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Review

Biomolecular basis of the role of chronic psychological stress in the susceptibility of HIV infection and progression of AIDS

Mahbub E. Sobhani[1], Bipradas Roy[1], Tauhidur R. N[1], Shirin Pervin[1] and Md Mahmudul Hasan[2]

[1]Biotechnology and Genetic Engineering Discipline, Khulna University, Khulna-9208, Bangladesh.
[2] Biotechnology, Claflin University, 400 Magnolia Street, Orangeburg, South Carolina, USA-29115

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Chronic Psychological stress (CPS) has several adverse effects both on HIV people and on HIV$^+$ patient. HIV$^-$ people with CPS are more susceptible to HIV infection than the HIV$^-$ people without CPS. T-cells have CXCR4 receptor and Macrophages have CCR5 receptor which can bind with both glucocorticoid and catecholamine hormone. HIV has GP120 residue which is able to bind with both CD4 and CXCR4/CCR5 receptor for its entry into the host cells. CPS increases glucocorticoid and catecholamine concentration in blood and thereby activates cAMP signaling pathway through binding the CXCR4/CCR5 receptors expressed on T cells and macrophages. This signal transduction pathway leads to the synthesis of more CXCR4 and CCR5 receptors by those cells, and in turn the cells become more susceptible to HIV infection. On HIV$^+$ patient stress hormones arrest the infected cell in G2 phase which is favorable for HIV replication. At the same time T-cells and macrophage are more susceptible to HIV, so HIV can infects a lot of immune cells and thereby makes the immune system weak. Stress also inhibits Th2 when the cell produces INF-γ as a response to viral attack. So that other cells remain vulnerable to viral infection. When T-cell count is decreased in the blood, the body cannot protect itself from other opportunistic infectious pathogens. As a result progression of AIDS increases rapidly.

Key words: HIV, chronic stress, IFN, CCR5, CNS, glucocorticoid.

INTRODUCTION

AIDS is the condition when groups of related symptoms that are caused by severe HIV infection prevail in the body. HIV makes the body vulnerable to incurable life-threatening illnesses called opportunistic infections. The official start of AIDS diagnosis occurred in 1981 when the US Centers for Disease Control and Prevention (CDC) reported on a cluster of *Pneumocystis carinii* pneumonia (PCP) in five homosexual men (Centers for Disease Control, 1981).

On the other hand, stress is a complex process involving social, psychological and physiological elements. According to psychological theories, stress is determined by "the balance between the perceived demands from the environment and the individual's resources to meet those demands". Stress contributes to the development of heart and cerebrovascular disease, hypertension, peptic ulcer, inflammatory bowel diseases, musculoskeletal disorders, absenteeism from work, negative emotional reactions and reduced work productivity. Prolonged stress, or very intense stress, can also influence performance and may impair attention and memory, and can contribute to human errors and accidents (Haque N., 2007).

Stress and depression might affect an immune-based disorder like AIDS/HIV, a disease where the variability in disease progression was largely unexplained and the population was at high risk for adverse mental health. There is much interest in whether depression and stress may explain the wide variability in the disease course of patients infected with human immunodeficiency virus (HIV). Biological mechanisms of HIV disease, such as alterations in glucocorticoids and catecholamines, which may help explain these psychoimmune relationships.

*Corresponding author. E-mail: t.tipu@yahoo.com Tel: +8801717726307

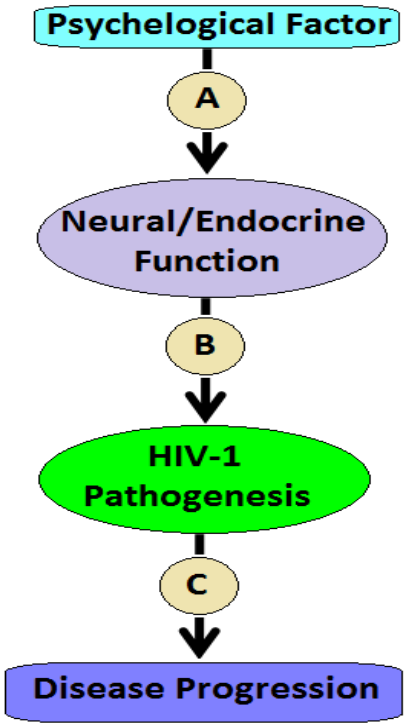

Figure 1. Theoretical model of biobehavioral influences on HIV-1 disease progression. Psychosocial factors = stress, depression, coping, social support, temperament, and other CNS-mediated influences on neural and endocrine activity, A = CNS-mediated effects of psychosocial factors on neural/endocrine activity, B = Neural/endocrine influences on HIV-1 replication, C = Effects of HIV-1 replication on clinical disease progression.

Chronic depression and stressful events may affect HIV disease progression.

A stressful condition is not a theoretic model but a concrete reality in the life of the special groups at risk for HIV: drug users and drug dependence individuals experience a continuous distress related to drug dependence, marginalization, and stigma; people vulnerable to human trafficking undergo an unimaginable suffering and violation of human rights making them continuously under stress; men having sex with men in many countries are stigmatized and experience difficult interpersonal relationships; prisoners in low income countries are closed in overcrowded jails with the lack of food and hygienic measures. Now the question arise, how depression and stress might affect HIV disease progression and what types of interventions might mitigate the negative impact of chronic depression and trauma? The main objective of this study is to identify the relationship between chronic psychological stress and the rate of progression of AIDS.

Psychosocial influences on HIV-1 disease progression

A substantial body of evidence has documented relationships between psychosocial characteristics and differential progression of HIV-1 infection (Ironson et al., 2008; Leserman, 2008; Leserman, 2003; Sloan, 2007; Temoshok et al., 2008;). Randomized controlled studies have shown that behavioral interventions can influence biological indicators of HIV-1 pathogenesis (e.g., $CD4^+$ T lymphocyte levels and HIV-1 plasma viral load) (Goodkin et al., 1998; Petrie et al., 2004), and experimental analyses of the closely related Simian Immunodeficiency Virus (SIV) model in rhesus macaques have demonstrated causal effects of social stress on viral replication and disease progression (Capitanio et al., 1998; Sloan et al., 2007). Neural, endocrine, virologic, and immunologic processes surveyed in the context of an integrative model (Figure 1) that focuses on two major questions:(Ironson et al., 2008) which physiologic signaling pathways transmit psychosocial influences into the body. (the “biobehavioral signal transduction pathway”), and (Leserman, 2008) which aspects of viral pathogenesis are modulated by those biobehavioral signals? (The “locus of impact on disease”). The available evidence is most consistent with a theoretical model in which CNS-induced alterations in neural and endocrine activity (Figure 1A) regulate aspects of leukocyte biology that influence HIV-1 viral replication (Figure 1B), and thereby affect the pathogenesis of immunodeficiency-related disease (Figure 1C). Technical and ethical constraints prevent the experimental

confirmation of the model as a whole, but individual links within the model have been empirically tested by experimental analysis in model systems (e.g., in vitro viral replication in human leukocytes or in vivo dynamics of the SIV animal model), and hypothesized systems of influence have been tested for consistency with observed associations in vivo using statistical mediation analyses (Baron et al., 1986). The theoretical model of Figure 1 is evaluated using three types of pertinent data: 77 experimental studies assessing causal effects of neural and endocrine factors on disease-related biology (e.g., viral replication in vitro, or in vivo viral load, $CD4^+$ T lymphocyte levels, or clinical disease),(Leserman, 2008) prospective relationships between neural/endocrine parameters and biological indicators of HIV-1 pathogenesis or disease progression in vivo, and (Temoshok et al., 2008) multivariate mediation analyses that simultaneously test transitive relationships among psychosocial risk factors, neural mediators, and HIV related outcomes.

The neurobiological interface to HIV disease progression

The progression of HIV-1 infection to clinical immunodeficiency and opportunistic disease driven fundamentally by viral replication in activated $CD4^+$ T lymphocytes and macrophages (Ho et al., 1995; Levy, 1993; Mellors et al., 1996; Perelson et al., 1996). HIV-1 replicates primarily in secondary lymphoid organs (e.g., lymph nodes and spleen) (Hasse et al., 1996), which house more than 90% of the body's total complement of leukocytes.

From a mechanistic standpoint, understanding how psychosocial factors such as stress, depression, or temperament might influence HIV-1 disease progression essentially involves determining how CNS perceptual, interpretive, and coping processes might affect the biology of viral replication in leukocytes residing within secondary lymphoid tissues. Two major physiologic signaling pathways are most often studied as possible mediators of biobehavioral influences on HIV-1 pathogenesis the hypothalamic-pituitary-adrenal (HPA) axis, which could potentially affect HIV-1-infected leukocytes through the blood-borne glucocorticoid, cortisol, and the sympathetic division of the autonomic nervous system (SNS), which would affect HIV-1-infected leukocytes via the catecholamines, epinephrine, and norepinephrine (NE) (Sapolsky et al., 19994; Weiner, 1992). Both the HPA/cortisol and SNS/catecholamine systems are activated by stress (Sapolsky et al., 19994; Weiner, 1992), and both have also been linked to other psychological or social risk factors for HIV-1 disease progression such as depression, social support, psychological inhibition, and social temperament. Activity of these signaling pathways has also been linked to biological indicators of HIV-1 pathogenesis in clinical natural history studies, experimental animal models, (Capitanio et al., 1998; Sloan et al., 2007) and pharmacologic intervention studies (Hofmann et al., 1996; Sloan et al., 2007). Other physiologic signaling pathways examined as potential mediators include hormones from the growth and gonadal axes and peptide neurotransmitters such as substance P (Douglas et al., 2001; Ho et al., 2004). However, much less known about how those factors might affect HIV-1 replication and disease pathogenesis. Both cortisol from the HPA axis and epinephrine from the SNS can reach HIV-1-infected leukocytes via blood plasma perfusion of secondary lymphoid organs, and during leukocyte recirculation through the vasculature. NE spillover from SNS innervation of the vasculature can also signal leukocytes in both of those compartments, but this catecholamine can also reach virally infected leukocytes via SNS innervation of secondary lymphoid organs (Bellinger et al., 2001; Sloan et al., 2006). T lymphocytes and macrophages harbor receptors for both glucocorticoids and catecholamines, and those signaling molecules are known to affect several aspects of leukocyte function, including cellular activation, cytokine production, cell trafficking and chemotaxis, and immune effector responses (Ader et al., 2007; Onard et al., 2007). Effects of neural mediators on cell localization are particularly pertinent because two key receptors for chemotactic molecules, CCR5 and CXCR4, also facilitate entry of HIV-1 viral particles into human cells (Deng et al., 1996; Dragic et al. 1996; Feng et al., 1996) and show relationships to biobehavioral risk factors and signaling pathways (Caulfield et al., 2002; Cole et al., 1999; Curnow et al., 2004; Leserman, 2008; 1998; Okutsu et al., 2005; Wang et al). Understanding how HPA and SNS activity might affect HIV-1 disease progression thus involves understanding how the net effect of these multiple host cell factors, the ability of the virus to complete its full replication cycle and disseminate infection to other cells.

Cortisol and the HPA axis

Several studies have documented relationships between psychological factors and circulating cortisol levels in HIV^+ individuals (Cole et al., 2001; Goodkin et al. 1998; Sloan et al., 2007), and cross-sectional studies have linked elevated cortisol levels to HIV-1 disease progression (Christeff et al., 1997; Kumar et al., 2002). Elevated cortisol levels predict subsequent onset of AIDS. Consistent with the later hypothesis, several studies have shown that progressing HIV-1 infection can activate the HPA axis and alter the adrenal gland (Mc et al., 2001; Sloan et al., 2007). In the most comprehensive study of HPA relationships to HIV-1 disease progression, high cortisol levels were found to be an additional risk

factor for AIDS onset that was independent of psychosocial risk factors (e.g., depression). However, studies experimentally manipulating glucocorticoid levels have not identified any consequent increase in HIV-1 plasma viral load, $CD4^+$ T lymphocyte loss, or clinical disease onset (Andrieu et al., 2004; Bellinger et al., 2001; Ho et al., 2004; Mc et al., 2001; Sloan et al., 2007). Several of those studies have shown that glucocorticoid elevation can actually reduce plasma HIV-1 viral load and $CD4^+$ T lymphocyte loss (Bellinger et al., 2001; Ho et al., 2004; Sloan et al., 2007). One nonrandomized observational study has suggested that administration of pharmacologic glucocorticoids to late-stage HIV-1 patients may precipitate the onset of full-blown AIDS (likely due to the immunosuppressive effect of glucocorticoids) (Shafer et al., 1985). No prospective study of HIV-1 disease progression has found HPA axis activity to be a plausible mediator of biobehavioral risk in multivariate statistical analysis, although one cross-sectional result is consistent with that hypothesis (Ironson et al., 2002). A decisive demonstration of HPA axis mediation would require experimental control of cortisol levels to abrogate the risk of disease progression associated with a known psychosocial risk factor. In the absence of such data, and in light of experimental studies documenting a suppressive effect of glucocorticoids on markers of HIV-1 pathogenesis, it remains unclear whether correlations between endogenous cortisol levels and HIV-1 disease progression reflect HPA axis mediation of stress effects or simply serve as a neuroendocrine marker of underlying disease progression. Experimental studies in cellular models have identified several molecular mechanisms by which glucocorticoids might potentially influence HIV-1 replication, including altered expression of the CXCR4 chemokine receptor that mediates cellular vulnerability to infection by some strains of HIV-1(Caulfield et al., 2002; Curnow et al., 2004; Okutsu et al., 2005; Wang et al., 1998), arrest of the cell cycle in the G2 phase favoring viral gene expression (117), and impaired activation of the Type I interferon system, which represents a key innate immune response to viral replication (Collado et al., 2006). However, most in vitro virology studies have shown minimal impact of glucocorticoids on overall viral replication rates (Kino et al., 2000; Laurence et al., 1989; Markham et al., 1986; Mitra et al., 1995). This is likely because, whatever stimulatory effects glucocorticoids have on specific elements of the HIV-1 replication cycle, they also profoundly inhibit the basic leukocyte activation signals required for productive viral gene expression (e.g., the NF- κ B transcription factor) (Kino et al., 2000). Such suppressive effects on lymphocyte activation are consistent with clinical effects of glucocorticoids in suppressing HIV-1 viral load and $CD4^+$T lymphocyte declines (Bellinger et al., 2001; Ho et al., 2004; Sloan et al., 2007). In vitro viral replication models do not capture the effects of adaptive immune responses to HIV-1 (e.g., cytotoxic T lymphocyte responses), which are believed to play a central role in establishing equilibrium rates of viral replication in vivo. One experimental system that does capture both basic viral replication dynamics and adaptive immune responses is the rhesus macaque model of SIV infection. Studies in this system have shown that experimentally imposed social stress can increase SIV replication and accelerate the onset of clinical immunodeficiency (Capitanio et al., 1998; Sloan et al., 2007). However, this system also showed reduced glucocorticoid levels in stressed animals, suggesting that stress-induced acceleration of SIV progression stemmed from some mechanism other than chronically elevated glucocorticoid levels. The present research literature provides mixed evidence regarding glucocorticoid regulation of HIV-1 replication in vitro, and no in vivo data currently support the hypothesis that increased HPA axis activity mediates observed relationships between psychosocial risk factors and HIV-1 (or SIV) disease progression in vivo.

Catecholamines and the SNS

Studies have more consistently linked increased SNS activity to HIV-1 pathogenesis. Initial research in this area motivated by data showing accelerated disease progression in people with socially inhibited personality characteristics (Cole et al., 1996; Cole et al., 1997), which have been linked to elevated SNS activity in previous research (Kagan et al., 1988). Subsequent studies directly assessed autonomic nervous system activity in HIV^+ individuals, and found those with constitutively high levels of SNS activity to show elevated plasma viral load set-points and impaired virologic response to the initiation of combination antiretroviral therapy (ART) (Ironson et al., 2008). Multivariate statistical analyses also supported the hypothesis that individual differences in SNS activity might account for much of the relationship between stress or temperament-related risk factors and individual differences in virologic or immunologic indicators of HIV-1 pathogenesis (Ironson et al., 2008). Those findings are also consistent with data from experimental pharmacologic studies that (inadvertently) activated the cAMP/PKA signaling pathway which mediates catecholamine response and found a consequent increase in HIV-1 plasma viral load (Douglas et al., 2001; Hofmann et al., 1996). Thus, both natural history studies and pharmacologic manipulation studies support the hypothesis that SNS activity may mediate some biobehavioral influences on HIV-1 pathogenesis. In vitro studies have shown that catecholamines can significantly enhance HIV-1 replication (Cole et al., 1998). Several molecular mechanisms of this effect have been identified, including up-regulated cell surface expression of the viral coreceptors, CXCR4 and CCR5 (Cole et al., 1999),

enhanced transcription of HIV-1 genes by cellular transcription factors, and catecholamine-mediated suppression of Type I interferon responses to infection (Collado et al., 2006). Signal transduction analyses identified beta-adrenergic receptor activation of the cAMP/PKA signaling pathway as the key mediator of catecholamine effects on HIV-1 replication, and showed that pharmacologic blockade of beta-adrenergic

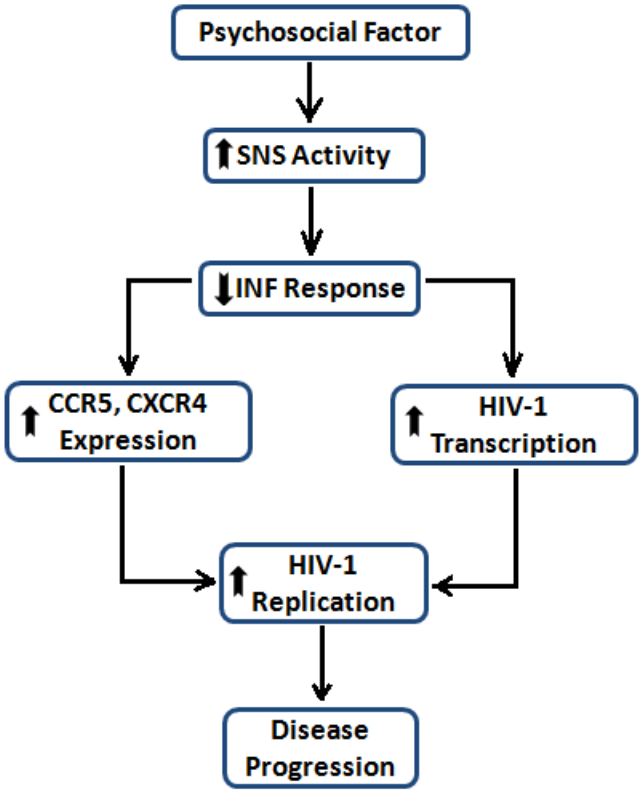

Figure 2: Theoretical model of SNS mediation of psychosocial influences on HIV-1 disease progression.SNS = sympathetic nervous system, IFN = Type I interferon. CCR5 and CXCR4 cell surface expression of cellular coreceptors that complement CD4 as mediators of HIV-1 infection.

receptors can abrogate those effects (Cole et al., 1998). Analyses of lymph nodes from the rhesus macaque model of SIV infection have revealed a key role of SNS neurons in regulating viral replication in secondary lymphoid tissue. Initial studies found increased SIV replication adjacent to the SNS neural varicosities that release catecholamines within the lymph node parenchyma (Sloan et al., 2006). Subsequent studies showed a surprising degree of behaviorally induced plasticity in the SNS innervation of lymphoid organs. Macaques subject to experimentally imposed social stress showed elevated density of catecholaminergic varicosities within the lymph node parenchyma (Sloan et al., 2007). Stress also enhanced SIV replication, and that effect was attributable specifically to the increased density of catecholaminergic varicosities. Consistent with in vitro cellular models, interferon-beta gene expression also suppressed in stressed animals, suggesting that impairment in innate antiviral responses might play a key role in the relationship between SNS innervation and viral replication (Figure 2).

A recent study has also shown that pharmacologically

induced enhancement of SNS innervation density is associated with increased SIV gene expression in macaque lymph nodes (Sloan et al., 2007), providing an experimental link between modulation of the sympathetic nervous system and viral replication in vivo. Figure 6 provides a theoretical model that integrates existing results from human clinical studies relating SNS activity to indicators of HIV-1 pathogenesis (Ironson et al., in press), in vitro analyses of catecholamine effects on HIV-1 replication (Cole et al., 1998; Cole et al., 1999; Collado et al., 2006;), and experimental analyses of the SIV lymphoid tissue model in vivo (Sloan et al., 2007). SNS activity is hypothesized to enhance viral replication by inhibiting the activity of Type I interferons (Collado et al., 2006; Sloan et al., 2007;), which increases viral replication through multiple mechanisms including impaired resistance to viral gene expression (via inhibition of the interferon-mediated antiviral state) (Collado et al., 2006) and enhanced cellular vulnerability to infection (via disinhibited expression of the viral coreceptors CCR5 and CXCR4, which occurs under physiologic conditions (Zang et al., 2001), but not in artificially stimulated cells (Yang et al., 2001). In conjunction with immune activation (e.g., via proinflammatory cytokines or ligation of the T cell receptor), these factors.

IL-4 and glucocorticoid up-regulate CXCR4 expression on human CD4$^+$ T lymphocytes and enhance HIV-1 replication

Th2 polarized cells expressed more CXCR4 than Th1 cells. Among a panel of cytokines and stimulants, a Th2 type cytokine interleukin-4 (IL-4) selectively up-regulated the mRNA level as well as surface protein expression of CXCR4 within 16 h. CXCR4 is also up-regulated by glucocorticoid, dexamethasone. Up-regulation of CXCR4 was also associated with the enhancement of HIV replication in human CD4$^+$T lymphocytes. The enhanced T-tropic HIV-1 infection to CD4+ T lymphocytes through up-regulation of CXCR4 by several immunomodulating agents, IL-4, and a glucocorticoid.CD4$^+$ T cells represent a functionally heterogeneous population and can be subdivided into different subsets based on their profile of cytokine production. Th1 cells produce interferon-γ (IFN-γ), interleukin-2 (IL-2), and lymphotoxin, whereas Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. The balance between Th1 and Th2 cell-mediated responses determines the type of immune reactions and influences the disease course. Th1 cells predominantly control cell-mediated immune responses and appear to be involved in chronic inflammatory conditions, whereas Th2 cells provide optimal help for humoral immune responses (including immunoglobulin E, IgE) and are dominant in the pathogenesis of allergic diseases. A switch from Th1 reported in HIV-infected individuals. HIV replicates preferentially in Th2 and Th0 cells rather than in Th1 cells. In association with these phenomena, a well-documented shift from macrophage-tropic (M-tropic) to T lymphocyte-tropic (T-tropic) HIV strains occurs during AIDS progression. The mechanism for these phenomena is presently poorly understood. Chemokines, a superfamily of small molecular weight leukocyte chemotactic polypeptides are key signals for recruiting specific types of leukocyte into inflammatory sites. Recent very unexpected findings have indicated that chemokines and their receptors play pivotal roles in HIV infection. CCR5 and CXCR4, at least nine other chemokine or orphan receptors, including CCR2b, CCR3, CCR8, GPR1, GPR15, STRL33, US28, V28, and ChemR23, can function as co-receptors to support the cellular entry of one or more HIV strains into various types of cells. Chemokines, such as macrophage inflammatory protein 1a (MIP-1a), MIP-1b, monocyte chemotactic protein 2 (MCP-2), eotaxin, and SDF-1, have been shown to block the entry of certain HIV strains into its target cells by the corresponding chemokine receptors Chemokine receptors are expressed differentially on leukocyte subsets and can be regulated by various stimulants, including cytokines and hormones. Expression of chemokine receptors is thought to determine the tropism of viral strains for different cell types, and also to influence susceptibility of the host to infection and rates of disease progression. Immunomodulating agents, such as IL-4 and dexamethasone, dramatically up-regulated the expression of CXCR4 in a short time and thus enhanced the infection and replication of HIV in human CD4$^+$ T lymphocytes (Wang et al., 1998).

Up-regulation of HIV coreceptor CXCR4 in human T lymphocytes is mediated in part by a cAMP-responsive element

DibutyrylcAMP (DcAMP), an analog of cAMP, has been shown to increase CXCR4 cell surface expression and HIV-1 infectivity, but the molecular mechanism(s) responsible is unknown. DcAMP treatment of purified human T-lymphocytes increased transcription of CXCR4 mRNA as well as cell surface and intracellular CXCR4 protein expression. DcAMP-mediated stimulation of human PBL increased T-trophic HIV-1 (X4) fusion and viral replication as measured by syncytia formation and p24 levels, respectively. To determine the region(s) of the CXCR4 promoter required for cAMP responsiveness, truncations and point mutations of the CXCR4 promoter fused to luciferase were constructed and transiently transfected into human PBL. Deletional analysis demonstrated that the -1098 to +93 region of the CXCR4 promoter construct could be eliminated; the residual (-93

to +59) promoter retained cAMP responsiveness. Site-directed mutagenesis of a putative cAMP-responsive element (CRE) in the 5' UTR (+41 to +49) significantly and specifically attenuated the ability of DcAMP to drive the minimal CXCR4 promoter. Electrophoretic mobility shift assays demonstrated the formation of a complex between the CREB transcription factor and the putative CXCR4 CRE site. CRE element within the CXCR4 promoter regulates CXCR4 transcription in response to changes in cAMP signaling. The cAMP-dependent up-regulation of CXCR4 mRNA results in increased CXCR4 intracellular and cell surface protein expression as well as increased HIV infectivity (Cristillo et al., 2002).

Glucocorticoid receptor type II complex is a target of the HIV-1 vpr gene product

The vpr gene of HIV type 1 (HIV-1) encodes a 15-kDa virion-associated protein that functions as a regulator of cellular processes that are linked to the HIV life cycle.
The interaction of a 41-kDa cytosolic Receptor interacting protein 1 (Rip-1) with Vpr in vitro displays a wide tissue distribution, including relevant targets of HIV infection. Similar to steroid hormone induced glucocorticoid receptor II (GR-II) mediated signal transduction, Vpr protein also induce the nuclear translocation of Rip-1. Importantly, Vpr and Rip-1 were coimmunoprecipitated with the human GR as part of an activated receptor complex. Mifepristone is a GR-II pathway inhibitor and an in vitro study has shown that, Vpr and GR-II actions were inhibited by mifepristone. The activity of the vpr gene products on glucocorticoid steroid pathway provide a biochemical mechanism for the cellular and viral activity of Vpr, as well as suggest that mifepristone (RU486), may influence HIV-1 replication (Michael et al., 2011; Refaeli et al., 1995; Suresh et al., 2012).

DISCUSSION

According to the Russian Schools of Physiology, all of the bodily changes following stress originate in the cerebral cortex. From there the stimuli reach the hypothalamic region through limbic system to produce changes in the autonomic nervous system and in the neuroendocrine apparatus. Autonomic nervous system is the component of the nervous system that regulates a variety of internal organs and functions. It is comprised of the sympathetic and parasympathetic branches. The sympathetic branch tends to trigger emergency responses; whereas the parasympathetic regulates repose activity. Their connections with the central nervous system are in the hypothalamus. Hypothalamus located beneath the cerebral hemispheres of the brain is responsible for regulating many endocrine functions, the autonomic nervous system, and immunity as well.

All organisms, from bacteria to humans, have evolved mechanisms to deal with significant changes in their external or internal environments, that is, stressors. First, the environmental and psychological stresses perceived and processed in the cerebral cortex of the forebrain. Then through cortical and limbic forebrain structure hypothalamus is stimulated. In mammals, this function carried out, in part, by the limbic–hypothalamo–pituitary–adrenal (LHPA) axis. This system integrates various inputs indicative of stress, converging on a final common path in the brain, the neurons of the medial parvocellular division of the paraventricular nucleus of the hypothalamus (mpPVN). These neurons synthesize CRH and arginine vasopressin (AVP), and project to the external layer of the median eminence. Activation by stressors leads to release of the peptides into the portal blood, carrying these secretagogues to the anterior pituitary. In turn, CRH and AVP receptors on the anterior pituitary corticotropes are responsible for the release into the total circulation of ACTH and related peptides derived from the common precursor proopiomelanocortin
(POMC) which are involved in pain reduction. These opioids can then inhibit CRH secretions. ACTH activates the biosynthesis and release of glucocorticoid, such as corticosterone in rodents, and cortisol in primates by the cells of the adrenal cortex. These steroids possess extremely broad actions mediated by specialized receptors affecting expression and regulation of genes throughout the body, and readying the organism for the changes in energy and metabolism required for coping.

Immune system can also influence the nervous system and the endocrine system. After an infection by a pathogen the macrophages and APCs secretes IL-1, IL-6 and IFN-γ, which act as communication molecules. These cytokines stimulates the hypothalamus and promote the secretion of CRH. The CRH then influence the production of glucocorticoid, which show immune regulatory activities.

Mental stress has some negative effects on both HIV- people and HIV+ patients. When the HIV^- people are in stress, they are more vulnerable to infected by the HIV. Stress active sympathetic nerves system through the CNS. When SNS become active then catecholamine concentration increases in the blood. CXCR4 and CCR-5 are the receptor of catecholamine and glucocorticoid. When these hormones are bind with CXCR4/CCR-5 receptors, then they become more active for HIV. For the entering of HIV in to the cell, HIV has to bind both CD4 and CXCR4/CCR-5 receptors. When catecholamine and glucocorticoid bind to to CXCR4/CCR-5 then cAMP/PKA signaling pathway activated. For this reason, that cell expresses more this CXCR4/CCR-5 receptor. Catecholamine also can influence TH_1 and then it cannot secret IFN-γ. As a result, NK cell shows poor virological response to HIV.

Stress also increases Catecholamine and Glucocorticoid in the HIV+ patients. Both hormones can

bind to the HIV infected cells and arrest them in the G_2 phase, which is favorable for viral gene expression. As a result, more and more HIV is produced form this cells, that can attack other immune responsive cells. Consequently, the number of $CD4^+$ lymphocyte decline rapidly. So progression of AIDS and other opportunistic disease are increase. In the opposite page the effect of stress on both HIV^- people and HIV^+ patient is shows diagrammatically (Figure 3).

CONCLUSION

HIV risk population and people living with HIV are easily susceptible to any disease and show the symptoms of AIDS. Stressful life events have been found to affect HPA axis and thereby triggers the endocrine system and immune system. The vulnerability condition pre-existing to depression among adolescents, often linked to risk behaviors included unprotected sex and substance abuse, has been found associated with a HPA axis

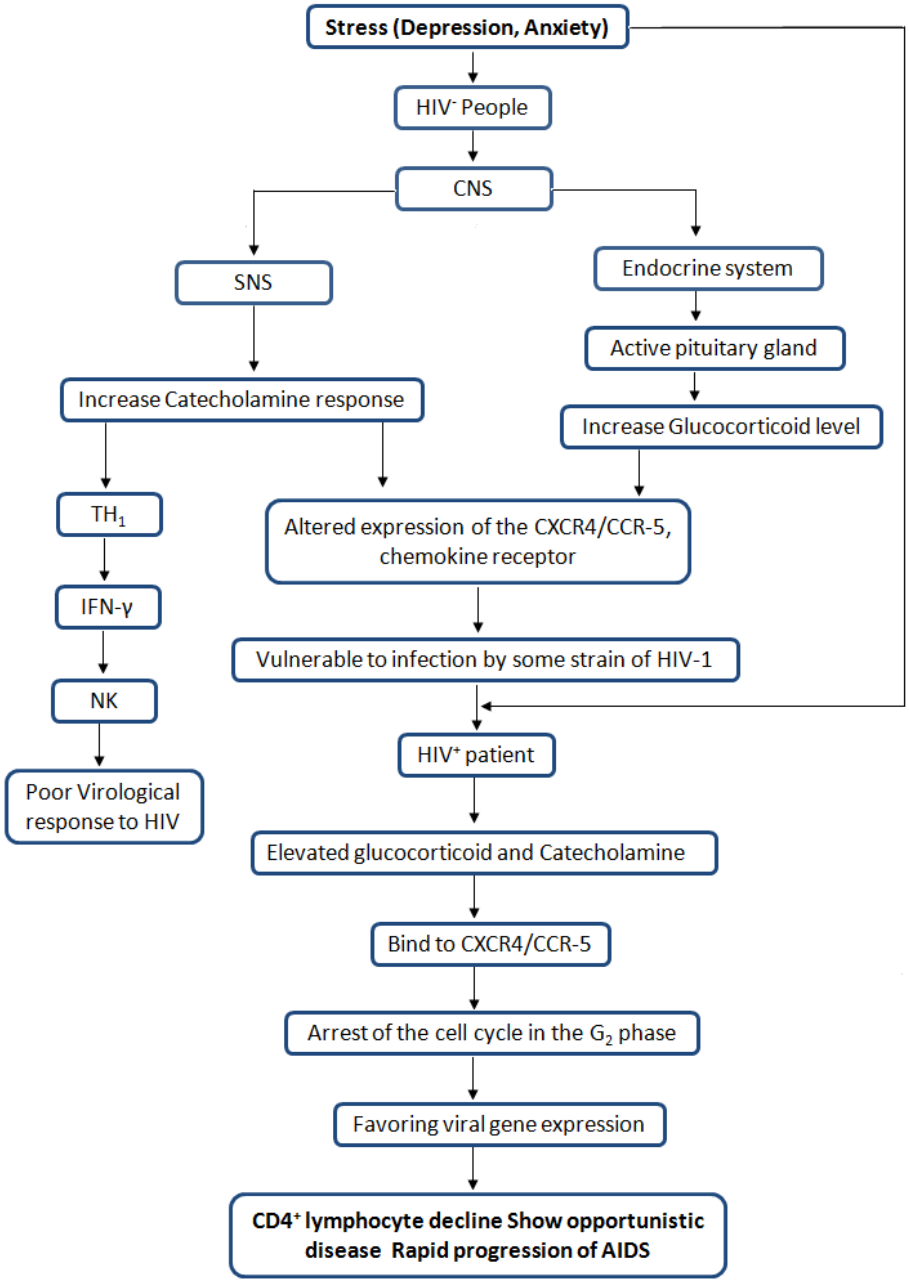

Figure 3: The effect of stress both on HIV^- people and on HIV^+ patient.

hyper-activation when the system is quiet and lack of response to stress when necessary. The intent of this review has been not only to summarize salient facts pertaining to the central role of CPS in the Susceptibility of HIV Infection and Progression of AIDS, but also to provide a conceptual framework for future studies that will infuse physiology, endocrinology, immunology and neurobiology into the better mechanistic understanding of complex stress-related diseases (eg. AIDS, stroke, diabetes mellitus, cancer, multiple sclerosis, autoimmunity) and their solution by every means available: biological, behavioral and sociological.

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