Endotext

AIDS AND HPA AXIS

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ABSTRACT

The Acquired Immunodeficiency Syndrome (AIDS), caused by infection with the Human Immunodeficiency Virus Type-1 (HIV), is characterized by profound immunosuppression, particularly of the innate, and T-helper (Th) 1-directed immunity. AIDS causes multisystem dysfunction, including impairment of the hypothalamic-pituitary-adrenal (HPA) axis, a major system coordinating the resting state and the adaptive response to stress. This neuroendocrine axis consists of three components: the hypothalamus, the pituitary gland, and the adrenal cortex with its end-effector molecules, the glucocorticoids. AIDS/HIV influence the HPA axis directly, through modulation of the host immune activity and alterations of the cellular biological pathways via HIV-encoded proteins, as well as indirectly, through immunodeficiency-associated opportunistic infections and various side effects of the therapeutic compounds employed, including those used in the highly active antiretroviral therapy (HAART). In this chapter, the interaction between AIDS/HIV and the HPA axis is reviewed and discussed.

INTRODUCTION

Patients with Acquired Immunodeficiency Syndrome (AIDS), caused by infection with the Human Immunodeficiency Virus Type-1 (HIV), develop profound immunosuppression, particularly of their innate and T-helper (Th) 1-directed cellular immunity (1). These patients may also present with dysfunction of many organ systems, including the hypothalamic-pituitary-adrenal (HPA) axis (2). During the last 25 years, numerous reports have provided evidence for alterations of the HPA axis and its influence on target tissues in HIV-infected patients (Table 1). Indeed,

AIDS has been associated with adrenalitis caused by opportunistic infections, adrenal dysfunction secondary to neoplastic infiltration into the adrenal cortices, and changes related to circulating cytokines and other bioactive molecules known to influence functions of the HPA axis (3). Glucocorticoid hormones secreted from the adrenal cortex act as end-effectors of the HPA axis and have strong anti-inflammatory effects (4). Thus, these hormones were considered for reversing HIV-mediated depletion of circulating CD4+ lymphocytes and slowing progression to AIDS, as well as to subside complications associated with HIV infection (5) (Table 2).

Table 1. Impact of HIV infection on the HPA Axis/Glucocorticoid/GR Signaling System

Manifestations	Virus-mediated	Treatment-mediated
Adrenalitis (Common) and adrenal insufficiency (Rare)	√	
Pituitary (corticotroph) dysfunction	√	
GR affinity-dependent generalized glucocorticoid resistance	√?	
Modulation of glucocorticoid metabolism	√	√
Modulation of GR activity	√	√
AIDS-related insulin resistance/lipodystrophy syndrome	√	√
Fatigue/muscle wasting	√?	

Table 2. Conditions/Manifestations in which Glucocorticoid Treatment is Considered in HIV-Infected Patients

Conditions/manifestations	Types of conditions/manifestations
AIDS-related lymphoma (Hodgkin and non-Hodgkin)	Complication
HIV-associated nephropathy	Complication
Kaposi sarcoma*	Complication
Appetite loss/fatigue	Complication
Opportunistic infections (mycobacterium tuberculosis, cryptococcus)	Complication
HIV-associated immune reconstitution inflammatory syndrome	Complication
Slowing of AIDS progression (increase of CD4+ counts)	Direct effect on HIV replication

*Acceleration of Kaposi sarcoma by glucocorticoids (110)

Although development of HIV vaccines targeting components of the viral particles is still challenging, establishment and clinical introduction of the highly active antiretroviral therapy (HAART) that employs combinatory use of the three different types of antiretroviral drugs, such as nucleoside and non-nucleoside analogues acting as reverse transcriptase inhibitors, non-peptidic viral protease inhibitors (PIs) and the compounds blocking entry of HIV to CD4+ lymphocytes, efficiently suppress HIV replication in infected patients and have dramatically improved clinical course and life expectancy of AIDS patients

(6-9). However, the prolongation of lives with long-term use of the above antiretroviral agents have generated novel morbidities and complications, which influence the patients' quality of life and add new risk factors for premature death. Central among them is the quite common AIDS-related insulin resistance and lipodystrophy syndrome (ARIRLS), which is characterized by a striking phenotype and marked metabolic disturbances that are reminiscent of Cushing syndrome (10). In agreement with above-indicated clinical background, acquired alterations in the sensitivity of tissues to glucocorticoids were originally hypothesized in AIDS patients, and this concept was further extended to other nuclear receptor (NR) family proteins. In addition, some PIs inhibit the cytochrome p450 enzyme CYP3A4, which is necessary to metabolize glucocorticoids into inactive forms (11). Thus, the pharmacologic action of glucocorticoids used in the AIDS patients treated with these compounds is pronounced due to slowing of their metabolism, and "iatrogenic" Cushing syndrome is subsequently developed in these patients (12).

AIDS patients frequently develop several different types of malignancies, such as lymphoma and Kaposi sarcoma, in part due to profound destruction of host immune system by HIV (13,14). Glucocorticoids are among the central compounds for the treatment of the patients harboring these malignancies (13,15). Glucocorticoids are also pivotal for the treatment of HIV-associated nephropathy, which is observed in about 10% of AIDS patients (16). Use of glucocorticoids is further considered for the patients with HIV-associated tuberculosis and other opportunistic infections as part of the immunoadjuvant therapy (17,18).

In this chapter, we will explain known interactions between HIV infection and the HPA axis, particularly focusing on glucocorticoid hormones. We also present our understanding on some emerging concepts of such interactions, and discuss their possible mechanisms and relevance to HIV pathogenesis.

HPA AXIS AND GLUCOCORTICOID ACTIONS

Humans face unforeseen short- and long-term environmental changes called "stressors", which can be external (e.g. excessive heat or cold, food deprivation, trauma and invasion by pathogens) or internal (e.g. hurtful memories, splachnic injuries, neoplasia's) (19-22). To adapt to these changes, humans have the stress-responsive system, which senses such stressors through various peripheral sensory organs, processes them in the central nervous system (CNS), and adjusts the CNS and peripheral organ activities (19-22). The hypothalamic-pituitary-adrenal (HPA) axis with its end-effectors glucocorticoids is one of the two arms of this regulatory system, together with the locus caeruleus/norepinephrine-autonomic system and their end-effectors, norepinephrine and epinephrine (19,21,22). At baseline, activity of the HPA axis and circulating glucocorticoid levels are in a typical diurnal rhythm, reaching their zenith in the early morning and their nadir in the late evening in diurnal animals including humans through input from a circadian rhythm center, the suprachiasmatic nucleus (SCN), and they participate in the maintenance of internal homeostasis (20,23,24). Upon exposure to stressors, the HPA axis is liberated from this regular circadian rhythm, and is strongly activated to modulate many biological activities including those of the CNS, intermediary metabolism, immunity and reproduction via highly elevated circulating glucocorticoids (4,19-25). However, this stress-induced activation of the HPA axis may also exert an array of adverse effects when its response is not properly tailored to the stressful stimuli (25). For example, acute hyper-activation of the HPA axis has been associated with development of post-traumatic stress disorder, while chronic activation of the HPA axis, and consequently prolonged elevation of serum glucocorticoid levels, induce visceral-type obesity

and insulin resistance/dyslipidemia, which are represented as metabolic syndrome (19,21-25).

The HPA axis consists of the hypothalamic PVN parvocellular corticotropin-releasing hormone (CRH)- and arginine vasopressin (AVP)-secreting neurons, the corticotrophs of the pituitary gland, and the adrenal gland cortex (3,21-24) (Figure 1A). The PVN neurons release CRH and AVP into the hypophyseal portal system located under the median eminence of the hypothalamus in response to stimulatory signals from higher brain regulatory centers (3,21-24). Secreted CRH and AVP reach the pituitary gland and synergistically stimulate secretion of the adrenocorticotropic hormone (ACTH) from corticotrophs (19,21-24,26). ACTH released into systemic circulation finally stimulates both production and secretion of glucocorticoids (cortisol in humans and corticosterone in rodents) from the *zona fasciculata* of the adrenal cortex (25). Secreted glucocorticoids modulate activity of virtually all organs and tissues to adjust their functions. In addition, these hormones suppress higher regulatory centers of the HPA axis, the PVN and the pituitary gland, ultimately forming a closed negative feedback loop that aims to reset the activated HPA axis and restore its homeostasis (19).

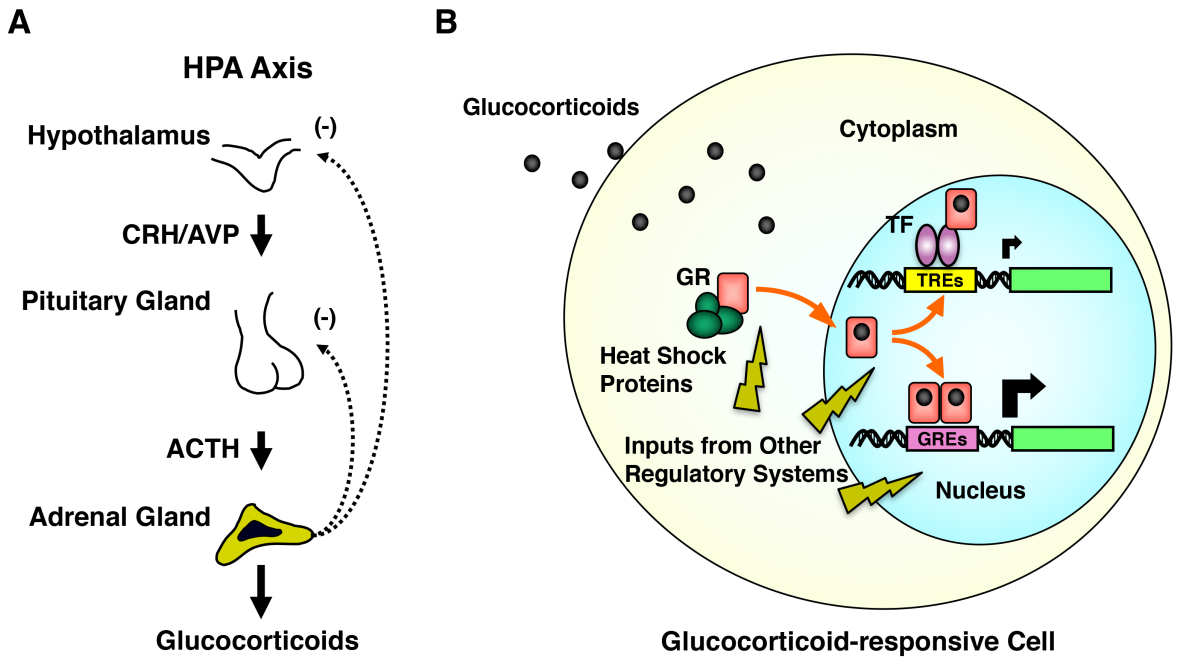

Figure 1. The HPA axis and intracellular actions of GR

Organization of the HPA Axis

The HPA axis consists of 3 components: the PVN of hypothalamus, the anterior pituitary gland and the adrenal cortex. Neurons residing in PVN produce CRH and AVP and release them into the pituitary portal vein under the control of upper centers, including the central circadian rhythm center, hypothalamic suprachiasmatic nucleus (SCN). Released CRH and AVP stimulate secretion of ACTH from corticotrophs of the anterior pituitary gland. ACTH then stimulates the production and secretion of glucocorticoids (cortisol in humans and corticosterone in rodents) from adrenocortical cells located in *zona fasciculata* of the adrenal gland.

Circulating glucocorticoids suppress upper regulatory centers including PVN and pituitary gland, forming a closed regulatory loop.

Intracellular Actions of GR

In the absence of glucocorticoids, GR resides in the cytoplasm forming a heterocomplex with several heat shock proteins (HSP). Upon binding to glucocorticoids, GR releases HSPs and translocates into the nucleus. In the nucleus, GR directly binds its specific sequence called glucocorticoid response elements (GREs) located in the promoter/enhancer region of glucocorticoid-responsive genes as a homodimer, and stimulates transcription by attracting many transcriptional cofactors and the RNA polymerase II complex. GR also modulates transcriptional activity of other transcription factors through physical protein-protein interaction without associating directly to DNA. After regulating transcription of glucocorticoid-responsive genes, GR moves back into the cytoplasm with help of the nuclear export system and returns to its ligand friendly condition by reforming a heterocomplex with HSPs. This complex regulatory system for the GR intracellular activity is sensitive to many inputs from other intracellular regulatory systems in order to adjust net GR actions upon local needs. [modified from (27)]

Infection of pathogens including HIV potently activates the HPA axis and induces subsequent secretion of glucocorticoids from the adrenal cortex (28,29). Pathogens generally stimulate central part of this regulatory system (e.g., brain hypothalamus and pituitary corticotrophs) directly with their structural and genetic components, and indirectly with cytokines and inflammatory mediators, such as the tumor necrosis factor α (TNFα), interleukin (IL)-1 and IL-6, secreted from activated immune cells and/or infected tissues (30). Secreted glucocorticoids in turn subside inflammation, functioning as a counter regulatory mechanism for otherwise overshooting immune response (31). Glucocorticoids do this mainly by suppressing release of humoral inflammatory mediators, granulocyte migration, cellular immunity and production of Th1 cytokines, such as IL-12, TNFα and the interferon (IFN) γ, while they stimulate humoral immunity and secretion of Th2-inducing anti-inflammatory cytokines, including IL-4, IL-10 and the transforming growth factor β (4,32,33).

Glucocorticoids exert profound influences on many physiologic functions by virtue of their diverse roles in growth, development, and maintenance of cardiovascular, metabolic and immune homeostasis (4,34,35). Excess amounts of glucocorticoids have strong effects on intermediary metabolism, developing insulin resistance/overt diabetes mellitus and hyperlipidemia (especially triglycerides and free fatty acids) through modulation of their broad target regulatory systems/molecules (4). As glucocorticoids possess potent anti-inflammatory and immunosuppressive activities, they are used as invaluable therapeutic means in inflammatory and autoimmune diseases (36). In addition, glucocorticoids are central components of the anti-cancer treatment especially for hematologic malignancies, such as leukemia and lymphoma (4).

Glucocorticoids exert their effects on their target cells through the glucocorticoid receptor (GR), a ligand-specific and -dependent transcription factor, ubiquitously expressed in almost all tissues and cells (21-24,28). There are two 3' splicing variants, GRα and GRβ, through alternative use of a different terminal exon termed 9α or 9β. GRα is the classic glucocorticoid receptor, which binds glucocorticoids and transactivates or transrepresses glucocorticoid-responsive genes (37). GRα shuttles between the cytoplasm and the nucleus; Binding of glucocorticoids to GRα causes it to dissociate from the cytoplasmic hetero-oligomer containing heat shock proteins and to translocate into the nucleus

through the nuclear pore (28) (Figure 1B). Ligand-bound and nucleus-translocated GRα binds as a homo-dimer to specific DNA sequences called glucocorticoid response elements (GREs) located in the promoter/enhancer regions of glucocorticoid-responsive genes to modulate their transcription (28). On the other hand, GRβ does not bind glucocorticoids and functions as a dominant negative inhibitor of GRα on GRE-containing glucocorticoid-responsive promoters, together with its intrinsic transcriptional activity on the genes not related to glucocorticoid transcriptional activity (37,38). However, its physiologic and pathophysiologic roles have not been fully determined as yet (37).

The GRE-bound GR (hereafter for GRα) attracts to the promoter regions of glucocorticoid-responsive genes numerous "coactivator complexes", including those with histone acetyltransferase (HAT) activity, such as the NR coactivator [p160, p300/CREB-binding protein (CBP) and p300/CBP-associated factor (p/CAF)] complex, the SWI/SNF and the vitamin D receptor-interacting protein/thyroid hormone receptor-associated protein (DRIP/TRAP) chromatin-remodeling complexes (39). Among them, p160-type NR coactivators bind first to the ligand-activated and DNA-bound GR through their coactivator LxxLL motifs, and attract other coactivators and chromatin modulatory complexes including p300/CBP to the promoter/enhancer region of glucocorticoid-responsive genes. Through these proteins and protein complexes, GR alters chromatin structure and facilitates access of other transcription factors, RNA polymerase II and its ancillary factors to the promoter region of glucocorticoid-responsive genes, and ultimately changes their transcription rates (28). In addition to these protein molecules, recent research identified that several long non-protein-coding RNA molecules, such as the steroid receptor RNA coactivator (SRA) and the growth arrest-specific 5 (Gas5), regulate the transcriptional activity of GR (40,41).

Complexity of the GR-signaling system residing in glucocorticoid target organs/tissues suggests that it provides potential regulatory "windows" to the GR-induced transcriptional network, which further indicates that glucocorticoid activity is under the tight regulation of numerous factors to adjust its activity upon local needs (25,28) (Figure 1B). This peripheral modulation of the glucocorticoid-signaling system is referred to as "sensitivity of tissues to glucocorticoids", which determines effectiveness of circulating glucocorticoids in local tissues (30). Depending on its directions -decreased or increased-, it is categorized into two subgroups; resistance and hypersensitivity. Both states may be generalized or tissue-specific, as well as congenital or acquired. The generalized, congenital form of glucocorticoid resistance, namely the familial/sporadic glucocorticoid resistance syndrome or Chrousos syndrome, was described and established approximately 30 years ago (42-45). It is characterized by partial, relatively well-compensated resistance of all tissues to glucocorticoids and is mostly caused by inactivating mutations in the *GR* gene (42-45). On the other hand, tissue-specific, acquired forms of glucocorticoid resistance/hypersensitivity have been inferred but not fully confirmed or elucidated (46). Such states may be limited to certain tissues, as for instance leukocytes or adipocytes, and present with the manifestations associated with deficiency or excess glucocorticoids specific to respective tissues (25). Allergic, inflammatory or autoimmune diseases, such as glucocorticoid resistant asthma, Crohn's disease, rheumatoid arthritis and systemic lupus erythematosus, may be glucocorticoid resistant states found in the components of the immune system (25,46). Conditions associated with chronic deprivation of energy resources, such as severe lean and anorexia nervosa, are considered as glucocorticoid resistance specific in the liver, fat and/or muscles, in part through activation of several kinases including the AMP-activated protein kinase and subsequent cytoplasmic segregation of a newly-identified GR coactivator, the CREB-regulated

transcription coactivator 2 and/or induction of the repressive molecules, such as the RNA corepressor Gas5 (41,46-49). In contrast, the conditions associated with excess energy resources, such as central obesity-associated insulin resistance, hyperlipidemia and hypertension, may be glucocorticoid hypersensitivity states in adipose and/or vascular tissues (46).

INTERACTION OF THE HPA AXIS AND HIV INFECTION

Pathologic Conditions Associated with the Adrenal Glands in AIDS Patients

The adrenal gland is one of the organs frequently found damaged by HIV infection at autopsy, mostly caused by the opportunistic infection of other pathogens due to immunodeficiency of AIDS patients (50-52). Incidence of adrenalitis has significantly dropped recently, because the immune function of AIDS patients is much better preserved and the incidence of opportunistic infection has been dramatically reduced due to introduction of HAART (53). Pathologic findings of AIDS-associated adrenalitis are intra-adrenal inflammatory lesions with or without necrosis, thrombosis, and/or fibrosis, as well as metastases of Kaposi sarcoma. Cytomegalovirus adrenalitis is the most common cause of the adrenal insufficiency seen in AIDS patients (51,52), while cryptococcus, mycobacteria, histoplasma, *Toxoplasma gondii,* and *Pneumocystis carinii* also affect the adrenal glands (50,53,54). Pathologic findings vary from mild focal inflammation to extensive hemorrhagic necrosis. Although several cases with extensive adrenal necrosis and profound adrenal dysfunction have been reported (55-57), infectious adrenalitis does not usually cause clinical adrenal insufficiency in most of the AIDS patients (2). Indeed, 17% of 74 hospitalized AIDS patients demonstrated abnormal response of serum cortisol against ACTH injection in one early study, whereas only 4% of these patients developed adrenal insufficiency (58). However, a report on 60 advanced AIDS patients with less than 50 cells/μl of peripheral CD4+ lymphocyte counts demonstrated that over 25% of these patients had abnormally low and high levels of respectively serum cortisol and plasma ACTH, reduced excretion of urinary free cortisol and/or blunted response of serum cortisol to exogenous ACTH (59). Thirty-eight (63.3%) patients had cytomegalovirus antigenemia. Furthermore, 16 out of the 36 patients followed up for at least one year developed overt adrenal insufficiency and half of them were treated with corticosteroid replacement. In conclusion, pathologic findings of the adrenal glands are frequently encountered at autopsy, yet these are mild and are not associated with overt primary adrenal insufficiency in the majority of cases. Presence of adrenal insufficiency, and hence, glucocorticoid replacement therapy should be considered in some end-stage AIDS patients with special caution. Indeed, one fatal case with severe adrenal insufficiency due to cytomegalovirus infection even under the treatment with pharmacologic doses of glucocorticoids was reported (60).

Change of the HPA Axis/Pituitary Gland in AIDS Patients

Because the adrenal glands are frequently affected in AIDS patients and common manifestations of these patients, such as weakness, fatigue and body weight loss, mimic those of adrenal insufficiency, many studies have examined basal and/or reserve activity of the HPA axis (2,61-63). A majority of publications indicates that basal levels of serum cortisol and plasma ACTH are normal or slightly elevated and their circadian rhythm is preserved in AIDS patients (54,64-68). Elevations of serum cortisol have been reported both in the early stages of AIDS and in severely affected, terminal patients (63,69,70). Twenty four-hour urinary free cortisol excretion was increased depending on severity of the AIDS-associated manifestations (71). The adrenocortical reserve capacity evaluated with a standard ACTH stimulation test is preserved in the majority of patients, while it is reduced in advanced cases (59).

In a large study of 350 patients with HIV infection, 30.9% of participants displayed serum cortisol levels below 100 μg/L with a median value of 55.48 μg/L (11.36-99.96 μg/L); however, only 16.3% of participants had stimulated serum cortisol levels below 180 μg/L with median of 118 μg/L (19.43-179.62) (60). Importantly, the authors found a high prevalence of hypocortisolism among HIV patients, especially in those who had been on ART for a longer time (72). Secretion of ACTH in response to CRH is blunted, especially in terminal-stage AIDS patients (62,63,73,74). Altered profiles of circulating cytokines are suggested as a cause of low responsiveness of the pituitary gland to CRH (62). Significant blunting of the ACTH response in AIDS patients was also reported in the cold immersion stress test (66).

Focal to widespread necrosis and/or fibrosis of the anterior pituitary gland was observed at autopsy in 10 out of the 88 AIDS patients; 5 showed apparent signs of cytomegalovirus infection in the absence of apparent inflammatory reaction, and one demonstrated severe cryptococcus infection (75). Based on the above evidence, it appears that the function of the pituitary gland (corticotrophs) for secretion of ACTH is generally preserved in AIDS patients. Hyponatremia and hypovolemia observed in AIDS patients at the end-stage of their disease is likely to be a result of the adrenal insufficiency due to dysfunction of the adrenal gland caused by specific adrenal lesions, such as infectious adrenalitis or neoplastic infiltration (51).

GLUCOCORTICOIDS IN THE TREATMENT OF AIDS PATIENTS

Protease Inhibitor-Mediated Inhibition of Glucocorticoid Metabolism and Development of Iatrogenic Cushing Syndrome

PIs, which inhibit activity of the viral-encoded protease and are widely used as part of HAART, act as inhibitors of one of the cytochrome P450 (CYP) enzymes, CYP3A4, which is necessary for metabolizing glucocorticoids into inactive forms in the liver (11). Ritonavir is the strongest suppressor of CYP3A4-mediated 6β-hydroxylation of steroids, while indinavir and nelfinavir are moderate suppressors and saquinavir is the weakest (11). All these PIs cause full-blown Cushing syndrome in AIDS patients treated even with inhaled or intranasal synthetic glucocorticoids (e.g., fluticasone, budesonide, mometasone and belclomethasone) by extremely reducing their metabolic clearance (12,76-82). Duration of the glucocorticoid-PI co-administration prior to the development of iatrogenic Cushing syndrome is highly variable, from 10 days to 5 years (mean: 7.1 years), while mean doses of administered glucocorticoids (e.g., fluticasone) are around 200-800 μg/day (mean: 400μg/day) in adults (12). Thus, glucocorticoids, even applied topically, should be used with caution in the patients treated with PIs. Changing ritonavir to other PIs or use of different classes of anti-viral drugs may help reducing this characteristic side effect.

Other Therapeutic Compounds That Potentially Affect Glucocorticoid Metabolism in AIDS Patients

Some other medications used for the treatment of AIDS patients are known to affect glucocorticoid metabolism and contribute to the development of adrenal insufficiency or Cushing syndrome. Ketoconazole, an anti-fungal compound frequently used for fungal skin infections especially in immunocompromised patients, such as those with HIV infection and those on chemotherapy, can suppress steroidogenesis by inhibiting the steroidogenic enzymes P450 side-chain cleavage enzyme and 17β-hydroxylase, and cause cortisol deficiency (83,84). This effect of ketoconazole is not observed with other similar compounds, such as fluconazole and itraconazole, and imidazole derivatives. Phenytoin and rifampicin, which are respectively an anticonvulsant and an antibiotic used

for the treatment of tuberculosis, can accelerate cortisol metabolism, and thus, potentially cause adrenal insufficiency particularly in AIDS patients with reduced adrenal reserve (53). Megestrol acetate, a progesterone derivative also known as 17α-acetoxy-6-dehydro-6-methylprogesterone, is often used at relatively high doses to boost appetite and to induce weight gain in AIDS patients with cachexia (85). This compound has some glucocorticoid actions, therefore, causes glucocorticoid excess and subsequent adrenal insufficiency upon its withdrawal or under stress (86).

Potential Use of Glucocorticoids for Slowing AIDS Progression and Treatment of AIDS Complications

Current therapeutic regimens, including HAART, have enabled us to control viremia and viral replication in HIV-infected patients, and thus, have expanded their life expectancy significantly (6,8). However, these therapeutic regimens are expensive and their adherence rates are sometimes low (87-89). In addition, compounds used for the treatment of AIDS often have chronic toxic side effects, such as the characteristic AIDS-related insulin resistance and lipodystrophy syndrome (ARIRLS), which will be discussed in a later section, as well as mitochondrial toxicity, lactic acidosis, hepatotoxicity, and cardiomyopathy (90). Thus, other antiretroviral agents have been developed, including inhibitors of viral integrase, host CXCR4 and CCR5, and fusion of HIV to CD4+ lymphocytes (91). In addition to these compounds that directly interfere with viral activities, immunosuppressive agents, such as glucocorticoids and cyclosporine A, have been tested in HIV-infected patients, as these agents may suppress HIV-mediated immune activation, which is one of the major factors for AIDS progression and reduction of peripheral CD4+ lymphocytes (5,92-95); The synthetic glucocorticoid prednisone at 0.3-0.5 mg/kg/day successfully increases peripheral CD4+ lymphocyte counts and prevents their reduction for up to 10 years (5,96). It also suppresses circulating levels of TNFα and IL-6, known indicators of HIV-mediated host immune activation and possible causative agents for AIDS-associated wasting syndrome (92,97,98). These cytokines may also participate in HIV replication by potentiating Tat-mediated activation of the HIV long terminal repeat (LTR) promoter via stimulation of the nuclear factor-κB (NF-κB) (99). This beneficial effect of glucocorticoids is more obvious in patients whose immune system is less damaged (5,95). Glucocorticoids do not alter peripheral viral load in the patients who have already been treated with antiretroviral drugs, and thus, have low viral load before initiation of therapy (5,94,95). However, one case report indicated that high doses of prednisone (100 mg for 9 consecutive days) demonstrated extremely strong suppression on the circulating virus titer of the patient infected with multi-drug-resistant HIV (100). The synthetic glucocorticoid dexamethasone inhibits elimination of CD4+ lymphocytes by macrophages isolated from HIV-infected patients *in vitro* (101). Glucocorticoids reduce circulating mature monocytes in monkeys (sooty magabey) infected with the simian immunodeficiency virus, a model virus of HIV used in animal studies (102). These monocytes act as the HIV reservoirs due to their ability to transfer the virus to CD4+ lymphocytes and their relatively long life (103). Furthermore, reduced diurnal amplitude of circulating cortisol in HIV-infected patients is correlated with their greater T cell immune activation, which is a known risk factor for immunologic and clinical progression of AIDS (104). This evidence suggests that healthy diurnal cortisol production is beneficial for slowing down the AIDS progression. Thus, at treatment-naïve or equivalent states, glucocorticoids appear to inhibit viral replication by suppressing HIV-mediated inflammation, subsequent production of inflammatory cytokines and viral transmission from monocytes to CD4+ lymphocytes. However, glucocorticoids are also risk factors for AIDS-associated complications, including sarcopenia, osteoporosis and/or osteonecrosis of the

hip, and are reported to accelerate development of human herpes virus-8 (HHV8)-associated Kaposi sarcoma in the patients with pleural tuberculosis, interstitial pneumonia and glomerulonephritis (105-113). Indeed, HHV8 encodes the latency-associated nuclear antigen (LANA), which functions as a coactivator of GR through direct physical interaction (114). Glucocorticoids are also risk factors for elective hip surgery (total hip arthroplasty and resurfacing), and may be a potential factor for the development of CD8 encephalitis in HIV-infected patients (111,115).

Thus, the therapeutic use of glucocorticoids in AIDS patients appears to be quite limited by several factors, particularly in the era of improved HAART, which can control viral replication with less side effects. Selective glucocorticoids or other non-steroidal compounds, with immunosuppressive actions but not metabolic side effects, might be beneficial in the treatment of AIDS patients. Indeed, some of such compounds (e.g., Compound Abbott-Ligand (AL)-438, ZK216348 and the hydroxyl phenyl aziridine precursor analogue Compound A) are under investigation for their selective glucocorticoid effects (116) (please see Endotext chapter in the Adrenal Diseases and Function section entitled "Glucocorticoid Receptor").

In addition to the effect on circulating CD4+ lymphocyte counts, glucocorticoids act as central components in the treatment regimens for HIV-associated lymphoma (such as Hodgkin and non-Hodgkin lymphoma and latter's subtypes Burkitt lymphoma and plasmablastic lymphoma), multi-centric, HHV8-associated Castleman's disease (also known as giant or angiofollicular lymph node hyperplasia, lymphoid hamartoma, angiofollicular lymph node hyperplasia) and HIV-associated nephropathy (13,16,117-120). Glucocorticoids are also used to subside some complications of opportunistic infections, such as those by *Pneumocystis carinii* and mycobacteria (pleuritis and pericarditis), and those associated with immune reconstitution inflammatory syndrome (IRIS), which sometimes happens in AIDS patients upon recovery of their immune system with antiretroviral treatment (121-124). One clinical study examining the beneficial effects of glucocorticoids for the treatment of AIDS-associated cryptococcal meningitis was performed (18). Moreover, a recent double-blind, placebo-controlled, cross-over study investigated the effects of a single low-dose administration of hydrocortisone (10 mg oral) on cognition in 36 HIV-infected women (125). The authors found that this low dose had beneficial effects in verbal learning and delayed memory, working memory, visuospatial abilities and behavioral inhibition (125). Further larger studies are clearly needed to verify these promising results. Finally, glucocorticoids are prescribed empirically for AIDS patients to treat their fatigue and appetite loss (126-130).

Adverse Effects of the Contraceptive Medroxyprogesterone Acetate for Increasing the Chance of HIV Infection through GR Activation

It is important for the HIV endemic area whether contraceptives increase/reduce the chance of HIV infection, therefore several clinical studies were previously performed to address this possibility (131). These compounds, regularly mixtures of progestins and estrogens, stimulate the progesterone (PR) and estrogen receptor for mimicking the hormonal profiles of pregnancy (132). There are 2 types of contraceptives with regard to their routes of administration; injection and oral intake (131). Recent studies revealed that one of the injectable contraceptives, medroxyprogesterone acetate (MPA), a compound widely used in sub-Saharan Africa, increases a chance of HIV infection particularly in young women with high exposure to this virus (131). Subsequent research revealed that MPA can bind GR in addition to PR with high affinity in contrast to other progestins, such as progesterone and norethisterone acetate, and strongly suppresses

inflammatory response in endocervical cells by activating local GR (131,133). Moreover, medroxyprogesterone acetate was found to increase HIV-1 replication in human peripheral blood mononuclear cells through mechanisms involving the glucocorticoid receptor, increased CD4/CD8 ratios and CCR5 levels (134). Further, this compound enhances Vpr-mediated apoptosis of human CD4+ lymphocytes by cooperating with GR, which further affects clinical course of HIV-infected patients (133).

GLUCOCORTICOIDS RESISTANCE/HYPERSENSITIVITY ASSOCIATED WITH AIDS PATIENTS

Glucocorticoid Resistance with Reduced GR Affinity to its Ligands

Norbiato *et al.* reported a distinct subgroup of AIDS patients who showed apparent adrenal insufficiency with fatigue, weakness, body weight loss, hypotension, and skin and mucosal hyperpigmentation associated with markedly elevated levels of serum cortisol and moderately increased levels of plasma ACTH (135). In these patients, affinity of the GR to its ligand was markedly decreased in peripheral leukocytes with concurrent elevations of receptor numbers, suggesting that the apparent adrenal insufficiency seen in these patients might be caused by decreased sensitivity of peripheral tissues to glucocorticoids. This research group estimated that up to 17 % of AIDS patients are likely to have altered GR actions (136).

Pathologic mechanism(s) underlying this characteristic condition with markedly reduced receptor affinity has(have) not been elucidated as yet. A similar glucocorticoid resistance state associated with reduced receptor affinity was previously reported in glucocorticoid resistant asthma patients. In the latter patients, the affinity change is limited to immune tissues, such as peripheral leukocytes, and is progressively reverted to normal when cells are incubated *ex vivo* (137). Since incubation of patients' peripheral lymphocytes with IL-2 and IL-4 preserves the decrease in receptor affinity (137,138), and since elevation of these cytokine levels is generally observed in asthma patients (139), it is likely that cytokine-related mechanisms are involved in the development/maintenance of the receptor affinity change observed in AIDS patients. It was subsequently reported that glucocorticoid resistant asthma was also associated with increased expression of the GRβ isoform, suggesting that this splicing variant receptor might participate in the pathogenesis of the glucocorticoid resistance of AIDS patients as well (140). Because many kinases and other molecules important for the cytokine and growth factor signaling potentially modulate GR activity (28,30), and cytomegalovirus alters GR transcriptional activity by phosphorylating this receptor through activation of the extracellular signal-regulated kinases (141), it is possible that some of such molecules might also contribute to the alteration of the receptor affinity in AIDS patients.

The exact prevalence of this glucocorticoid resistance associated with reduced receptor affinity observed in AIDS patients is not known. Although similar patients were reported by another group just after appearance of the initial cases (142), very few reports followed subsequently, suggesting that this characteristic AIDS-related pathologic condition may be rare and/or associated with some special condition of AIDS patients, which may be disappeared after introduction of HAART. In this instance, severe uncontrollable immune dysregulation and/or inflammation by HIV observed at an early and/or specific period may be required for developing this characteristic phenotype.

AIDS-Related Insulin Resistance and Lipodystrophy Syndrome (ARIRLS): A Complex Pathologic Condition to Which Dysregulation of the Glucocorticoid/GR Signaling System

Contributes

In late ’90s, an acquired form of lipodystrophy, which partially mimics the clinical presentation of Cushing syndrome, was reported in AIDS patients (10,143-146). The patients had a characteristic redistribution of their adipose tissue, with an enlargement of their dorsocervical fat pad (“buffalo hump”), axial fat pads (bilateral symmetric lipomatosis), lipomastia, and expansion in their abdominal girth ("Crix-belly" or "protease paunch") [lipohypertrophy in trunk and abdomen]. Since these manifestations are reminiscent of the typical phenotype of chronic glucocorticoid excess or Cushing syndrome, this condition was initially referred as a pseudo-Cushing state, a term reserved for obese, depressive or alcoholic patients with biochemical hypercortisolism who are frequently hard to differentiate from true Cushing syndrome (31). In addition to these initial characteristic manifestations, some patients develop lipoatrophy in face, buttocks and limbs (147). Furthermore, they frequently demonstrate metabolic complications, such as severe insulin resistance, hyperlipidemia and hepatic steatosis, similar to some of the congenital lipodystrophy syndromes (29,46,147). Taken together, this AIDS-related characteristic syndrome has 3 major components in its manifestations, lipohypertrophy, lipoatrophy and metabolic complication, such as insulin resistance and dyslipidemia.

Pathologic causes of ARIRLS are not known, but appear to be multifactorial. ARIRLS patients demonstrate manifestations shared with or district from those of other lipodystrophies unrelated to HIV infection, suggesting that it is caused by the pathologic mechanisms somewhat different from the latter conditions (148). Alteration of the HPA axis and/or the glucocorticoid/GR signaling system appear(s) to be involved in the development of certain part of this syndrome, as we will discuss below.

Factors Contributing to the Development of ARIRLS

ANTIRETROVIRAL DRUGS

Protease Inhibitors (PIs)

Possible mechanisms contributing to this characteristic syndrome are listed in Table 3 and summarized in Figure 2. As several previous reports indicated, one of the earlier suggestions was that the syndrome was outcome of adverse effects of antiretroviral drugs including PIs, nucleoside reverse transcriptase inhibitors (NRTIs) and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs) (147,149). PIs interfere with viral replication by efficiently inhibiting the activity of the viral-encoded protease, which normally digests the Gag-Pol p160 kDa precursor protein, producing several polypeptide fragments with distinct functions (149,150). NRTIs and NNRTIs, on the other hand, inhibit viral replication by suppressing the activity of the reverse transcriptase also encoded by HIV (149). The effects of various antiretroviral drugs on the development of lipodystrophy and metabolic complications are listed in Table 4. Since prototype drugs were significantly associated with the development of ARIRLS, new compounds with less association were subsequently developed.

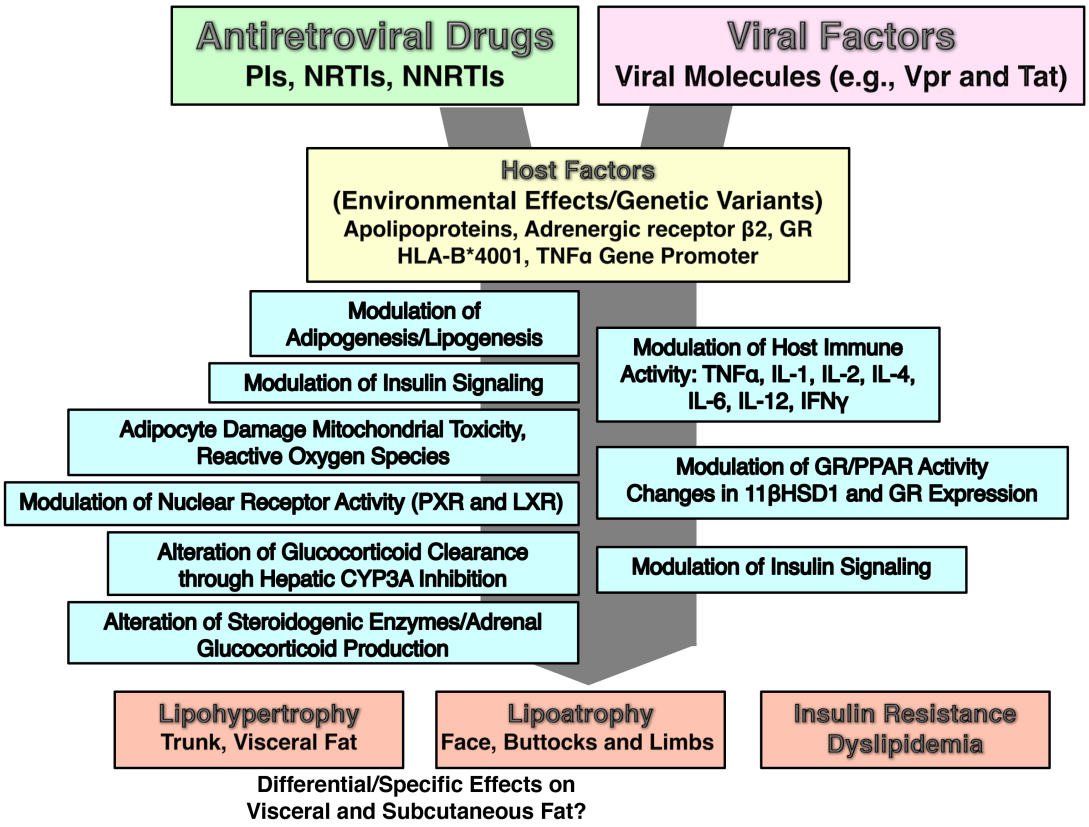

Figure 2. Major proposed mechanisms in the genesis of ARIRLS. Three major components, antiretroviral drugs, viral factors and host factors differentially contribute to the development of ARIRLS by respectively modulating adipogenesis, lipogenesis, and tissue insulin action through induction of/responsiveness to inflammatory cytokines, damage to adipocytes (e.g. by mitochondrial toxicity and reactive oxygen species) and/or through modulation of host cellular mechanisms, such as NR (GR, PPAR, PXR and LXR) signaling systems and inhibition/modulation of p450 enzyme activity (such as CYP3A and steroidogenic enzymes). Some changes can also alter tissue glucocorticoid action (glucocorticoid sensitivity) through expression of the GR and/or 11βHSD1 that converts inactive cortisone to active cortisol. As sum of these changes, major manifestations, lipohypertrophy, lipoatrophy and insulin resistance/dyslipidemia are finally developed in which modulation of the glucocorticoid metabolism/signaling system play a significant part. Their specific actions on visceral and subcutaneous fat may contribute to the development of lipohypertrophy and lipoatrophy in different body areas. [from (29,46,147,151)]

Table 3. Potential Contributing Factors to AIDS-Related Insulin Resistance and Lipodystrophy Syndrome (ARIRLS) Before and After Treatment with Antiretroviral Drugs

	Before Rx	**After Rx**
Nonspecific, disease-related		
Sickness-related starvation	+	Refeed
Sickness-related change in body composition	Lean body mass	Fat mass gain*

	loss*	
Infection-induced hypercytokinemia	+	
Cytokine-induced adipose tissue 11βHSD1 stimulation	+	-
Stress- and starvation-induced hypercortisolism	+	-
Specific, HIV-related		
Virally-induced muscle, liver, and fat glucocorticoid hypersensitivity	+	+
Virally-induced adipose tissue PPARγ inhibition	+	+
Virally-induced adipose tissue 11βHSD1 stimulation	+	+
Antiretroviral drug-related		
Rx-induced-insulin resistance/dyslipidemia	-	+
Alteration of glucocorticoid clearance through hepatic CYP3A inhibition	-	+
Modulation of NR activity (PXR and LVR) by acting as ligands	-	+
Genetic/constitutional predisposition	+	+

+: presence, -: absence, ?: unknown, * During stress and starvation, both fat and lean body mass are lost. Post stress and starvation body weight gain is primarily due to fat accumulation.

Table 4. Differential Effects of Antiretroviral Drugs on Fat and Metabolism Associated with AIDS-Related Insulin Resistance and Lipodystrophy Syndrome (ARIRLS)*

Class of drugs	Name of drug	Abbreviation	Lipo-atrophy	Lipo-hypertrophy	Dyslipidemia	Insulin resistance
PIs	Ritonavir	RTV	+/-	+	+++	++
	Indinavir	IDV	+/-	+	+	+++
	Nelfinavir	NFV	+/-	+	++	+
	Lopinavir	LPV	+/-	+	++	++
	Amprenavir Fosamprenavir	APV FPV	+/-	+	+	+/-
	Saquinavir	SQV	+/-	+	+/-	+/-
	Atazanavir	ATV	-	++	+/-	-
	Darunavir	DRV	-	+	+/-	+/-
NRTIs	Stavudine	D4T	+++	++	++	++
	Zidovudine	AZT, ZDV	++	+	+	++
	Didanosine	ddI	+/-	+/-	+	+
	Lamivudine	3TC	-	-	+	-
	Abacavir	ABC	-	-	+	-
	Tenofovir	TDF	-	-	-	-

	Emtricitabine	FTC	-	-	-	-
NNTRIs	Efavirenz	EFV	+/-	+/-	++, increased HDL	+
	Nevirapine	NVP	-	-	++, increased HDL	_
CCR5 inhibitor	Maraviroc	MVC	?	?	-	-
Integrase inhibitor	Raltegravir	RAL	?	?	-	-
Fusion inhibitor	Enfuvirtide	T20	?	?	-	-

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* These data should be considered with caution because discrepancies exist among studies that cannot be presented in one table.

Mechanistically, PIs act as inhibitors of the CYP3A4 enzyme, which metabolizes and inactivates glucocorticoids as we discussed above (11). Thus, these compounds may slightly increase circulating levels of endogenously produced cortisol by reducing its clearance in the liver, and participate in the development of ARIRLS. PIs also decrease hepatic lipase activity and modulate differentiation of pre-adipocytes (152-154). A possible underlying mechanism for this PI-mediated modulation of adipocyte activity is that these compounds change the expression levels of the peroxisome proliferation receptor (PPAR) γ and the CAAT/enhancer-binding protein **(**C/EBP) α (148). PPARγ is a NR family protein and acts as a pivotal regulator of glucose and lipid metabolism and development/differentiation of adipocytes (155). C/EBPα is a bZip family transcription factor, and plays also a key role in adipogenesis and adipocyte differentiation (156). In addition, PIs increase IL-6 and TNFα production by activating the NF-κB pathway in subcutaneous fat (157). These cytokines are known to play important roles in local inflammation and lipid accumulation in adipose tissue (158). The adverse effect of PIs may also result from induction of the endoplasmic reticulum stress or inhibition of the proteosomes (159,160).

NRTIs and NNRTIs

In addition to PIs, these classes of antiretroviral drugs are also associated strongly with development of ARIRLS. Among them, thymidine NRTI (tNRTI) stavudine and zidovudine cause severe lipoatrophy in AIDS patients, thus they were removed from the list of the first-line antiretroviral compounds in Western countries (161). These compounds demonstrate mitochondrial toxicity by inhibiting the mitochondrial DNA polymerase γ, facilitating generation of the reactive oxygen species in adipose tissues and possibly causing lipoatrophy in AIDS patients (147). Although weak, NNRTIs, such as efavirenz and nevirapine, also have an activity to develop lipodystrophy and dyslipidemia (147).

Modulation of NR Activity by Antiretroviral Drugs

In addition to above-indicated potential actions of antiretroviral drugs on the development of ARIRLS, some of these compounds can modulate the transcriptional activity of several NRs, such as the pregnane X receptor (PXR), constitutive androstane receptor (CAR), liver X receptors (LXRs) and the estrogen receptor α (ERα), and directly stimulate their transcriptional activity. Interestingly, these antiretroviral drugs were demonstrated to act potentially as ligands for the receptors in *in silico* structural analysis on the ligand-binding pocket of these receptors (154). PXR and CAR act as xenobiotic sensing receptors and induce drug metabolizing enzymes with broad ligand specificity for many chemical compounds, and several PIs can stimulate *CYP3A4* and *CYP2B6* promoter activity through activation of these receptors (154). Activation of PXR, either by its known ligands or transgenic expression of PXR, increases production of glucocorticoids in the adrenal glands by stimulating expression of the steroidogenic enzymes, such as CYP11A, CYP11B1, CYP11B2 and 3β-hydroxysteroid dehydrogenase, and develops Cushingoid manifestations in rodents (162), suggesting that PIs may increase cortisol production and participate in the development of ARIRLS indirectly through activation of PXR. Furthermore, PIs (ritonavir, atazanavir and darunavir) and maraviroc (CCR5 antagonist) activate the transcriptional activity of LXRα and/or LXRβ, while NNRTIs (tenofovir and efavirenz) stimulate ERα (but not ERβ) (154). Since LXRs are the receptors for regulating cholesterol/fatty acid metabolism and insulin actions, activation of these receptors by antiretroviral drugs may underlie pathophysiology of ARIRLS (163). In addition, LXRs and ERα cooperate with GR for expression of glucocorticoid-responsive genes, thus it is likely that these antiretroviral drugs enhance glucocorticoid actions indirectly through stimulating these NRs (164,165).

VIRAL FACTORS

Although antiretroviral drugs are generally accepted for causing ARIRLS, a small percentage of HIV-infected patients develop characteristic features of this syndrome prior to their introduction; HIV-infected patients who are not receiving antiretroviral therapy often have lipid abnormality, including elevated triglyceride levels, a high proportion of small and dense LDL particles, and low HDL cholesterol levels, similar to ARIRLS patients (166). Furthermore, different classes of chemical compounds that target different components of HIV/adipocyte biological pathways can develop similar ARIRLS manifestations in AIDS patients (147). These pieces of evidence thus suggest that the HIV infection itself could nonspecifically, -in part via inflammatory cytokine elevations and stress induced cortisol hypersecretion-, induce an insulin resistant phenotype (31). Pro-inflammatory cytokines, such as TNFα, IL-1 and IL-6, which are released from the HIV-infected macrophages localized in adipose tissues, do cause resistance to insulin and fat accumulation in neighboring adipocytes (158). In addition, these cytokines indirectly activate GR in adipose tissues by stimulating expression of the 11β-hydroxysteroid dehydrogenase-1 (11βHSD1), which converts inactive cortisone into active cortisol (167). Moreover, increased expression of GR is also reported in subcutaneous fat of zidovudine-treated AIDS patients (168). In this context, antiretroviral drugs might just exacerbate already present, smoldering insulin resistance and lipodystrophy, not expressed because of the known malnutrition of sick AIDS patients and the absence of sufficient calories to build visceral and other fat deposits (10,30,169). As manifestations of the sickness syndrome subside with treatment, the emaciated patient goes through refeeding with body weight gain of mostly fat, tilting the ratio of fat to lean body mass upward, further worsening insulin resistance.

HIV, in its 9.8 kb genomic information, encodes and produces 3 precursor proteins, the Gag, RNA polymerase and envelope polypeptides, whose processed products are the reverse transcriptase, protease, integrase, matrix, and capsid, as well as 6 accessory proteins, Tat, Rev, Nef, Vif, Vpr and Vpu (170) (Figure 3). Some of these polypeptides are virion-associated proteins incorporated in the viral particle and others are expressed in host cells where they direct viral replication and gene expression and several host cell functions. Since infection with HIV has a dramatic impact on host target cells, it is quite possible that some of these viral proteins modulate host cell glucose and lipid metabolism by changing the activity of GR in local tissues, such as in adipose tissue, skeletal muscles and liver, and participate in the development of ARIRLS. Indeed, there are several pieces of evidence indicating that AIDS patients have altered tissue sensitivity to glucocorticoids. First of all, they all develop reduction of innate and Th1-directed cellular immunity. Levels of plasma IL-2, IL-12 and IFN-γ, which direct cellular immunity, are suppressed in AIDS patients, while levels of IL-4 are increased (171,172). All changes can be induced by exogenously introduced glucocorticoids and are seen in hypercortisolemic patients with classic Cushing syndrome (173). AIDS patients also frequently present with muscle wasting and myopathy, as well as dyslipidemia and visceral obesity-related insulin resistance (174-176). Therefore, some unknown viral factor(s) might modulate tissue sensitivity to glucocorticoids in AIDS patients in a tissue-specific fashion, sparing their HPA axis preserving normal negative feedback sensitivity to glucocorticoids.

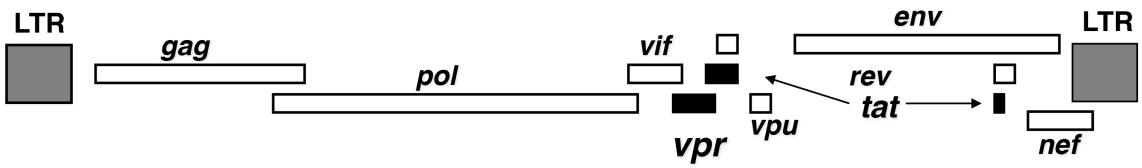

Figure 3. Lineralized structure of the HIV genome and localization of *vpr* and *tat* coding region (shown in black boxes). HIV, in its 9.8 kb genomic information, encodes and produces 3 precursor proteins, the Gag (*gag*), RNA polymerase (*pol*) and envelope polypeptides (*env*), whose processed products are the reverse transcriptase, protease, integrase, matrix, and capsid, as well as 6 accessory proteins, Tat, Rev, Nef, Vif, Vpr and Vpu. LTR: long terminal repeat [modified from (170,177)]

In agreement with these reported findings, one of the HIV proteins, Vpr, which is a 96-amino acid virion-associated accessory protein with multiple functions, including influencing transcriptional activity and having a cell cycle-arresting effect, increases the action of GR by several fold, functioning as a potent GR coactivator (178). The GR coactivator activity of Vpr is biologically evident in the suppression of IL-12 production from monocytes and the expression of activated NF-κB ligand (RANKL) in lymphocytes (179,180). Similar to host p160 type coactivators, Vpr contains one LxxLL coactivator motif through which it binds to the ligand-activated and promoter-bound GR (178). GR-bound Vpr then attracts p300/CBP, and ultimately potentiates the transcriptional activity of GR by acting as a molecular adaptor between GR and p300/CBP (177,181) (Figure 4). p300/CBP are HAT coactivators also known as integrators or regulatory “platforms” for many signal transduction cascades by providing docking sites for many transcription factors, including NRs, CRE-binding protein (CREB), activator protein-1 (AP-1), NF-κB and the signal transducers and activators of transcription (STATs) (182) (Figure 4). Vpr easily

penetrates the cell membrane to exert its biologic effects (183,184), thus its effects may be extended to tissues not infected with HIV.

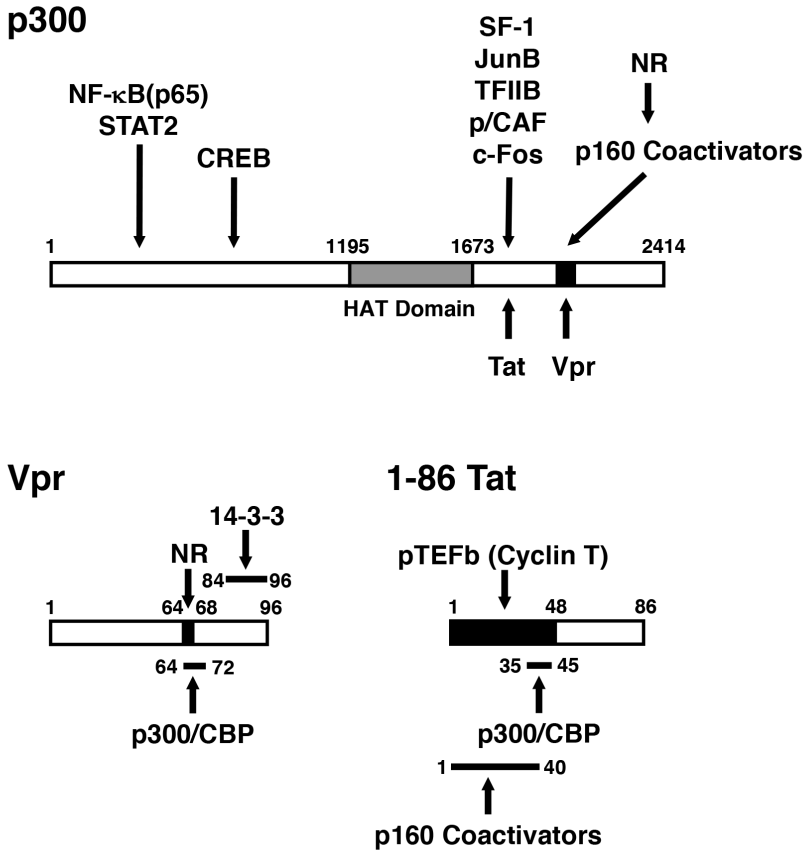

Figure 4. Linearized Vpr, Tat and p300 molecules and their mutual interaction domains. Vpr interacts with cellular molecules, such as NR, p300/CBP coactivators and 14-3-3, while Tat is physically associated with pTEFb elongation factor through its component Cyclin T1. Tat also binds p300/CBP and p160 type coactivators. Numerous transcription factors, transcriptional regulators and viral molecules bind the transcriptional coactivator p300. Binding sites of p160 NR coactivators and Vpr overlap with each other and they both bind NRs and p300/CBP. Thus, Vpr mimics the host p160 NR coactivators and enhances NR transcriptional activity. p300 facilitates attraction of transcription factors, cofactors and general transcription complexes by loosening the histone/DNA interaction through acetylation of histone tails by its histone acetyltransferase (HAT) domain. [modified from (29,30)]. CREB: CRE-binding protein, HAT: histone acetyltransferase, NF-κB: nuclear factor-κB, NR: nuclear hormone receptor, p/CAF: p300/CBP-associating factor, pTEFb: positive-acting transcription elongation factor b, Rb: retinoblastoma protein, SF-1: steroidogenic factor-1, STAT2: signal transducer and activator of transcription 2, TFIIB: transcription factor IIB.

Another HIV accessory protein, Tat, the most potent transactivator of the HIV long terminal repeat promoter, also moderately potentiates GR-induced transcriptional activity, possibly through accumulation of the positive-acting transcription elongation factor b (pTEFb) complex, that is comprised by the cyclin-dependent kinase 9 and its partner molecule cyclin T, on glucocorticoid responsive promoters (185) (Figure 4). Because Tat, like Vpr, also circulates in blood and exerts its actions as an auto/paracrine or endocrine factor by penetrating the cell membrane (186), it is possible that Tat modulates tissue sensitivity to glucocorticoids irrespectively of a cell's infection by HIV. Concomitantly with Vpr, Tat may induce tissue hypersensitivity to glucocorticoids that might contribute to viral proliferation indirectly, by suppressing local immune system activity and by altering the host's metabolic balance, with both functions being governed by glucocorticoids (30,46).

Vpr reduces tissue sensitivity to insulin not only through potentiating the actions of glucocorticoids, but also by modulating insulin's transcriptional activity via interaction with the protein of the 14-3-3 family, which participates in the cell cycle arrest activity of Vpr (29,187). Insulin uses the forkhead transcription factors (FoxOs) to control gene induction; baseline unphosphorylated FoxOs are active, reside in the nucleus, and bind to their responsive sequences in the promoter region of insulin-responsive genes; in contrast, insulin activates Akt kinase, which phosphorylates specific serine and threonine residues of FoxOs rendering it inactive (188). Indeed, once FoxOs are phosphorylated at specific residues, they lose their transcriptional activity, by binding with 14-3-3 through phosphorylated residues and subsequently segregated into the cytoplasm (188). We found that Vpr moderately inhibited insulin-induced translocation of FoxO3a into the cytoplasm through inhibiting its association with 14-3-3 (187). Thus, Vpr may participate in the induction of insulin resistance by interfering with the insulin signaling through FoxOs/14-3-3 (29,151,177).

We further found that Vpr-mediated insulin resistance might be compounded by the ability of the viral protein to interfere with the signal transduction of PPARγ (183). Indeed, Vpr suppresses the c-Cbl associating protein (CAP) mRNA expression in pre-adipocyte cells and associated with the PPAR-binding site located in the promoter region of this gene. CAP is predominantly expressed in insulin-sensitive tissues and positively regulates insulin action, directly associating with both the insulin receptor and the c-*Cbl* proto-oncogene product (189). Vpr delivered either by exogenous expression or as a peptide added to media suppresses PPARγ agonist-induced adipocyte differentiation (183). Thus, circulating Vpr, or alternatively Vpr produced as a consequence of direct infection of adipocytes, may suppress differentiation of preadipocytes by acting as a corepressor of PPARγ-mediated gene transcription (29,183,190). We further found that Vpr regulates the transcriptional activity of PPARβ/δ as well, and alters cellular energy metabolism organized by mitochondria (191). Vpr disturbs the insulin signaling and induces hepatic steatosis by disrupting the transcriptional program of PPARs in the liver and adipose tissue in the animal models, such as the transgenic mice expressing Vpr specifically in these organ and tissue and the mice inoculated with the pump that continuously releases the synthetic Vpr peptide into circulation (192). Moreover, Vpr was demonstrated to induce fatty liver in mice via LXRα and PPARα dysregulation (193). Taken together, based on these pieces of evidence, Vpr may be a key factor for the development of lipodystrophy, insulin resistance and hyperlipidemia observed in HIV-infected patients through modulation of the GR/PPARs/LXR and FoxOs/14-3-3 activities.

HOST FACTORS

Several host factors may influence susceptibility and manifestation of ARIRLS. Variant alleles of *APOC3*, *APOE* contribute to an unfavorable lipid profile in patients with HIV infection, while application of antiretroviral therapy further worsens it (194). Another study identified that *APOE* polymorphism is also associated with the dyslipidemia seen in AIDS patients treated with PIs (195). One recent study demonstrated that polymorphisms of the genes involved in apoptosis and adipocyte metabolism are significantly related to the development of ARIRLS (196). Among the polymorphisms examined, ApoC3-455 variant is associated with lipoatrophy, while two variants of the adrenergic receptor β2 influence fat accumulation in ARIRLS patients (196). A polymorphism in the *TNFα* gene promoter is associated with development of lipodystrophy in one study, while this association was not confirmed in larger studies (194). Stavudine-induced lipoatrophy is associated with the HLA-B100*4001 allele among the genetic variants of HLA-A, HLA-B HLA-C, HLA-DRB1, HLA-DQB1 and HLA-DPB1 (190). A newly identified polymorphism (*Tth111*I) in the *GR* gene is negatively associated with the development of some manifestations of ARIRLS in the African-American population (197). Finally, toxicity of antiretroviral drugs depends on their metabolism in each patient, which is partly determined genetically (196).

Summary for ARIRLS

Above pieces of evidence indicate that ARIRLS is most likely caused by multiple factors, including the infection itself, - via nonspecific inflammatory cytokine - and stress-induced hypercortisolism causing insulin resistance-, several HIV products disturbing the cellular functions of the host, and antiretroviral drugs, all acting on a genetic and constitutional background of variable predisposition to the syndrome. It is highly possible that alteration of glucocorticoid/GR signaling system by any of the above indicated factors contributes to the development of ARIRLS. Further studies are necessary to characterize this syndrome further, to better define the mechanisms involved in its development, and devise ways to prevent it from occurring or for reversing it.

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