Role of Progesterone in HIV and Parasitic Infections

Edith Cabrera-Muñoz[1], Galileo Escobedo[2], Carolina Guzmán[2] and Ignacio Camacho-Arroyo*[,1]

[1]*Facultad de Química, Departamento de Biología, Universidad Nacional Autónoma de México, México;* [2]*Unidad de Medicina Experimental, Hospital General de México, México*

Abstract: Progesterone (P4) plays different physiological roles, including reproductive and non-reproductive actions. Most of P4 effects are mediated by its interaction with its nuclear receptor (PR). Among the non-reproductive functions of P4, the regulation of the immune response, particularly during pregnancy, is remarkably important. P4 is able to modulate the immune response during normal physiological processes, as well as in infectious diseases, including parasitic and viral infections. During parasitic infections, P4 not only exerts its action upon the immune system, but also directly acts on the parasite, as it has been shown for helminthes and protozoans. Variations of P4 levels during the menstrual cycle could be involved in changes in susceptibility to infection, such as that caused by the human immunodeficiency virus (HIV). P4 could be involved in the acquisition and development of HIV disease, regulating infection susceptibility. Further investigations could open new application fields, where the differential effects of P4 upon the immune response represent the keystone of a successful hormonal therapy as well as the design of new drugs with more specific actions on parasites and virus.

Keywords: Progesterone, Progesterone receptor, HIV, parasitic infection, cysticercosis.

INTRODUCTION

Progesterone (P4) is a sex steroid hormone that plays different physiological roles, being well documented its effects on ovulation, establishment and maintenance of pregnancy and sexual behavior [1-2]. However, this hormone also participates in non-reproductive processes including neuronal excitability, neuroprotection, learning and memory, sleep, and immune response [3]. P4 functions are mainly exerted via its nuclear receptors, the progesterone receptor (PR) which modifies gene expression pattern in the cell [1, 2, 4].

In the case of innate immune response, P4 inhibits the activation of the nuclear factor kappa B (NFκB) and increases the expression of the suppressor of cytokine signaling (SOCS1) protein in macrophages [5].

P4 has been involved in different immunoregulatory functions that allow successful pregnancy. During the first trimester, in trophoblasts [6] and mesenchymal stem cells (MSCs) [7], P4 up-regulates the expression of several molecules from the major histocompatibility complex class I, which are involved in the maintenance of the immune balance between the mother and the fetus. Other molecules involved in this immune balance such as Human Leukocyte Antigen (HLA)-G and HLA-E in JEG-3 are also regulated by P4 [7].

In hybridoma B cells, P4 diminishes the interleukin (IL)-6 induced gp130 expression in a dose-dependent manner, whereas the expression of janus kinase (JAK) 1 is not

significantly affected. At 10^{-6}M concentration, P4 inhibits the phosphorylation of gp130 and diminishes the IL-6-induced Signal transducer activator of transcription (STAT)-3 phosphorylation and translocation to the nucleus. Maximal expression of the progesterone-induced blocking factor (PIBF) is observed in hybridoma cells with 10^{-10}M P4 [8]. The treatment of lipopolysaccharide (LPS)-activated mature bone marrow-derived dendritic cells (BMDCs) with P4 suppresses production of the pro-inflammatory response-promoting cytokines tumor necrosis factor-alpha (TNF-α) and IL-1β in a dose-dependent manner but it does not affect production of the pro-inflammatory response-inhibiting cytokine IL-10. P4 also down-regulates the expression of the co-stimulatory molecule CD80 and MHC class II molecule RT1B. In addition, P4 promotes maturation of dendritic cells [9], and inhibits dendritic cell-stimulated proliferation of T cells. The immunoregulatory effects of P4 are primarily mediated via its interaction with P4 receptor (PR) and the suppression of pro-inflammatory response-promoting cytokine production by P4 is prevented using the PR antagonist RU486 [10, 11].

In this paper we evaluated the role of P4 during several parasitic diseases and viral infections, particularly HIV infection.

MECHANISM OF ACTION OF P4

P4 is mainly synthesized in ovary, adrenal gland, placenta and the central nervous system (CNS) [12]. Once released, P4 passes to the blood stream where it circulates either unbound or bound to plasmatic proteins such as albumin or globulin [13].

P4 diverse physiological functions are related to its multiple mechanisms of action. Two main mechanisms have been described: the classical and the non-classical one [14].

*Address correspondence to this author at the Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, Coyoacán 04510, México D.F. México, USA; Tel: 525556223473; Fax: 525556223369; E-mail: camachoarroyo@gmail.com

In the non-classical mechanism, P4 exerts its actions interacting with PR located in the plasma membrane and in cytoplasm, modifying ion conductance and inducing second messengers production including cAMP and the activation of kinases. The classical mechanism of action involves the interaction of P4 with PR. This interaction is followed by a conformational change in the receptor that induces the dissociation of heat shock proteins, followed by phosphorylation and dimerization of the receptor. The resulting structure possesses high affinity for specific sequences in the DNA, known as P4 response elements (PRE) which are present in the promoter region of P4 targeted genes. Once bound to PRE, PR is able to recruit coactivator and corepresor proteins [4, 15] regulating gene transcription (Fig. **1**) [16].

Progesterone Receptor Isoforms

PR exists as two main isoforms: a long one PR-B (112-120 kDa) and a short one PR-A (80-94 kDa). Both PR isoforms are encoded by the same gene, but they are transcribed from two different promoters, one distal from −711 to +31 corresponding to PR-B and one proximal from +464 to +737 for PR-A. In general, PR-B is a stronger activator compared to PR-A [17]. It has been shown that PR isoforms are functionally distinct in their capacities to activate transcription of target genes and in this way regulate different physiological processes [18].

Besides nuclear PR, different P4 receptors have been identified in the plasma membrane (mPR). P4 could induce rapid nongenomic responses in target cells through the interaction with these mPRs which have been located in different cells, such as human sperm [19]. mPRs belong to the seven transmembrane domains protein family and mediates signaling via G-protein coupled pathways [20].

PROGESTERONE EFFECTS DURING PARASITE INFECTIONS

Recent experimental evidence suggests that sex steroids play a key role during parasite infections, mainly through two different mechanisms: a) modulation of the host immunoendocrine network (IEN) [21-23], and b) direct regulation of parasite reproduction and differentiation [24, 25].

The IEN is formed by the dynamic interaction between the immune and the endocrine systems that share ligands and receptors [21, 26]. A pathogen organism produces a disturbance in the IEN balance, with major consequences to the host fitness and homeostasis. Among the elements of the IEN, sex steroid hormones have been described as critical modulators during parasite infections [27]. Particularly, P4 has received increased attention due to its multiple roles in the modulation of the IEN, in response to a pathogen [28-32].

In physiological conditions, the highest levels of P4 are detected during pregnancy. This particular endocrine condition has serious repercussions on the immune system, and concomitantly on the resistance or susceptibility to parasite invasions [33, 34]. In fact, pregnant women exhibit a significant decrease in the CD4/CD8 cell ratio [29], with a parallel increase in the susceptibility to *Toxoplasma gondii* infection [30]. This immune phenotype favors *Toxoplama gondii*,
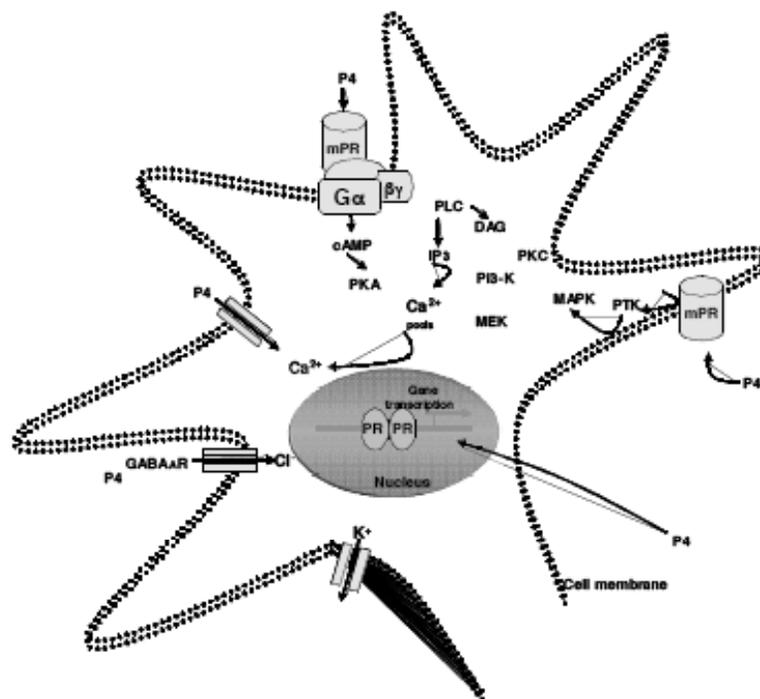

Fig. (1). Mechanisms of P4 action. P4 exerts its effects through genomic and non-genomic mechanisms. The former are mediated by nuclear PR and produce changes in gene expression whereas the latter are mediated through a variety of pathways including the interaction of P4 with: membrane receptors, ionic channels, modulatory sites in neurotransmitters receptors, and growth factors and neurotransmitters receptors coupled to G proteins. These interactions produce changes in ionic conductance, second messenger cascade, cAPM production, phosphoinositide turnover and protein kinase C and MAP kinases activation [16].

probably due to the up-regulation of PIBF, which inhibits CD8 and NK cell activity [29, 31, 35], and by the down-regulation of IL-12 from infected macrophages produced by P4 [30]. Furthermore, human pregnancy has also been associated to an enhanced helmintho-toxicity against *Trichinella spiralis* larvae, depending in part on P4 and its influence on circulating IgG, IgE and IgA antibodies [32].

On the other hand, when wild rodent *Calomys callosus* females were ovarectomized, an increase in the parasitemia by the protozoan *Trypanosoma cruzi* was observed. Interestingly, P4 administration diminished parasite load at the same level than in non-infected groups, suggesting that P4 is a restrictive factor to *T. cruzi* establishment and reproduction in rodents [36].

This protective effect of P4 is also observed during *Schistosoma haematobium* infection in the golden hamster *Mesocricetus aureatus*. The administration of the contraceptive medroxiprogesterone acetate (an analogue molecule of P4) to infected golden hamsters decreases the number of recovered worms and egg load, when this progestin is administered with the antischistosomal atorvastin (an HMG-CoA reductase inhibitor) [37]. In addition, P4 administration to gonadectomized mice of both sexes prevents against murine experimental cysticercosis with higher efficiency than any other vaccine tested in this parasitism model [38].

Moreover, P4 induced an increase in PR-A expression in lymphocytes from spleen, with no effects on the expression of IL-4 and IL-10. In contrast, ewes infected with the nematode *Haemonchus contortus*, showed higher number of worms when they were treated with P4 [39]. Thus, protective or permissive effects of P4 depend on the parasite and the host, among other factors [40].

A strong board of evidence suggests that P4 affects the outcome of an infection for having direct effects upon the parasite, modulating several aspects such as pathogen reproduction, differentiation and establishment [25, 40, 41]. Data from our laboratory have demonstrated that P4 increases asexual reproduction of *Taenia crassiceps* by inducing parasite's budding [41]. Apparently, *T. crassiceps* presents a PR that up-regulates the expression of parasitic *c-fos* and *c-jun*, which in turns induces proliferation [41, 42]. Moreover, P4 also augments the *T. crassiceps* infectivity, when parasites are exposed to this hormone before infection in mice of both sexes [41].

In contrast, when *Trichinella spiralis* newborn larvae were *in vitro* exposed to increasing physiologic doses of P4, an induction of parasite mortality was observed [28]. This effect was abrogated by RU486 [3]. These results suggest that P4 can directly affect helminth parasites, having differential consequences for different parasites, such is the case of the cestode *T. crassiceps* and the nematode *T. spiralis*.

As we have described, the immune system is clearly affected by P4, exhibiting major consequences for parasite infection outcome. Concomitantly, P4 also directly acts on parasite reproduction and growth. The consideration of this knowledge will bring several benefits to our concept of the dynamic host-parasite relationship, which include a more specific drug design that exclusively affects the parasite with minimal secondary effects on the host, as well as a better comprehension of the sexual dimorphism of the immune response during health and pathogenic processes.

ROLE OF PROGESTERONE IN THE SYNDROME OF HUMAN IMMUNODEFICIENCY (AIDS)

Acquired immunodeficiency syndrome (AIDS) is the main infectious risk of death in adults across the world. The human immunodeficiency virus (HIV) represents one of the major infectious agents worldwide. Epidemiological data show that worldwide in 2007, 33 million people live with HIV (UNAIDS, 2008).

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 co-receptor. Several factors of the host have been involved in the establishment and development of HIV infection [43, 44] such as the presence of HIV co-receptors [45, 46].

Diverse HIV co-receptors have been characterized, being the most important CCR5 (40 KDa) and CXCR4 (40.5 kDa). Both co-receptors are located in the host cell and are used by the virus to carry out the fusion of viral envelope and host cell membrane [47]. CCR5 is mainly used in the early phase of infection by HIV strains that infect macrophages (M HIV-tropics or R5), while CXCR4 interacts with a strain of the virus that infect T lymphocytes (T-HIV tropics or X4) mainly to the third advanced stage of infection. It is noteworthy that a third type of virus can interact with both co-receptors (HIV R5X4) [48, 49].

According to the time of infection, progression has reached the following classification: rapid progression in which the patient develops AIDS 3-5 years after acquiring the virus; typical progression (TP) with development of AIDS in an estimated time of 7 years and slow progression (SP) if patients present symptoms of AIDS approximately 10-15 years after HIV first infection.

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, exhibiting a greater progression to AIDS in women than in men [50-52].

Intrinsic factors of the virus and host factors that regulate the pathogenesis of HIV, have been described [43, 44], for example the presence of CCR5 and CXCR4 co-receptors plays an important role in the establishment and development of the infection [45, 46, 48].

The levels of sex hormones have been associated with viral and immunological factors of HIV. There is scarce data on hormone levels among women infected with HIV.

Results obtained in our laboratory showed that estradiol (E2) and P4 levels are within normal menstrual cycle values in seronegative (SN) women and TP during the early proliferative phase (days 2-3 of menstrual cycle). Interestingly, P4 concentration was 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 hypo-

thalamus-pituitary-ovary axis [53]. In agreement with our data, Cu-Uvin and cols. reported normal levels of E2 and P4 during the menstrual cycle in both SN and HIV seropositive women [54].

EFFECT OF P4 ON THE CONTENT OF CCR5 AND CXCR4.

There is evidence that indicates a regulation of CCR5 and CXR4 by sex hormones both in reproductive tissue and peripheral blood from healthy subjects [55-58]. 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 peripheral blood mononuclear cells (PBMCs) from healthy women, P4 (50 ng/ml) increases the content of CXCR4 mRNA. In addition, *in vivo*, it has been observed that during the secretory phase of the menstrual cycle, when P4 levels are high (1.6-23 ng/ml), the number of CXCR4 positive cells is higher than in the proliferative phase of the menstrual cycle when P4 levels are lower (0.15-1.4 ng/ml). The number of CCR5 positive cells is higher during the proliferative phase and lower during the secretory phase [56, 59].

In agreement with previous reports, we have found that P4 (10 and 100 nM) exerts a negative effect on CCR5 content in PBMCs from SN and TP women, while P4 has a positive regulatory effect on CXCR4 content in PBMC from SN women and TP at doses of 3.13 ng/ml (10 nM) and 31.3 ng/ml (100 nM), contrary to the report of Vassiliadou and cols. in PBMC from healthy women treated with higher doses of P4 (314.4 ng/ml-3.14 g/ml).

It is noteworthy that P4 exerts a dual effect depending on the dose. Thus, the decrease in CCR5 content was higher in TP compared with SN, both in 10 nM (and 100 nM, while the increase in CXCR4 content was higher in SN than in TP at 10 nM and 100 nM.

The mechanism involved in P4 effects on CCR5 and CXCR4 content could implicate the interaction of P4 with PR [45]. In mast cells it has been observed that the differential expression of PR isoforms modifies the migration of these cells in response to CXCL12, a specific ligand of CXCR4, after treatment with P4 (1 nM-1 μM) [60]. Furthermore, the presence of PR is correlated with nuclear localization of CXCR4. In breast cancer cells without PR, there was an increase in nuclear localization of CXCR4 [61], indicating that the PR is important for CXCR4 function.

Table 1.   Progesterone Effects in the Regulation of the Immune Response During Viral and Parasite Infections. P4 regulates Both Innate and Acquired Immune Response, Affecting Specific Target Cells, Through Binding to PR-A and PR-B. Participation of Membrane Receptors in P4-Effects has also been Reported. P4 also Directly Affects Protozoan or Helminth Parasites, Through Specific Modulation of Pathogen Reproduction, Differentiation and Establishment Without Mediation of the Host Immune System. ↑=Increasing, ↓=Decreasing

Target cell/tissue	Effect	Proposed mechanism	Reference
Mesenchimal stem cells	Immunomodulation	Up-regulation of HLA-G	6
Trophoblast	Immunomodulation	Up-regulation of HLA-G	5
JEG=3 cells	Immunomodulation	Up-regulation of HLA-G	5
JEG=3 cells	Immunomodulation	Up-regulation of HLA-E	6
Hybridoma B cells	↓ gp130 expression induced by IL-6	Down regulation of gp130	7
Mature bone marrow-derived dendritic cells	↓ Pro-inflammatory cytokines	Diminishes TNF-α and IL-1β and CD80 and MHC class II molecule RT1B	8
Dendritic cells	↑ Denditric cell maturation	Promotes maturation	8
T cells	↓ Dendritic cell presentation and maturation	Lower proliferation of stimulated DC	9
CD4/CD8	↓ Number of cells	Unknown	27
NK cell	↓ Activity	Increases P4-induced PIBF expression	33
Plasmatic cell	↑ IgG, IgE, IgA plasma levels	Unknown	30
Spleenocytes	↑ IL-4, IL-10	Increasing in the PR-A of spleenocytes	37
PBMCs *in vitro*	Immunomodulation	Down-regulation of CCR5 and CXCR4	56
PBMCs	Immunomodulation	Up-regulation of CXCR4	56
Mastocytes	Immunomodulation	Up-regulation of CXCR4	58
T. crassiceps	↑ Reproduction, Infectivity	Increasing in *c-fos* and *c-jun* transcription factors	40
T. spiralis	↑ Mortality	Mortality induction by expression of a progesterone receptor-like in the parasite	26

With these data we suggest that P4 is involved in the acquisition and development of HIV disease. During early stages of infection when the viral tropism is mainly directed to CCR5, P4 may be a protective factor, while in advanced stages of infection, when there is a switch to CXCR4 tropism, P4 may be a permissive factor that promotes disease progression. This could be one of the explanations for differences in susceptibility and AIDS progression between women and men.

CONCLUSIONS AND PERSPECTIVES

P4 regulates many functions both in vertebrates and invertebrates, from the well known reproductive functions to the recently described immunomodulation in infectious diseases (Table **1**). Most P4 effects are mediated by its interaction with nuclear PR, which are expressed in immune cells and tissues. Interestingly, P4 effects are not restricted to the host; since this hormone is able to directly act upon pathogens, playing an important role in regulation, susceptibility and progression of infectious diseases. The knowledge of the effects and mechanisms of action of P4 on various diseases may be helpful to determine the treatment of several infectious diseases.

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