12}

This review examines the elements that confer noninfected high-risk groups greater susceptibility to HIV and how chronic distress hastens HIV progression, increasing morbidity and mortality. Can interventions limiting the effects of stress be potentially therapeutic in slowing the progression of HIV and can they improve prevention efforts? New molecular targets that modulate homeostasis may provide molecular probes into neuroimmunity and also eventually offer additional behavioral and pharmacologic therapeutic options for managing complications and improving survival.\textsuperscript{5,13,14}

**Vulnerable populations**

Persons living with HIV and some who are at risk show chronic activation of stress hormone secretion.\textsuperscript{15–18} MSM who have frequent or infrequent sex without barrier protection have a high risk of contracting and/or spreading HIV. Concurrent drug use increases the frequency of casual sex and the likelihood of infection and transmission. Finlayson et al.,\textsuperscript{19} reporting from the National Behavioral Surveillance System, estimated 54% of MSM have unprotected sex, with 25% in casual circumstances. Additionally, concurrent drug use was reported in 46% of their subjects. Others have found similar results in relevant populations.\textsuperscript{20,21}

Despite several studies focusing on sociobehavioral characteristics and the prevalence of risk behaviors within the MSM population(s) impacting disease transmission and progression, little is known about pre-seroconversion immune functions in this vulnerable population. Longitudinal studies of non-HIV-infected seronegative MSM show long-term dysfunction in cellular immunity equivalent to the impairment seen in early HIV infection with CD4 counts >500.\textsuperscript{22} Palmer et al reported higher levels of immune activation in a group of HIV-negative self-identified “high-risk” MSM compared to age- and ethnicity-matched self-identified “healthy, low-risk” male control individuals.\textsuperscript{23} These observations need to be further validated in larger trials and substantiated in particular by studies focusing on the etiological factors of the immune compromise in this vulnerable population. HIV clinical studies have indeed shown that pre-seroconversion elevated levels of immune activation are associated with increased risk for development of AIDS after HIV-1 seroconversion.\textsuperscript{24} In active IDU, the pre-seroconversion state of immune dysfunction and reduced CD4+ counts negatively predict the pace of peripheral CD4+ decline once infected. The type of substance(s) used did not affect immune decline, though, as one might expect, the injecting frequency did correlate with immune deterioration.\textsuperscript{25} Low levels of CD4+ cellular activation, a favorable measure of immune integrity, is associated with diminished susceptibility to HIV seroconversion.\textsuperscript{26}

Sexual promiscuity (sexual activity with multiple partners without barriers), continuous exposure to other antigens in community networks with high prevalence of STD infections, use of drugs, and chronic stress are all potential contributors to the establishment of an altered immune activation in this vulnerable population.
CRH, a critical neuropeptide, orchestrates stress responses
The central stress system

The neuroendocrine immune system is a multifaceted network of neuropeptides, neurotransmitters, and endocrine hormones, which regulate and are regulated by a complex array of immune modulators and hormones. These are multiple feedback and feedforward circuits that regulate homeostasis that are differentially activated under acute and chronic conditions. CRH is of particular interest as it has been identified as a principal (but far from the only) stress activator with CRH through CRH receptor type 1 (CRHR1), a critical molecular target. As mentioned elsewhere, CRH and CRHR1 are found in the CNS, in the peripheral nervous system, and throughout the immune system.35-40

CRH is a member of a family of stress-related peptides with two main receptors with multiple active and inactive subtypes.41 Stress peptides and their receptors show wide species variation in both their actions and anatomic distribution. In the primate, CRH has high affinity and physiologic activity at the CRHR1. In the CNS, CRH and CRHR1 are highly concentrated in the hypothalamus, areas of the cortex related to cognition, and the EA. The hypothalamus regulates stress hormones from the pituitary and adrenals. Salience, behavioral arousal, and the sympathetic nervous system (SNS) are controlled by brainstem structures, principally the pontomedullary and raphe nuclei and the locus caeruleus. Hypothalamic CRH is released to the anterior pituitary, activates CRHR1, and, with vasopressin, stimulates adrenocorticotropic (ACTH) release. ACTH is a potent adrenal secretagogue releasing cortisol and adrenal androgens, including dehydroepiandrosterone (DHEA). The hypothalamus activates the systemic SNS and the adrenal medullary catecholamines epinephrine and norepinephrine (NE). Direct autonomic innervation and circulating epinephrine and NE stimulate visceral and lymphoid tissues and activate metabolic, cardiovascular, immune, and other physiologic responses to adverse stimuli.

In addition to the hypothalamus, pituitary, and SNS, CRH and CRHR1 are expressed in the neocortex, which is important for executive and cognitive processing and motivational behaviors. The EA is a complex structure composed of discrete but tightly linked nuclei. The bed nucleus of the stria terminalis; central, basolateral, and medial nuclei of the amygdala; insulae; and medial nucleus accumbens form the hub of the EA.42,43 The EA forms a functional interface between the higher cognitive functions of the cortex to the endocrine hypothalamus and to autonomic regulation from the brain.
stem to the peripheral nervous system. The EA is the seat of memory, emotion, and motivational behaviors, fundamental to impulsivity, drug abuse, and sexual drive. Functional disruption of the EA is seen in stress-related disease such as major depressive disorder (MDD), generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), chronic pain, metabolic syndrome, chronic medical conditions, substance abuse, addiction, and other compulsive disorders.6,7

**CRH as cytokine and stress immune modulator**

**Peripheral CRH actions**

CRH is secreted peripherally as a proinflammatory cytokine. It is expressed in lymphocytes, eosinophils, mast cells, monocytes, microglia, enterochromaffin cells, lymphatic and stromal cells, parasympathetic ganglia, cellular elements regulating the blood–brain barrier (BBB), colonic epithelium, gut immune tissues, integument, and others.44–50 It acts in a paracrine manner and increases inflammatory responses to infection and autoimmune diseases. CRH is mobilized in infection and inflammation, causes disruption of mucosal membranes and the BBB, and is a locus of tissue injury in autoimmune diseases.51–53

CRH and CRHR1 are important in gut immune integrity, being highly concentrated in intestinal mucosa, lymphoid tissue, and parasympathetic ganglia. CRH is secreted locally and then systemically in response to regional inflammation and infection. CNS activation of the SNS and parasympathetic nervous system stimulates regional CRH secretion. Mucosal tissues show high CD4+ expression, and the gastrointestinal (GI) mucosa is an especially critical organ for HIV exposure and infection.44,54–57 CRH activates CD4+ lymphocytes, and CRH blockade may represent a target to diminish CD4+ activation to limit systemic HIV dissemination.39,46 It remains somewhat controversial as to the exact mechanism(s) by which a proinflammatory immune system affects disease progression, even though inflammation has undisputed deleterious mucosal effects. Inflammation increases GI mucosal permeability and increases microvascular translocation, increasing systemic bacterial load and circulating lipopolysaccharide, a biomarker for systemic immune activation, bacterial invasion, and systemic HIV progression.29,58

CRH stimulates the HPA axis, and excess GC/cortisol modulates immune responsivity. Under chronic stress, integrated daily cortisol secretion is elevated; compared to normal individuals, GC/cortisol concentrations may approach pharmacologic levels.59 Diminished sensitivity of the HPA axis and the CRH-containing hypothalamic neurons to GC/cortisol negative feedback is at least partially responsible for GC/cortisol overproduction. In the acute setting, endogenous cortisol as well as synthetic GC acutely causes immunosuppression, diminishing the inflammatory response to infection and inflammatory and other immune insults. Acute activation of the HPA axis and GC release are very effective in suppressing inflammation. When the stress system and the HPA axis are chronically activated, immune responsivity can convert to a smoldering proinflammatory state; this can be seen in autoimmune disorders, malignancy, atherosclerosis, and metabolic conditions. Responses to acute inflammation and infectious insults may be blunted, resulting in a suboptimal host defense during chronic stress-related proinflammatory states.5,38,39,60 Immune suppression can stem from cortisol overproduction causing acquired dysfunction of the GCr. GC hyper-sensitivity or GC resistance (R) can be tissue specific and may be present in the individual simultaneously, inhibiting or stimulating an inflammatory host response.61 GC hyper-sensitivity or GCR has been associated with neuroimmune dyshomeostasis and is also a marker of host vulnerability and disease progression.52

**Immune modulation of the CNS CRH stress system**

Stress activation regulates cytokines at multiple sites in the neuroendocrine immune cascade. When a proinflammatory environment is present, there is both passive and active transport of cytokines/chemokines and other inflammatory mediators into the brain. In areas where the BBB is absent (circumventricular organs) or less restrictive (median eminence), there is direct cytokine penetration.62–65 In addition, carrier transport proteins have been identified for some interleukins (ILs) and for tumor necrosis factor (TNF)-alpha.62,66,67 Rodent models show that proinflammatory mediators IL-1-beta, IL-2, IL-6, and interferon (IFN)-alpha activate hypothalamic CRH that stimulate pituitary ACTH and adrenal cortisol; also, cytokines increase CRH production in the EA and other subcortical brain structures.68–71

CRH stimulates mast cells. Mast cells are highly concentrated in the stroma of the BBB and, when activated by CRH, they are degranulated and increase BBB permeability.72–74 CRHR1 knockout animals show decreased BBB penetrability and peripheral immune activation.75 This is important in HIV. Observations that neuro-AIDS is not correlated with peripheral circulating viral load suggest that active and passive viral transport due to increased BBB permeability may be a factor in early viral colonization and the development of CNS HIV infection.76,77
Figure 1 demonstrates some of the neurohormonal interactions with the immune system in the setting of immune activation during HIV-1 infection.

**Neuroinflammation and CNS HIV disease**

**Molecular actions within the infected brain**

Delineation of the CNS as a potential target for anti-stress therapies stems from the high prevalence of neurologic complications with HIV infection. HIV-associated neurocognitive disorder and HIV-associated dementia prevalence has dropped in those living with HIV/AIDS with the adoption of highly active antiretroviral therapies (HAARTs). Prior to HAART, the prevalence of dementia in HIV+ individuals was estimated at >15% and is now estimated to be <5%. Less severe forms of “asymptomatic” neurocognitive disorders have increased to >30% despite HAART and controlled viremia.

Microglial activation is seen in HIV-associated dementia, “asymptomatic” cognitive disruption, and IDU. Illicit drug-associated neuroinflammation impairs cognition, may contribute to ongoing risk behaviors, and may be additive after infection. The prevalence of addiction, depression, and other psychiatric disorders in HIV+ patients are independent causes of neuroinflammation, and all may contribute to the neuroimmune burden. The mechanism by which HIV-1 enters and infects cells in the CNS is complex. HIV-1 invades the CNS early after systemic infection and productively infects macrophages, microglial cells, and monocytes.

During HIV infection, CNS viral replication occurs principally in macrophages and microglia. These cells express CCR5 receptors necessary for viral entry. The two most potent effects of microglial and macrophage infection are the production of new virions and the induction of proinflammatory cytokine production. Microglia, macrophages, and monocytes release viral gp120 and transactivator of transcription (TAT) proteins, which are cytotoxic to neurons by generating free glutamate (GLU), an excitotoxic neurotransmitter, as well as by increasing free radical production. Along with extracellular calcium influx and cytokine/chemokine production, these insults can disable neuronal function and accelerate apoptosis.

![Figure 1](https://www.dovepress.com/)

**Figure 1** The complex feedback and feedforward relations of neuroendocrine immune mediators in regulating the central nervous system and peripheral immune responses to HIV infection.

**Notes:** Disruption of homeostatic mechanisms by infection is evident at multiple control points in stress and immune system regulation. HIV infection has direct and indirect effects on non-hypothalamic CRH and the hypothalamic–pituitary–adrenal axis to disrupt immune defenses.

**Abbreviations:** ACTH, adrenocorticotropin; CRH, corticotropin-releasing hormone; IL, interleukin; IFN-γ, interferon gamma; ROS, reactive oxygen species; TAT, transactivator of transcription; TNF-α, tumor necrosis factor-alpha.
Neuronal death furthers neuroinflammation with the release of additional cytokines/chemokines, toxic cell membrane and synaptic molecules, free radicals, and more GLU.

Figure 2 shows the interface of HPA axis activation and bipartite actions of GCs/cortisol on inflammation in neuronal elements and neurons during HIV infection.

The inflammatory milieu and the presence of toxic viral proteins (VP) have demonstrable neurotoxic effects. Between 1% and 20% of astrocytes are reported to be HIV-1 DNA-positive in HIV-1-infected patients, eg, at a level similar to what is reported for lymphocytes in lymph nodes. There is no evidence of newly synthesized virions or VP generated from infected astrocytes in vivo. Microglial elements harbor HIV, and this reservoir can be activated and produce infectious virions, making it a potentially long-lived and significant reservoir even in successfully treated patients.

Early entry of virus through the BBB suggests initial infection at a vulnerable time for colonization. CRH at the BBB may be a target for early intervention with CRHR1 antagonists to prevent or limit viral entry. Administering CRHR1 antagonists at or near the time of seroconversion might be optimal, though logistically difficult. The importance of CRH in BBB permeability is unknown; testing CRHR1 antagonists in early SIV infection may prove useful in understanding CRH and the potential efficacy of antagonists in maintaining barrier function.

Clinical premorbid conditions impact HIV CNS progression
Depression studies show inflammation is activated through several pathways; markers of inflammation involve T-cell activation with a Th1 shift from Th2. This facilitates CNS release of cytokines, stimulating astrocytes and microglia. In depression and schizophrenia, as in HIV/AIDS cognitive impairment, microglial activation provokes a proinflammatory cascade increasing prostaglandin E (PGE) and quinolinic and kynurenic acid production, as well as cyclooxygenase-2 expression. Arachidonic acid (AA) and cell membrane changes related to inflammation are critical components of HIV neurodegeneration and other neuropsychiatric disorders.

Sickness syndrome manifests with stress activation, which contributes to the symptomatology and morbidity

Figure 2 Some of the complex interactions of HIV infection in the central nervous system.
Notes: HIV infection triggers chronic stress hormone release; elevated levels of cortisol can trigger glucocorticoid resistance in susceptible immune cells and tissues. This engenders a proinflammatory environment, which generates a feedforward cascade of neuroinflammation. Inflammatory stimuli from virions, viral proteins gp120 and TAT, increased glutamate, cytokines/chemokines, free radicals, and membrane destabilization agents all contribute to neurodegeneration. This culminates in locoregional neuronal dysfunction on a microscale, which eventually translates to both structural and functional deficits leading to clinical neurologic and cognitive impairment.
Abbreviations: ACTH, adrenocorticotropic; CRH, corticotropin-releasing hormone; SNS, sympathetic nervous system; TAT, transactivator of transcription.
in patients with HIV, as well as other chronic illnesses. Inflammatory PG and AA are implicated in sickness syndrome. Subtypes of PGE receptor are found throughout the hypothalamus, striatum, brainstem, and EA, where they are colocalized on CRH-, dopamine (DA)-, NE-, and serotonin (5HT)-containing neurons.93-96 Activation of PGE receptors stimulates neurons and neurotransmitter release in these structures and their projections. PGE and AA facilitate CRH-stimulated ACTH release and cytokine synthesis, release, and action, as well as febrile responses to inflammatory challenge, sickness syndrome symptoms, and stress-related behaviors. As important as PGE and AA are in maintaining physiologic homeostasis, it is not clear how chronic stress impacts AA and PGE generation and functionality.90-93

The mechanisms of neuroinflammation and stress may be supra-additive in HIV infection. Early inflammatory changes seen in CNS HIV disease add additional risks for psychiatric disease. Activation of membrane inflammatory pathways enhances degradation of 5HT and its precursor tryptophan, due to increased indoleamine 2,3-dioxygenase activity. GLU production is increased, with devastating effects on neuronal integrity and neurodegeneration (Supplementary materials). DA and N-methyl-D-aspartate (NMDA) signaling is also disrupted. Much of the current pharmacology for depression and affective disorders involves increasing 5HT, NE, DA, and other neurotransmitters from a purported depleted state by decreasing transmitter degradation, lengthening synaptic residence, increasing direct receptor stimulation, and/or stimulating transmitter synthesis. Inflammation increases the production of two neurotransmitters: kynurenic (a GLU agonist) and quinolinic acid, resulting in increased glutamatergic/excitatory neurotoxic neurotransmission through the NMDA receptor. These neurotransmitters are markers of inflammation and increase susceptibility to psychiatric disorders as they can deplete 5HT, DA, and NE. Other essential neurotransmitters such as acetylcholine at muscarinic and nicotinic cholinergic receptors are also impacted.93,94

GLU, over time, is important in the neurodegenerative processes, degrading neural plasticity and generating a hostile neurochemical milieu.95,96 The impact of these molecular events on CNS HIV progression is unknown, but may be cumulative with other known pathologic processes. These mechanisms would be expected to be additive to the progressive neurodegenerative processes in HIV. Demonstration of these effects will require both prospective observation studies and improved methods to track these effects in vivo.

Additive effects of substance abuse on neuroinflammation

Drugs of abuse, including psychostimulants, compromise BBB integrity and promote oxidative stress damage; methamphetamine (MA) is a commonly abused drug. SIV models of MA abuse show both higher CNS viral load and disruption of the BBB.97 MA use is independently associated with neurodegeneration through several mechanisms, including oxidative stress and DA neurotoxicity.97-101

Opiates have deleterious effects on immune function, and in vitro studies suggest that there is the potential for adverse clinical outcomes.102,103 Opiates can accelerate HIV replication, principally through mu-opiate receptor activation. Independent of HIV infection, opiates induce microglial, astrocyte, and neuronal inflammation. This causes glial cytokine and chemokine expression and accelerated macrophage apoptosis, which limit immune surveillance.104 In the setting of CNS HIV infection, opiate abusers show enhanced microglial activation.105,106 Opiate receptor subtypes can have opposing effects on CNS immune modulation; kappa receptor agonists (endogenous dynorphin peptides) can inhibit HIV replication and reduce microglial activation.107,108 Mu agonists (ie, endogenous endorphin, encephalin peptides; drugs: heroin, morphine, methadone, hydrocodone, codeine) increase viral production.102-105 Excitatory amino acid production, GLU, kynurenic acid, and NMDA are synergetic with mu-opioid agonist effects, which could enhance HIV replication and DA neuronal damage.109

Alcohol abuse and dependence are frequent in HIV-infected individuals and is associated with high-risk sexual activity.110 Alcohol abuse increases the severity of neurocognitive or neuropsychological impairment in HIV infection, and alcohol independently has deleterious effects on cognition, immune function, and nutrition.111 Alcohol has neurotoxic effects by sensitizing the brain to excitatory neurotoxic amino acid neurotransmission, a common mechanism of glial and neuronal inflammation. NMDA antagonists, which block excitatory neurotransmission, can reduce neurotoxic effects from chronic alcohol exposure.112 CRH is a critical factor in alcohol abuse and dependence; under conditions of stress activation, CRHR1 knockout animals showed increased alcohol intake. This was linked to functional upregulation of the NMDA receptor, increasing sensitivity to ethanol.113-114 Blockade of CRHR1 blocks alcohol intake in rodents by modulating neurotransmitters associated with reward and reinforcement.115

Stress activation is critical for inducing and maintaining substance abuse and regulating neurochemical systems that
modulate CNS neurotoxicity. CRH stimulation of NMDA and glutamatergic pathways sustains inflammation.116 This, with other stress dysfunction, increases behavioral susceptibility to drug use. Stress, both acute and chronic, heightens vulnerability to the acquisition and maintenance of substance abuse. The mechanisms whereby CRH impacts addictive behaviors and HIV are complex; the vulnerability to HIV and disease progression involve underlying neuropathologic and psychiatric processes, the pharmacology of abused substance(s), immune integrity, and other as-yet ill-defined factors.30,116–119 Chronic exposure to drugs generates a chronic activation of the HPA axis with resultant hypercortisolemia associated with diminished feedback responsivity, leading to increased overall GC actions, leading to immune and neurotransmitter dysfunction. Overproduction of CRH in EA and the neocortex distorts executive functioning, impulsivity, and motivational behaviors, which are all critical in maintaining addiction.30,118 The molecular actions of drugs of abuse in the setting of CNS HIV colonization likely constitute a supra-additive neuroinflammatory milieu with clinical relevance in those with addictive illness.

The epigenetics of stress, inflammation, and behavior
Stress and CRH have both central and peripheral immune-modulating effects. As noted in the CRH as cytokine and stress immune modulator section, this is relevant in active infection and those susceptible to HIV transmission. Tung et al examined epigenetic immune gene regulation in a rhesus macaque model of dominant and subordinate social hierarchy.120 Subordinate individuals in social groups with behavioral and HPA axis markers of stress, presumably regulated through CNS CRH overproduction, suffer chronic stress associated with behavioral, immune, reproductive, and metabolic morbidity.121,122 A proinflammatory state was seen in subordinate animals;120 proinflammatory cytokine/chemokine gene activation in peripheral blood mononuclear cells was associated with group social ranking. Enhanced IL signaling, T-cell activation, and proinflammatory cytokine and chemokine overexpression with GCR was prevalent in subordinate, behaviorally stressed macaques. Lower social rank also correlated with higher cortisol levels.

During social isolation, a standard measure of inescapable stress, subordinate animals showed maladaptive responses. This poses clinical relevance, as social isolation and conditions of inescapable stress provide established models of psychiatric illness in nonhuman primates. When animals reentered social groups in a dominant rank, proinflammatory genes and peripheral markers were suppressed with immune reconstitution. Epigenetic analysis showed a majority of immune-regulating histones were demethylated, causing gene reactivation and shift to a noninflammatory state in response to a new dominant social rank. Reducing social stress leads to dynamic epigenetic changes in the expression of immune defense genes. Maladaptive IL signaling, T-cell activation, proinflammatory cytokine/chemokine overexpression and GCR, found in subordinate macaques, reversed, with possible long-term survival benefits.120

Tung et al’s study of epigenetic immune regulation is a clinically relevant translational model of immune competence. This study links chronic stress and immune dysfunction to established markers of CRH overproduction, including elevated cortisol secretion and conditioned fear behaviors, suggesting centrally mediated chronic stress has a potent influence on immune physiology. These patterns of neuroendocrine disruption are frequently clinically demonstrated, and the behaviors tested here (conditioned helplessness) in similar stress models are responsive to intervention with a high-affinity CRHR1 antagonist, such as antalarmin.6,123 Preclinical experiments such as these are commonly used to model mental illness. The sociobehavioral milieu is critical to immune defense and supports clinical observations of increased morbidity and mortality in HIV-infected and vulnerable groups and how effective psychiatric interventions can restore immune and neuroendocrine homeostasis.5–7,59,120–124 These observations and molecular mechanisms will show increasing importance as the field of neuroendocrine immunology matures and, with that, their relevance to those living with HIV and individuals at risk.

Molecular actions of stress hormones
Chronic stress activation, CRH/HPA axis, and inflammation
Clinical studies show progressive increases in cortisol production are associated with impaired immunity and advancing disease progression.5,59,124–130 Chronic exposure to elevated levels of cortisol can adversely shift cytokine production and cellular immunity. In addition, in the setting of inflammation and infection, peripheral CRH together with other immune activators, such as histamine and catecholamines, induces production of IL-1, IL-6, IL-8, IL-18, TNF-alpha, and C-reactive protein, thereby driving inflammatory processes.131–133

When proinflammatory cytokines cross the BBB, they stimulate the HPA axis.39,69 Disease states characterized by chronic inflammation, such as granulomatous and
autoimmune diseases, are frequently associated with behavioral and cognitive dysfunction and sickness syndrome. Depression is common with active inflammation, and clinical disease remission often results in symptom resolution. Sickness syndrome seen in chronic medical disorders can be partially attributed to inflammation and cytokine actions in the CNS. Proinflammatory biologics (ie, IFN and ILs) used in treatment of malignancy, multiple sclerosis, hepatitis C, and other disorders have well-recognized and frequent psychiatric and cognitive complications; concurrent treatment with antidepressants and other psychotropics is often recommended. With discontinuation of these therapies, CNS symptoms often resolve.

**Chronic stress, the GCr, and GCR**

GCR syndromes are important in HIV pathology. Excess cortisol can induce and exacerbate target organ disease such as visceral obesity, metabolic syndrome, GI disorders, immune suppression, opportunistic and other infections, atherosclerosis, and bone loss, conditions all seen in HIV infection. Tissue sensitivity to cortisol enhances risk to these and related disorders in susceptible and infected populations. Sensitivity to cortisol is a critical factor in multiple immune tissues. Lymphocytes, eosinophils, mast cells, monocytes, and dendritic cells all express GCr and have been demonstrated to manifest GCR in a wide variety of immune disorders. The interactions between GC and development of GCR in cells, tissues, and immune organs and how they induce and amplify stress-related disorders are not well understood.

Expression of GCr in the CNS and pituitary play a counterbalancing regulatory function enabling negative feedback integrity for controlling and muting physiologic stress responses. Receptors in hypothalamic nuclei and the anterior pituitary direct negative feedback control on ACTH and adrenal cortisol. Changes in GCr expression and sensitivity are seen in the hippocampus, EA, and cortical areas and, in the setting of chronic inflammation, in neuropsychiatric and neurodegenerative diseases leading to GCR. CRHR1 and GCr are frequently coexpressed on neurons where they are upstream modulators of neurotransmitters including GLU, 5HT, DA, and NE, as well as numerous neuropeptides and brain-derived neurotropic factors.

GCR can be caused by competition for cortisol for the GCr binding by inducing expression of nonfunctional receptor isoforms, reducing ligand availability to functional native receptors. Reduced ligand binding affinity, decreased nuclear translocation of the activated GC–GCr complex, and decreased efficacy in modulating responsive transcription factors are key in the development of tissue GCR.

**GCR and HIV replication**

GCs with their receptor(s) translocate to nuclei of HIV-infected T-cells. GCr activation has multiple cellular regulatory functions in HIV-infected cells and tissues, and GCR impacts HIV infection, replication, and progression. Cytokines and chemokines induce GCR and are, in turn, suppressed by GCR. IFN, TNF-alpha, IL-2, IL-6, IL-15, and IL-3 act to increase production of inactive competing GCr isoforms and decrease GCr HIV nuclear translocation, DNA transcription, and RNA synthesis and can reduce ligand receptor sensitivity up to fivefold in GCR HIV patients. The GC/GCr complex is synergistic with gp120 and can induce apoptosis in immunocompetent lymphocytes, hastening HIV progression. RU486 exerts transcriptional control over viral replication. Early in the course of infection, VP with the GC/GCr complex enable proviral migration from cytoplasm into the nucleus, allowing RNA integration into the host cell. As infection progresses in CD4+ cells, GCr co-regulates critical aspects of viral replication through complexing with VP within cells. Ligand-bound GCr and VP complex can suppress cellular protective genes, ie, NF-κB, which can upregulate proinflammatory genes. An activated GCr-VP can also stimulate transcription of poly (ADP-ribose) polymerase 1 (PARP-1), a protein which can induce DNA repair, aiding HIV genome nuclear integration and propagation; activating PARP-1 increases cell depletion and immunosuppression. Activated GCr shows a synergistic effect on viral replication in the presence of proinflammatory cytokines. Activating the GCr complex with the GC dexamethasone potentiates TNF-alpha and IL-6 HIV transcription, viral RNA expression, and viral assembly. In vitro, the GCr antagonist RU 486 inhibited the GC stimulatory effects on replication. Despite the fact that GCr activation is critical in HIV replication, RU 486 failed to reduce HIV viral load in vivo. The reason for failure of reduction in viral load is unclear; RU 486 blockade of GCr in the cell may not be complete or sufficient to block intracellular trafficking of GC/GCr complex to inhibit viral replication. The molecular mechanism(s) of how RU 486 and GCr interact are far from being fully understood.

**Modulation of the stress–immune system interaction: treatment implications**

Stress, inflammation, and neuropsychiatric disorders in HIV

Affective disorders, ie, MDD, GAD, PTSD, and substance abuse, are overrepresented in at-risk populations. Behavioral and hormonal dysfunction characterizes these
disorders with pathologic HPA axis activation from overproduction of CNS CRH in critical neurocognitive and limbic sites.6,161

The interface of CRH, neuropeptide, and neurotransmitter disruption in depression is well recognized; neurocognitive deficits in depression and affective disorders show commonalities with the neuropsychological effects of HIV infection. How CRH overproduction and central stress axis derangements impact neurocognitive decline with and without comorbid psychiatric disease needs better delineation.

The incidence of psychiatric comorbidity in substance abusers is high. A large study of IDU found high prevalence of MDD, GAD, alcohol dependence, personality disorders, and multiple substance use.162 Similar psychiatric disorders are found in MSM with negative societal bias; cultural milieu has a profound influence on psychological state and development of depression.163–164 Depressive affect is associated with higher mortality in infected men and was found to predict a more rapid decline in CD4 count.165,166

Changing demographics in 2013 found increasing numbers of women contract HIV through heterosexual exposures. The majority of those living with HIV remain white MSM, but African American (AfAm) MSM are overrepresented in HIV populations, as are Hispanic MSM. AfAm heterosexual women comprise the largest number of new infections, at 20%, and IDU make up 8% of new cases.167 HIV is a leading cause of death in AfAm and Hispanic women aged 25–44 years.168 In these women, nearly half reported chronic depressive symptoms and had nearly a fourfold increased prevalence of psychiatric disorders compared with matched noninfected women.134,169 Similar psychiatric disorders are observed in women as are seen in men. Chronically depressed women were found to be twice as likely to die as women without persistent symptoms; in addition, the trajectory of CD4 decline was significantly faster.134 Untreated depression delays women accessing care and instituting HAART and reduces their adherence with medical therapy. Comorbid substance abuse impairs effective treatment compliance further.170,171

The presence of a positive affect and resolution of depressive symptoms in longitudinal studies of HIV-infected men improves peripheral inflammation, including serological markers of active infection; increases CD4; lowers viral loads; and improves medication adherence. Importantly, improved mental health decreased disease mortality over a 3-year period.134,136,172

Somatic and psychological stressors have been linked to higher viral loads and more rapid disease progression despite HAART.173–177 Leserman et al reported that cortisol elevations were independent of psychosocial factors as a risk for disease progression.136,176 Reductions in psychosocial stress and decreases in cortisol secretion are reported to precede immune reconstitution in the setting of behavioral therapy.136,177 These data suggest that neuroendocrine immunity and its behavioral manifestations may act autonomously in hastening the transition of HIV to AIDS, and stress activators may be credible molecular targets for controlling disease.

Depression, anxiety, and PTSD are common in HIV patients.178 Carrico and Antoni analyzed 31 randomized controlled trials of various psychological interventions in HIV patients. Fourteen studies included physiological measures.177 Though studies varied in treatment and study design, those involving psychological interventions showed improvement in patients’ well-being and neuroendocrine markers of stress and immunity. The authors concluded that psychosocial and behavioral therapies provide benefit, though larger and more standardized investigations are necessary.

Pharmacologic and behavioral psychiatric interventions

Membrane rescue agents

Preclinical studies support a role for mood stabilizers as membrane rescue agents. Mania, though far from fully understood, appears to have membrane inflammation as an important part of the disease constellation.89,93 Membrane stabilization by decreasing AA synthesis and turnover through decreased brain cyclooxygenase-2 activity and PGE are possible ancillary mechanisms for mood stabilizers (ie, lithium, valproic acid, lamotrigine, and carbamazepine); this may contribute to their anti-seizure effects.91,92,94,96 Reducing inflammation and stabilization of cell membranes may offer therapeutic options for treatment of cognitive disorders and related comorbid psychiatric conditions. HIV proteins compromise cell membrane integrity and have detrimental effects on neurotransmitters (ie, GLU, DA) and stress activation.50 Lithium, valproic acid, lamotrigine, and carbamazepine are primary and adjunct medications for major mental illness, so their use could be a future consideration for HIV pharmacotherapy.

Modulation of GCR and HPA axis homeostasis

Central CNS actions of GC and GCR have been incompletely explored, though normalization in cortisol and resultant reduction in nuclear GCr decrease cytokine expression and translation.179 Stress levels of GC have been shown in vitro to be toxic to cortical and hippocampal neurons.179–181 Delineation of epigenetic mechanisms within the CNS in vivo awaits substantial refinements in pharmacology, surrogate
markers of gene expression, and imaging technologies. In vivo imaging of second messenger and related gene/receptor expression in oncology may allow future applications in neuroscience.\textsuperscript{182-184} Stress activation, HPA axis, and GCR markers would offer measurable refinements to correlate CNS immune activation with possible synergistic therapeutic future targets.\textsuperscript{185,186}

Preclinical studies have shown that anti-GC medications such as RU 486 are neuroprotective.\textsuperscript{185,186} Administration of RU 486 in immune and behavioral models of neuroinflammation partially inhibits or completely blocks glial inflammation. Clinical studies with RU 486 show varying degrees of efficacy in treatment of major and psychotic depression, though the mechanisms for these effects are unknown.\textsuperscript{187-190}

In GCR, an activated HPA axis with CRH overproduction can contribute to neuroinflammation; might GC antagonists such as RU 486 reduce CNS inflammation? In vivo imaging of glial and neuronal inflammation is progressing; current agents will benefit from increased sensitivity, specificity from these technologies, and comprehensive clinical validation. Imaging probes to study CNS disease progression await more refinement for assessment of treatment response and clinical efficacy of neuropharmacologic intervention.\textsuperscript{191-195} Further studies are needed to discern the actions of GC antagonists (and other therapeutics) in the progression of CNS HIV infection.

**CRHR1 antagonist medications**

Clinical depression is the best studied area for CRH and CRHR1 medications. No in vivo marker for CRHR1 is yet available, so surrogate measures and autopsy material are best validated and most frequently studied. Increased cerebral spinal fluid CRH and/or decreased CNS binding density of CRHR1 postmortem has been identified in patients with suicide, depression, addiction, PTSD, and other disorders.\textsuperscript{196-201} These findings may extrapolate to immune-compromised individuals with psychiatric and comorbid medical illness. As shown, CRH overproduction with resultant excess adrenal cortisol secretion is important in the genesis of mental illness, addiction, and inflammatory changes mediated by the GCr.\textsuperscript{15,36,37}

Its many physiologic actions and associations with disease have made CRHR1 an important molecular target for drug development. There has been a concerted effort by the pharmaceutical industry to develop non-peptide CRHR1 antagonists as antidepressant and anti-stress medications.\textsuperscript{201} The first clinical trial by Zobel et al with the CRHR1 antagonist R121919 showed some efficacy in treatment of patients with MDD.\textsuperscript{202} This was an open-label trial, and its design is frequently criticized; however, when medication was withdrawn, some patients had symptom relapse. A number of other non-peptide antagonists were developed and brought to clinical trials. Indications to date have been depression, anxiety, and irritable bowel syndrome (IBS). The exact number of sponsored trials is unknown, though multiple Phase I and Phase II trials have been registered on ClinicalTrials.gov. The results of the clinical studies to date have been disappointing.\textsuperscript{201} No successful Phase III trials have been reported. CRHR1 antagonists have not been consistently successful as antidepressants, though newer-generation compounds are being developed with better pharmacologic characteristics.\textsuperscript{203,204} There are many speculations as to the reasons for the clinical trial failures; first, studies have been conducted on patients with chronic psychiatric disorders which may complicate the interpretation of the data. Second, these agents may have limited efficacy in reconstitution of homeostasis, as opposed to disease prevention and progression. Yet, despite challenges, interest remains in this molecular target for these and other indications relevant to HIV.

The CRHR1 antagonist antalarmin is effective in susceptible rodent strains in reducing gut inflammation and joint destruction in an adjuvant-induced model of rheumatoid arthritis.\textsuperscript{52,61} CRH acts as an inflammatory cytokine at the involved joints. Antalarmin blocks CRHR1 expressed on immune cells/tissues as well as ameliorating the chronic activation of the HPA axis; it regularizes circadian rhythms disrupted in chronic stress.\textsuperscript{201} Reducing GC production may also contribute to improvements in target tissue GCR seen in autoimmune disorders. Administration of the CRHR1 peptide antagonist alpha-CRH blocked distension and electrically induced abdominal pain in patients with IBS. IBS is characterized by peristaltic dysregulation, intestinal inflammation, and increased gut permeability with a lowered threshold to gut-induced pain. Anticipatory anxiety is a prominent feature of IBS.\textsuperscript{46,206,207} CRHR1 antagonist peptides do not cross the BBB and show peripheral actions through locoregional anti-inflammatory, SNS, and/or other non-CNS effects.\textsuperscript{29,46} How and if these observations are relevant to HIV proliferation in the gut are unknown; further assessment of CRHR1 antagonists as anti-inflammation agents in this and other conditions may guide future clinical investigations.

Overproduction of CNS CRH in cognitive processing, executive decision making, and emotional response areas of the brain causes CRHR1 downregulation in preclinical models of depression, anxiety, and addiction, as well as in patients with depression and stress-related diseases.\textsuperscript{197-200} Cerebral spinal fluid CRH, a surrogate marker, decreases
with effective depression therapy, but this has not been demonstrated in HIV-related depression. Treatment of depression in HIV patients with medications and/or behavioral therapy improves viral load, CD4+ counts, inflammation, and immune integrity. The dual and potentially synergistic actions of reducing peripheral inflammation and CNS CRHR1 action may prove beneficial in the HIV-infected host. Improving emotional and cognitive symptoms and normalizing the HPA axis and cortisol, GCR, and proinflammatory states, especially in the gut and brain, hold promise for these agents; testing in SIV could be a productive next step.

**Behavioral therapies**

In randomized controlled trials of cognitive behavioral therapy, stress reduction, and other psychological interventions in HIV, patients showed benefits in neuroendocrine stress and immune markers. Positive affect significantly reduces the risk of dying from HIV. Pharmacotherapy is a common adjunct with psychotherapy for MDD, GAD, and PTSD.

Cognitive behavioral therapy with stress reduction administered to HIV-positive men improved neuroendocrine and immune markers of active infection in those who successfully completed 10 weeks of therapy. These included reductions of stress hormones and catecholamines and increased gonadal and adrenal androgens. Increased CD8, CD4, and antibody production were also seen along with reductions in herpes simplex type 2 antibodies.

Symptomatology of chronic medical illness and psychiatric disease is often blurred. The usual tools and instruments for evaluation of psychiatric and neurocognitive impairment have limited validation in populations with chronic medical conditions and HIV (ie, Center for Epidemiologic Studies Depression Scale, the Hospital Anxiety and Depression Scale, the Beck Depression Inventory II, and the Patient Health Questionnaire). These populations may share common biological mechanisms of medical disease; psychiatric symptomatology can exacerbate the somatic manifestation(s).

Immune activation is important in sickness syndrome and PGE, AA, CRH, and stress activation are factors in disease presentation and progression. Neocortical dysfunction impacts cognitive and executive functioning, adversely shaping patient decisions for seeking and adhering to treatment. Targeting these systems with anti-stress medications with combination therapies makes theoretical sense, though application and efficacy remain unknown.

**Does substance abuse add greater risk?**

Substance abuse, especially injection drug use, is associated with twice the mortality rate when compared with non-IDU HIV-positive individuals; also, there is less adherence to effective treatments in infected IDU, compromising therapeutic response. Pharmacologic interventions and substance abuse treatment have been generally less effective in HIV patients and add vulnerability to those at very high risk. Stabilization of patients with illicit or prescription opiate abuse using substitution therapy, ie, methadone or buprenorphine, results in reduced stress activation after months of treatment. Despite reductions in HPA axis hormones, treatment with chronic opiate therapy has a detrimental effect on neuronal integrity through increased glial and astrocyte stimulation and neuroimmune cell proapoptosis. This can accelerate progression to dementia in some individuals.

There is no established effective pharmacology for stimulants such as MA and cocaine, though new molecular treatment targets continue to be explored. Associated comorbidity of drug use with other psychiatric disorders is associated with poorer outcomes, especially mood disorders such as concurrent MDD and PTSD. There is limited consensus on effective pharmacotherapies for the dual-diagnosed patient. Approaching patients with comorbid psychiatric disease and those with and at risk for HIV adds further diagnostic and therapeutic challenges. These individuals would be expected to have a higher incidence of central and peripheral stress activation based on infectious immune activation, addiction, and concurrent mental illness. Animal models of substance abuse show CRHR1 antagonists reduce self-administration, susceptibility to environmental stressors, and stress-induced drug relapse. Clinical studies of CRHR1 antagonists to prevent stress-induced relapse may prove to be effective.

Preclinical models of psychoimmune disorders have not been developed, so this area is unexplored. The drug abuse literature is replete with primate drug self-administration, neuro receptor imaging, and relapse models; there is potential to adapt these to SIV infection. Effectiveness of these agents in comorbid populations, let alone those with immunodeficiency, has yet to be established.

**Antidepressants and immune recovery**

In addition to behavioral effects, 5HT targeted and mixed monoamine medications have been shown to increase GCR expression, translocation, and gene transcription, resulting in diminished GCR. Effective antidepressant therapy also reverses proinflammatory cytokine production. The mechanisms of immune reconstitution from antidepressants and other medications are largely based on observational clinical and in vitro studies. Distinctions in immune effect between classes of medications have not
been ascertained, principally because of the limited number of controlled studies and overriding clinical indications for patient therapy. Reductions in C-reactive protein are a commonly reported outcome measure in these observational clinical studies. Use of pharmacotherapy for treatment of psychiatric disease in HIV is associated with better survival and adherence to treatment. Mechanistic understanding of these agents in the HIV-infected host requires active investigation.

Peripheral inflammation: a therapeutic role for anti-stress medications?

CRHR1 antagonists have shown anti-inflammatory action in preclinical models of rheumatoid arthritis. Limited clinical studies with peripheral CRHR1 peptide blockers show these may have benefit in IBS. Many inflammatory disorders manifest both chronic inflammation and sickness syndrome. Target organs for HIV transmission represent critical sites for infection and progression. Bowel inflammation can increase susceptibility to HIV infection, and BBB integrity is critical to CNS transmission; CRHR1 antagonists could target both. HIV is characterized by a systemic proinflammatory state and by neuropsychiatric illness, so reduction in peripheral inflammation may be synergistic.

Anti-GC therapeutics

Administration of the GCR antagonist RU 486 inhibited the GC stimulatory effects on HIV replication in vitro. However, its in vivo administration to HIV infected patients did not show benefits in decreasing plasma viral load.

This study did not assess behavioral effects or include patients with psychiatric illness. Activation of the stress axis with resultant GCR alters tissue GC sensitivity and can promote neuroinflammation. Some subgroups of patients with major and psychotic depression show response to these agents, with GCR as a possible factor. The degree to which GCR is responsible for HIV-related disease may predict clinical response. The actions of GC are complex with HIV, as they are with other medical and psychiatric disorders; further elucidation of the mechanism of action is needed.

Individuals at risk for infection show behavioral and immunologic vulnerability. Stress levels of GC have been shown in vitro to be toxic to cortical and hippocampal neurons. Substance abuse, depression, and immune stimulation with associated chronic stress activation may have as a common underpinning factor the development of GCR, as noted in sections on HPA and excess GC secretion.

Conclusion

Individuals living with HIV and those at high risk for infection carry a disease burden that involves neuropsychiatric, neuroendocrine, and immune dysfunction. The discovery of new molecular targets in the stress system, such as CRH, may be the intersection of seemingly disparate functions and disease manifestations. The stress system provides a commonality to better understand these disorders and for future therapeutic interventions. Central and peripheral stress mediators maintain homeostasis, and CRH has a central role in the choreography of neuroendocrine immunity.

Individuals at heightened risk for contracting and spreading HIV have frequent comorbidity with psychiatric disease, high-risk sexual behaviors, and substance abuse. These contribute to neuroendocrine immune dysfunction and may be supra-additive in determining risk for disease acquisition and progression.

The importance of CRH and its associated receptors is belied by their widespread distribution and varied physiologic functions. They are found in high concentration in the central and peripheral nervous system, immune cells and tissues, and organs integral to immune integrity. CRH is a psychosomatic molecular link critical in cognitive, emotive, immune, endocrine, and autonomic regulation. Central and peripheral feedback and feed forward pathways to and from the HPA axis, autonomic nervous system, immune system and CNS allow both acute and chronic modulation of homeostasis to adjust to internal and external environmental insults.

Immune regulation by cytokines/chemokines provides a control circuitry to the CNS stress system critical in neuro-AIDS and neuroinflammation. The CNS remains vulnerable to infection in ways not yet clear; CRH and the proinflammatory milieu enhance BBB permeability to viral entry, and CRH may be an important preventive target. New approaches are needed to help explain the mechanism of neural infection and inflammation and why peripheral viral loads do not predict the development and progression of cognitive dysfunction despite HAART. Membrane inflammatory markers (PGE, AA, gp120) from microglial activation and neurotransmitter shifts (GLU neurotoxicity, monoamine depletion) are associated with CNS disease. CRH and central stress activation is seen, though whether these are primary or secondary events is uncertain. Membrane integrity contributes to both psychiatric and somatic manifestations of disease such as depression and “sickness syndrome” evident in other chronic inflammatory conditions (ie, other neurodegenerative conditions/autoimmune disorders); this is an important area for future studies.
Substance abuse with other psychiatric comorbidities as well as direct pharmacologic actions of drugs result in hypothalamic CRH, HPA axis disequilibrium, neuroinflammation which accelerate HIV progression and risk susceptibility. Addiction, with associated neural and peripheral inflammation and psychiatric and adverse metabolic consequences, increases HIV morbidity and mortality. CRHR1 antagonists may have the potential for substance abuse treatment; however, possible benefits to immune integrity are unknown.

Chronic stress causes detrimental epigenetic changes in behavior and peripheral immunity; reversal engenders recovery in preclinical models. How behavioral therapies and conventional and/or anti-stress drugs improve immune function remains to be demonstrated.

Molecular actions of cortisol are critical in viral replication. GCR from chronic overproduction of GC has detrimental effects on immunity and viral production. Our understanding of GCR is incomplete; simple blockade of the GCr with RU 486 holds no clinical benefits. The molecular complexity of GCR is considerable, and the interactions with neuroendocrine immune functions remain unclear.

Clinical observations and trials demonstrate improvements in psychiatric disease from behavioral and pharmacological treatments, with concomitant normalization of neuroendocrine immune integrity. Assuming similarities with MDD and GAD, CRH antagonists may provide a viable if only adjunctive target in well-selected populations.

The field of HIV and immunity awaits the development of new, more pharmacologically active CRHR1 antagonists as anti-stress medications and improved clinical trial methodology. When better drugs are found, trial study design should include assessment of immune parameters, the neuroendocrine stress state, presence of GCR, and neuroinflammation; improved standardized testing methodology for psychosocial disorders and neurocognition in these populations is critical. Preclinical investigations of CNS and regional immunity with CRHR1 blocker compounds can be performed in well-characterized models of SIV infection using basic immune methodologies. Studies of neuroinflammation, cellular immunity, and neuropharmacology will lead to improved translational models. The actions of CRH and the pharmacology of CRHR1 antagonists hold promise in improving health outcomes for those at risk and with disease, though much lies ahead.

Disclosure
The authors report no conflicts of interest in this work.

References


Supplementary materials
HIV-induced neurodegeneration
Neurotoxicity from inflammation in the HIV-infected host comprises a highly complex series of molecular events; its severity and trajectory can be altered by pathologic conditions in a vulnerable host prior to infection. Despite highly active antiretroviral therapies (HAARTs), earlier intervention, and more effective disease control, neurocognitive impairment and dementia remain major causes of disability, increased morbidity, and mortality. Underlying chronic distress and neuroinflammation add to disease burden and susceptibility in those at risk. Psychiatric disorders, addiction (especially with stimulants and opiates), high-risk sexual behaviors, sickness syndrome, and other chronic medical conditions characterize patient populations infected with HIV or those at high risk of HIV infection. Progressive neuronal injury leads to clinical sequela of neural degeneration and cognitive impairment.

Loss of blood–brain barrier (BBB) integrity
Those with early HIV infection and those at risk suffering from medical and behavioral conditions, ie, chemical/pharmacologic (drug) insults, psychiatric disorders, and medical illness, show blood–brain barrier (BBB) compromise. Stress-associated mast cell activation with corticotropin-releasing hormone (CRH) release, “leaky” basement membranes, permeability of perivascular endothelial cells, and active transport of high concentrations of circulating cytokines/chemokines contribute to BBB failure. Infected macrophages and T-cells invade the central nervous system (CNS) extracellular space and brain parenchyma. The loss of BBB integrity is complex and incompletely understood. This cascade of inflammatory events results in early HIV colonization of the brain.

Multifaceted neurotoxicity
The trajectory of HIV neurotoxicity involves HIV transit into the CNS by T-cells and perivascular and mobile macrophages which infect resident monocytes, macrophages, and microglia; astrocytes, though not shown to harbor HIV, are target cells that promote neuronal injury. Infected monocytes and macrophages release cytokines/chemokines, intact virions, and component viral proteins, mainly gp120 and transactivator of transcription (TAT), which perpetuate infection and neurotoxicity. Noninfected monocytes/macrophages respond to immune insults releasing cytokines/chemokines and other agents, which disrupt astrocyte glutamate (GLU) regulation. GLU dysregulation with excess production in astrocytes is a critical component of neuronal degeneration.

Astrocytes are critical in maintaining GLU homeostasis. GLU is a toxic excitatory neurotransmitter which becomes disrupted at multiple steps in its metabolic pathways. Increased production and reduced clearance and metabolism of GLU elicit toxic neuronal activation. Excitatory amino acid transporters (types 1 and 2) are downregulated, decreasing glial and astrocyte GLU uptake. The enzyme glutaminase is upregulated, which generates glutamine, a GLU precursor to GLU, increasing intracellular/extracellular and intrasynaptic GLU. GLU increases from downregulation of GLU degradation enzymes (GCP I and GCP II). GLU astrocyte exocytosis increases extracellular GLU. GLU is excitotoxic through N-methyl-D-aspartate (NMDA) receptors which, when activated, increase intracellular Ca\(^{2+}\) release. Excess Ca\(^{2+}\) activates second messenger pathways responsible for gene transcription and signaling, ie, nuclear factor kappa B (NF-κB), JNK/STAT-1, and ERK 1/2. These trigger genomic events that accelerate production of proinflammatory agents, apoptosis, and oxidative stress, as well as further increasing GLU production and release. Cumulatively, these events decrease synaptic integrity and plasticity and perpetuate neuron apoptosis.

Excess GLU also enhances glial inflammation (gliosis) in concert with neural dysfunction; mounting glial activation generates a cascading effect that perpetuates neuroinflammation, neuronal dysfunction, network integrity, and cognitive decline.

CNS HIV infection of neuronal support cells and tissues generates a proinflammatory microenvironment. Neuronal damage is multifactorial, with toxic insults from increased intracellular, extracellular, and intrasynaptic GLU; cytokines. Oxidative stress from reactive oxygen radicals/nitric oxides; and membrane destabilization from prostaglandins/arachidonic acid promotes neuronal damage. This is magnified by depletion of intracellular antioxidant detoxification molecules, ie, glutathione. Active viral replication maintains and progressively compromises CNS immunity with deteriorating neuron viability and neuronal networks. Degeneration of neocortical and limbic structures and their connectivity are principal sites responsible for cognitive decline and increased susceptibility to neuropsychiatric conditions.

Figure S1 represents some of the multiple molecular mediators generated by HIV infection within the CNS and the multiple neurotoxic and inflammatory effects on both neuronal support cells/tissues and neurons.

Effects of chronic stress
During acute stress, glucocorticoids (GC) provide neuroprotection, blunting glial and other CNS inflammatory...
responses, indicative of their immunosuppressive effects. Induction of chronic stress in models of Parkinson’s disease results in long-term pathologically elevated concentrations of GC. Chronic exposure to GC during conditions of prolonged stress induces GC resistance (GCR) in immune/lymphoid tissues and organs. This progressively increases inflammation from HIV in the CNS. There is a limited understanding of GCR; excess GC has complex interactions with intracytoplasmic GC receptors. Activated GC receptors upregulate genes for proinflammatory cytokine production, viral replication in T-cells as well as in monocytes/macrophages, and glial and other support elements;7–10 GCR also enhances astrocyte GLU neurotransmission. In Parkinson’s disease, this contributes to dopamine neuronal toxicity and cell death; this pattern is seen in other neuroinflammatory conditions.

**Chronic neurodegeneration**

Once infection is established, viral reservoirs remain within the brain despite low/absent cerebral spinal fluid viral load. Glial elements, monocytes, and perivascular/circulating macrophages are long-lived in the CNS, with glial cells lasting years to lifetime. With the advent of HAART, the prevalence and severity of neurocognitive disorders have decreased, with dementia dropping from >15% to less than 5%. “Asymptomatic” neurocognitive impairment, however, has increased to >30% over time. How pre- and post-infection comorbid conditions from disrupted stress homeostasis influence CNS HIV infection is largely unknown.

For progressive cognitive impairment, current recommendations include utilization of antiretrovirals with improved BBB penetration to decrease viral replication, free virion passage, and viral component (gp120/TAT) production. When effective, HAART blocks GLU production/action and the proinflammatory milieu.11,12 Reduced viral replication and medications purported to improve general cognition in practice have limited clinical utility.

**Future directions**

HIV neurotoxicity involves critical action points that determine the rate and severity of neurocognitive deterioration. When HIV enters the CNS, infection of monocytes, microglia, and macrophages; generation of intact virions and viral components (gp120/TAT); and cytokines/chemokines all contribute to activate astrocytes. GLU toxicity leads to neuronal damage, apoptosis, and overall loss of cognitive...
function. Once initiated, these processes feed forward, increasing involvement of more and more neuronal networks, with greater disability and functional impairment. To date, targeted therapies have been disappointing. Most antiretrovirals lack physicochemical properties to effectively cross the BBB and suppress the virus. GLU/NMDA receptor antagonists and synthesis inhibitors have not demonstrated therapeutic effects. Anticholinergics (used in Alzheimer’s disease), serotonin, and noradrenergic agonists have also failed to show significant benefits. These findings are not unexpected, given the inability to modify the course of other neurodegenerative disorders. Targeting chronic stress, GCR and CRH may offer limited potential as adjunctive therapies, but the overall complexities of these systems, the chronicity of ongoing infection, and the relative lack of sensitive surrogate markers for inflammation will limit treatment options in the near and mid-term future. Advances in basic neuroscience will be necessary to determine better therapeutic interventions for HIV-related and other neurodegenerative disorders.

References


