Role of Estradiol and Progesterone in HIV Susceptibility and Disease Progression

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Abstract: The Acquired Immunodeficiency Syndrome (AIDS) constitutes the main infectious cause of death in adults worldwide. Epidemiological data suggest the existence of differences in viral load and $CD4^+$ T lymphocytes cell counts related to gender. Women have more favorable clinical and viro-immunological patterns than men in early infection, although once established the infection these patterns are reversed.

Increasing evidence shows that estradiol (E) and progesterone (P) participate in the regulation of several infections, such as that produced by human immunodeficiency virus (HIV). Several functions of these hormones involve the interaction with their intracellular receptors (ER and PR, respectively). During infection, E and P not only exert their action upon the immune system, but also directly act on the virus. Effects of E and P depend on their concentration or the phase of HIV infection but in general terms, they could exert a protective role against HIV infection.

Keywords: AIDS, estradiol, HIV, progesterone.

INTRODUCTION

Estradiol (E) and progesterone (P) play a fundamental role in different reproductive and non reproductive processes, such as ovulation, sexual behavior, pregnancy, neuroprotection, learning and memory, as well as immune response [1]. E and P functions are mainly exerted via their intracellular receptors, which modify gene expression pattern in the cell, although these hormones can also act by a non genomic pathway that implicates the modification of transduction signal pathways [2, 3].

E and P have a role in the regulation of immune response. E has anti-inflammatory effects. In T lymphocytes cells, macrophages and dendritic cells, this hormone inhibits the production of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6. E also induces the production of IL-4, IL-10 and transforming growth factor beta (TGF-β). During the proliferative phase of the menstrual cycle when the pick of E occurs, TNF-α and interferon-gamma (IFN-γ) levels are reduced [4-7].

In the case of innate immune response, P inhibits the activation of nuclear factor kappa B (NF-κB) and increases the expression of the suppressor of cytokine signaling (SOCS1) protein [8]. P treatment of lipopolysaccharide (LPS)-activated, mature bone marrow-derived dendritic cells (BMDCs) suppresses production of the pro-inflammatory response-promoting cytokines TNF-α and IL-1β in a dose-dependent manner but it does not affect the production of the pro-inflammatory response-inhibiting cytokine IL-10. The immunoregulatory effect of P by the suppression of pro-inflammatory response-promoting cytokine production is mediated via its nuclear receptor (PR) [9]. Hormonal environment could influence HIV-1 disease progression by two ways: 1) altering the host immune system or 2) through direct effects on the virus [10-13]. In this paper we review the role of E and P in HIV infection.

MECHANISM OF ACTION OF E AND P

E and P are mainly synthesized in ovary, adrenal gland, placenta and the central nervous system (CNS) [14]. Once released, P passes to the blood stream where it circulates either unbound or bound to plasmatic proteins such as albumin or globulin [15]. Two main mechanisms have been described: the classical and the non-classical one [16]. In the non-classical mechanism, these hormones exert their action on the plasmatic membrane modifying ion conductance and inducing second messengers' production including cyclic adenosine monophosphate (cAMP) and the activation of kinases [17].

Many actions of E and P are mediated by the classical mechanism of action that involves their specific nuclear receptors, ER and PR, respectively, which are members of the nuclear receptor superfamily of ligand-dependent transcription factors [18]. Two main PR isoforms have been reported in humans: a full-length form (PR-B, 114 kDa) and an N-terminal truncated form (PR-A, 94 kDa), which are encoded by the same gene, but are regulated by distinct promoters [19]. In general, PR-B is a much stronger transcriptional activator than PR-A, due to an additional activation function (AF) domain in the amino terminus of PR-B [20]. Intracellular ER exists as two subtypes, ER-α (66 kDa) and ER-β (55 kDa), which are transcribed from different genes [21]. Cell culture experiments indicate that ER-α is a stronger transcriptional activator than ER-β due to

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differences in the AF-1 region of the amino terminus [22]. It has been shown that PR and ER isoforms are functionally distinct in terms of their ability to activate target genes in the same cell and regulate different physiological and pathological processes.

According to the classical model of ER and PR action, in the absence of ligand, nuclear receptors are associated with heat shock proteins (HSP70 and HSP90). When the hormone interacts with its specific intracellular receptor, it induces conformational changes that allow the dissociation with HSP; promoting dimerization, phosphorylation and high affinity binding to specific DNA sequences named hormone responsive elements (HRE) located within the regulatory regions of target genes. ER and PR modulate target gene transcription by recruiting components of the basal transcriptional machinery and by interacting with coregulatory proteins. Nuclear receptor coregulators (coactivators or corepressors) are required by the receptors for efficient transcriptional regulation [17]. ER and PR can also modulate the expression of genes without directly binding to DNA, by tethering to other transcription factors, including specificity protein 1 (Sp1), activator protein 1 (AP1) and NF-κB, that interact with gene promoters that lack canonical HRE sequences [23, 24].

Besides the above mentioned intracellular receptors different P receptors have been identified in the plasma membrane (mPR). Through the interaction with these mPRs, P induces rapid non genomic responses in target cells. The mPRs are localized in different cells such as human sperm, myometrial cells, granulose cells, leukocytes and T lymphocytes [25]. The mPR family of proteins has seven integral transmembrane domains and mediates signaling via G-protein coupled pathways [26]. E can also associate with G protein-coupled estrogen receptor-1 (GPR30), a seven transmembrane receptor, and activate the trimeric G protein. The data obtained using GPR30 KO mice and the G-1, a GPR30 agonist, indicate that GPR30 plays an important role in the cardiovascular and immunological systems [27, 28].

ROLE OF E AND P IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

AIDS is the main infectious cause of death in adults across the world, and it is one of the major health problems worldwide. Epidemiological data show that 33.4 million people live with HIV worldwide in 2008 [29] (UNAIDS, 2009).

Epidemiological data suggest differences in levels of viral load and $CD4^+$ T cells related to gender. It has been observed that women have a better prognosis in early stages of infection compared with men, but once the infection is established this behavior is reversed, and women exhibit a greater progression to AIDS than men [30, 31]. There are viral factors such as the strain, viral load and long terminal repeated (LTR) promoter or LTR activation, as well as host factors such as vaginal microenvironment, levels of cytokines and presence of coreceptors (CCR5 or CXCR4) that determine the susceptibility and progression of HIV infection [32-35].

Sex hormone variations during menstrual cycle have effects on the properties and the number of immune cells, cytokines, chemokines secretion, antibodies production and antigen presentation [36], which can influence susceptibility and progression of HIV infection.

Results obtained in our laboratory showed that E and P levels are within normal values during menstrual cycle in healthy (SN) and HIV seropositives (TP) women during the early proliferative phase (days 2-3 of menstrual cycle) and although E levels showed no significant differences between SN and TP women, P levels were higher in SN. Previous studies performed in HIV infected women have shown that the length of the menstrual cycle and the duration of the menstrual bled were not different from non-infected HIV patients, suggesting that most HIV-infected women have normal ovulatory and menstrual cycles and have no significant alterations in the hypothalamus-pituitary-ovary axis [37, 38]. In agreement with our data, Cu-Uvin *et al.*, reported normal levels of E and P during the menstrual cycle in both SN and TP women [39].

Postmenopausal women (that have very low E and P levels) have a 4-8 fold increase in their risk of being infected with HIV compared with premenopausal women [40, 41]. Besides, women exposed to oral contraceptive pills or depo-medroxyprogesterone acetate (DMPA) had an increased progression disease than women using other contraceptive method [42].

ROLE OF E IN HIV INFECTION

Sexual intercourse is the main HIV route of transmission. E has anti-inflammatory and proliferative effects in vaginal stratified epithelium which can modulate the susceptibility and progress of HIV infection. E induces thickening of the

Table 1. Effects of P on the Content of CCR5 and CXCR4 in PBMC from SN and TP

	CCR5		CXCR4	
	SN	TP	SN	TP
V	100 %	100 %	100 %	100 %
P 10 nM	- 24 ± 0.9$^+$	- 31 ± 4.5*$^+$	+ 78 ± 11.1$^+$	+ 26 ± 2.8$^+$*
P 100 nM	- 28 ± 3.6$^+$	- 41 ± 5.8*$^+$	+ 119 ± 12.1$^+$	+ 64 ± 1.8$^+$*
RU 486 (1 μM)	- 4.5 ± 13.7	- 10 ± 15.5	+ 25 ± 4.0$^+$	+ 24 ± 1.8$^+$
P + RU	- 32 ± 9.1$^+$	- 42 ± 10.6$^+$	+ 84 ± 10.1$^+$	+ 66 ± 3.77$^+$*

SN: healthy women; TP: HIV seropositives. The results are expresed as percentage average ± S.E.M. +$p<0.05$ vs V; *$p<0.05$ vs SN, Mann-Whitney U test n = 4.

vaginal stratified epithelium in women and female macaques [43- 48]. The increase in thickness might block the access of the virus to target cells such as Langerhans cells (LCs), $CD4^+$ T cells, and macrophages. At local level, it has been observed an inverse correlation between vaginal epithelium thickness and rate of infection with HIV [43, 45, 49]. E also produces a change in vaginal pH that is not favorable for HIV infection. In ovariectomized *rhesus macaques*, the pretreatment with E and the subsequent no traumatic vaginal inoculation with simian immunodeficiency virus (SIV) results in a protection against infection with SIV due to increased epithelial thickness [31].

E can regulate HIV expression through the long terminal repeated (LTR) promoter or by the regulation of accessories HIV protein, such as Tat [50, 51]. The stimulation of cultured human vascular endothelial cells with HIV Tat protein specifically activates transcription factor NF-κB and leads to the up-regulation of inflammatory mediators which is reverted by E pretreatment [51] Heron *et al.*, found that in human fetal astrocyte cells (SVGA), E attenuated Tat-induced HIV LTR promoter activation [52]. In addition to viral Tat proteins, transcriptional regulation of HIV-1 gene expression is controlled by cooperative and cell-specific interactions between Tat and several host-cell transcription factors, including AP-1, Sp1, Ets-1 and NF-κB. These data suggest that E can modulate the transcriptional activity of HIV-1 [53-57].

ROLE OF P IN HIV INFECTION

The data about the effects of P on the HIV infection are controversial. These discrepancies could be due to different doses of hormone used, analyzed tissues and immunological conditions of studied subjects. DMPA increases 2-3 fold the rate of HIV-1 infection in women, and 7.7 fold the vaginal transmission of SIV, by a marked thinning of vaginal epithelium [31]. On other hand, P diminishes the infectivity of HIV in cultures of peripheral blood mononuclear cells (PBMC) [58].

The entrance of HIV to the cell requires the interaction of the viral protein gp120 with the host CD4 receptor and at least the participation of one coreceptor. Several factors of the host have been involved in the establishment and development of HIV infection [59, 60] such as the presence of HIV coreceptors [33, 34].

Diverse HIV coreceptors have been characterized, being the most important CC chemokine receptor 5 (CCR5, 50 kDa) and CXC chemokine receptor 4 (CXCR4, 40.5 kDa).

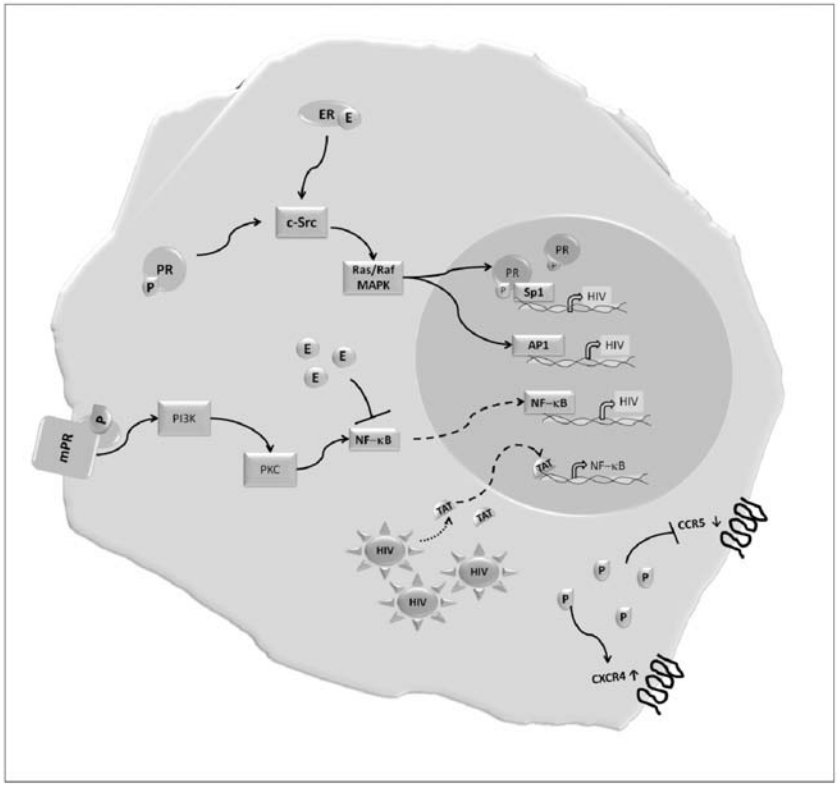

Fig. (1). Integration of endocrine and viral signaling in HIV transcription. Classically, ligand-activated ER and PR dimers contact with other transcription factors that interact in the promoter region of virus LTR to initiate transcription. Hormones also mediate non-classical gene transcription through extranuclear rapid activation of the c-Src, and MAPK cascade to stimulate phosphorylation of hormone receptors. ER or PR tether to Sp1 and AP1 to regulate HIV transcription. Additionally, rapid MAPK activation may regulate HIV transcription independently of ER or PR transcriptional activity. Other mechanism implicates membrane receptors that activates PI3K cascade to induce HIV transcription. Besides, HIV can regulate its own transcription through viral protein TAT. P can down-regulate or up-regulate the expression of CCR5 and CXCR4 coreceptors, respectively; E can also inhibit NF-κB.

Both coreceptors are located in the host cell and are used by the virus to carry out the fusion of viral envelope with host cell membrane [61]. CCR5 is mainly used in early phase of infection by HIV strains that infect macrophages (M-HIV tropics or R5), while CXCR4 interacts with viruses that infect T lymphocytes (T-HIV tropics or R4) in the advanced stage of infection. It is noteworthy that a third type of virus can interact with both coreceptors (HIV R5X4) [62, 63].

There is evidence that indicates a regulation of CCR5 and CXCR4 by sex hormones both in reproductive tissue and peripheral blood from healthy subjects [12, 58, 64-66]. The data about regulation of CCR5 and CXCR4 by sex hormones and oral contraceptives are contradictory and depend on the tissue, immunological activation and hormone concentration.

In PBMC from healthy women, P (50 ng/ml) increased the content of CXCR4 mRNA, in addition, it has been observed that during the secretory phase of the menstrual cycle, when levels of P are high (1.6-23 ng/ml), the number of CXCR4 positive cells is greater than in the proliferative phase of the menstrual cycle when P levels are lower (0.15-1.4 ng/ml), while the number of CCR5 positive cells is higher during the proliferative phase than in secretory phase [65, 66].

In agreement with previous reports, we observed that P (10 and 100 nM) has a negative effect on CCR5 expression in PBMC from SN and TP women, in contrast to data reported by Vassiliadou *et al.*, in healthy women but with higher doses of P (1 and 10 μM) [58]. Besides, we observed that P has a positive effect in the regulation of CXCR4 expression in SN and TP women at 10 and 100 nM.

It is noteworthy that P can have a dual effect depending on its dose. Interestingly, the decrease of CCR5 expression was higher in TP compared with SN, both in 10 nM and 100 nM, while the increase of CXCR4 expression was higher in SN than in TP (Table **1**).

The effect of P in the regulation of CCR5 and CXCR4 is not PR-mediated since RU 486, a PR antagonist, did not block the effect of P. We cannot discard that P effects could be mediated through its mPRs which have been detected in PBMC and T lymphocytes [67].

We suggest that during early stages of infection when the viral tropism is mainly directed to CCR5, P should play a protective role against HIV infection, while in advanced stages of infection, when the switch to CXCR4 tropism occurs, P should be a factor that increases the disease progression. This could be one of the explanations for differences in susceptibility and disease progression between women and men.

CONCLUSION

E and P regulate many functions related to HIV infection in both host and virus. Interestingly, these hormones are able to directly act upon pathogens, playing an important role in susceptibility and progression of HIV infectious disease, by modifying the urogenital tract stratified epithelium or through the regulation of viral transcription, as well as the regulation of HIV coreceptors (Fig. **1**). The knowledge of the effects and mechanisms of action of E and P may be helpful to have a better treatment of HIV disease.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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