Endocrine Immune Interactions in the Host-Parasite Relationship: Steroid Hormones as Immune Regulators in Parasite Infections

Aguilar-Díaz H[1], Nava-Castro KE[2], Cerbón-Cervantes MA[1], Meneses-Ruiz DM[3], Ponce-Regalado MD[4] and Morales-Montor J[3*]

[1]Facultad de Química, Departamento de Biología, Universidad Nacional Autónoma de México, México
[2]Departamento de Ciencias Ambientales, Centro de Ciencias de la Atmósfera, Universidad Nacional Autónoma de México, México
[3]Departamento de Inmunología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, México
[4]Universidad de Guadalajara, Centro Universitario de los Altos-Departamento de clínicas, México

Abstract

There is a close relationship between hormones, cytokines, neuropeptides, and neurotransmitters that modulate the host immune response by several effector mechanisms, including both cellular and humoral immunity. Disruption of this communication balance results in disease or in a higher susceptibility to infections. The relationships between parasites and hosts are complex and there is substantial interaction, communication and biochemical co-evolution. The role of certain hormones in parasitic infections has been demonstrated, and there are documented direct effects of hormones on parasites. Many parasites induce the secretion of molecules that influence the physiological and immunological responses in hosts, including intermediaries and vectors. Conversely, the parasites secrete many factors that alter hormone host levels. In some cases, hormones have positive or negative effects on the parasites status. In other cases, effects are mediated indirectly via the host's immune system. In vertebrates, the parasite presence also has a major influence on the host's endocrine status and the normal suite of processes governed by hormones. These processes include host development, establishment, metamorphosis, and reproduction. Thus, understanding the mechanisms involved in immunoendocrine modulation and its effects on parasites is essential for developing new drugs, finding vaccine targets and devising new therapies for several infectious diseases.

Keywords: Sexual steroids; Hormones; Parasites; Immune system

Introduction

Hormones and parasites

Parasites comprise a group of organisms that cause a massive infectious disease problem for humans and several animals of veterinary importance. These organisms are major causes of mortality and morbidity and are detrimental to both the social and economic progress of the developing world. Sex differences in parasitic infections are a biological phenomenon of considerable significance for individual health and disease. The general rule is that females are more resistant to infectious diseases than males [1,2]. However, there are many notable exceptions to this rule and illustrate a female bias in susceptibility to infection [3]. This paradigm implies that the sexual dimorphism in response to parasites is mediated primarily by the immune system of the host, which disregards the ability of some parasites to directly respond to the distinct sex steroid hormone profiles of their female and male hosts [2,4]. Sex hormones play an influential role in the control of parasitic infection by modulating different components of both the innate and adaptive immune responses. Conversely, parasites themselves are phylogenetically diverse, target a range of different tissues, and have evolved numerous alternative strategies to evade or inhibit protective immune responses by strategies, such as antigenic variation, molecular mimicry or affecting antigen processing and presentation. Moreover, parasites exploit host systems for their benefit during establishment, growth, or reproduction [4]. Consequently, the influence of sex hormones on these infective agents can be complex. Sex hormones also exert their effects through genomic and non-genomic mechanisms by interacting with cell cytoplasmic or surface receptors and triggering signaling pathways. The main biological activity occurs by the activation of specific intracellular receptors that function as ligand-activated transcription factors and coordinates the expression of target genes [5]. Our current understanding of the relationship between hormones and parasite infection suggests that parasites can synthesize proteins, such as receptors with the ability to bind host hormones, and cause downstream transcriptional gene activation. As a result, parasites can positively or negatively affect the course of infection [6,7]. Based on the above data, this review examines how hormones effect on the immune system and their implications in parasite infections.

Immune response and hormones

The immune cells: Parasite-induced host response is orchestrated by the complex interactions of molecular and cellular effectors. The innate immune system is the first line of defense that is activated soon after parasite exposure. The cells involved in the host defense are neutrophils, macrophages, natural killer cells (NK) and dendritic cells (DCs) [8]. However, the primary response is performed by neutrophils using two basic mechanisms involving phagocytosis and the release of potent and toxic oxygen-free radicals (respiratory burst) [9]. Macrophages also participate in phagocytosis and respiratory bursts. These cells have the additional ability to present antigens and secrete cytokines, growth factors, and tissue-remodeling agents to alter tissue development [10,11]. DCs are professional antigen presenting cells that function by antigen-presentation on the cell surface to activate T lymphocytes. Finally, NK cells have a cytotoxic phenotype and secrete

small proteins called perforins and proteases known as granzymes. These proteins are involved in the host-rejection of tumors and virally infected cells. In general terms, these responses do not require prior exposure and can be initiated immediately following exposure to a novel parasite. Interestingly, the activity and number of cells associated with innate immunity could differ between the sexes. In females, professional antigen presenting cells (APC) are more efficient at presenting peptides than APC from males. Additionally, the phagocytic activity of macrophages and neutrophils is higher in females than males [12-14]. After parasitic or antigenic stimulation, the production of prostaglandin, thromboxane, and nitric oxide (NO) is higher in females than males [15]. In contrast, other studies demonstrate that several pro-inflammatory cytokines (including IL-6 and TNF-α) are higher in males following trauma [15]. Women with regular menstrual cycles and women during the luteal phase exhibit lower NK cell activity than men. These results correlate with experimental work in mice that demonstrated estradiol could reduce both the number and activity of NK cells [16-18]. However, males and females differ in their innate immune responses. This finding suggests there are sex differences. Previous studies of both humans and rodents have shown that inflammatory immune responses are generally higher in females than males. Thus, these results could explain the higher female susceptibility to developing inflammatory rheumatic diseases, such as rheumatoid arthritis and systemic lupus erythematous [19].

The acquired immune response after parasitic infection is mediated by humoral and cellular activation that includes an antigen-specific mechanism. Antigen presenting cells (macrophages and DCs) have a critical role in this response and stimulate B cells and T cell subsets [20]. B cells are grouped into B1 and B2 cells and are responsible for antibody secretion [21]. T cells are categorized into four distinct subtypes based on transcriptional factors, cytokine production, and function. These subtypes include Th1, Th2, Th17 and regulatory T cells (Treg) [22]. In this cell-mediated immune response there is a marked difference between males and females. Thus, T-cells (particularly CD4 T-cells) can be differentiated depending of the cytokine release and are functionally and phenotypically heterogeneous. Similarly, T cells present different subsets (i.e., Th1 or Th2 cells) to overcome infection and differ between males and females. Females have stronger Th2 responses (i.e., higher IL-4, IL-5, IL-6, and IL-10 production) than males [23]. There are also reports that females have a higher Th1 response (i.e., higher concentrations of IFN-γ) than males. In rodent models, females show higher mitogen-stimulated lymphocyte proliferation, faster wound healing, and increased immunological intolerance to foreign substances than males [15,24,25].

Hormones

Estrogens: Estrogens (E2) are predominantly produced in gonadal tissue and are principally produced by theca and granulosa cells in the ovary and mesenchymal cells [26]. The E2 immunomodulatory role enables the autoimmune disease incidence and age-associated diseases such as hormone-dependent cancer, osteoporosis, and cardiovascular diseases [27]. It has been observed that E2 has immunological roles and suppresses bone marrow leukocyte production, including neutrophils [28]. Estrogens also modulate leukocyte chemotaxis during ischemia and myocardium reperfusion in rat by inhibiting TNF-α production and limiting the binding of deleterious ICAM-1 leukocytes to injured myocardium. Therefore, estrogens protect against myocardial ischemia-reperfusion injury [29]. Previous in *vitro studies* have shown antioxidant effects by limiting superoxide anion production in human neutrophils [30]. E2 administration in mice before spinal cord injury reduces the production of tissue associated cytokines, such as TNF-α, IL-6, and IL- 1β (Table 1) [31].

During the first week of pregnancy in mice when E2 peak occurs, there is an increase of peritoneal macrophage phagocytic activity [32]. Additionally, exogenous *in vivo* E2 replacement significantly elevates sera lipopolysaccharide-binding protein levels and the cell surface expression of Toll-like receptor 4 (TLR-4) and CD14 (Table 1) [33].

In other murine model studies, exposure to E2 *in vitro* promotes differentiation into functional CD11c$^+$ and CD11b$^+$ DCs from bone marrow precursor cells. However, this differentiation is inhibited in E2-deficient medium and also, by estrogen receptor (ER) antagonists (ICI 182, 780 and tamoxifen). The differentiation can be restored by E2 addition in physiological amounts [34]. Moreover, E2 increases DC activation marker expression, including the expression of major histocompatibility complex II (MHCII), CD80 (B7.1), CD86 (B7.2), CD40, CD14, CXCL8 and CCL2 in murine bone marrow-derived DCs (Table 1) [35].

Conversely, the exposure of bone marrow-derived dendritic cells (BMDCs) to E2 enhances IL-12 production in response to the TLR ligands (as CpG and LPS) and induces killer DCs (IKDCs) activity and IFN-γ production. However, there is no difference between the number and function of DCs isolated from spleens of female C57BL/6 mice ovariectomized and ovariectomized mice with E2 replacement (Table 1) [36]. The DCs and monocytes derived from rat spleens with experimental autoimmune encephalomyelitis and differentiated with IL-4 and GM-CSF produce more NO when incubated with E2 (Table 1) [37].

The results of *in vitro* experiments show that NK and NKT cell numbers are increased by E2 stimulation [38]. The cell increase is probably caused by the up regulation of MCM7 and MCM10, which control cell proliferation [39]. However, E2 stimulation reduced NK and NKT cytotoxicity by decreasing the expression of soluble factors, such as granzyme B and FasL. Additionally, CD69, NKp46, NKG2DL and 2B4 receptors were downregulated, which inhibited NK cell activation (Table 1) [40].

In general, E2 exerts different effects on T-lymphocytes by altering cytokine production and modulating cell proliferation. Thus, low E2 concentrations can promote the Th1 response and cell-mediated immunity. However, high concentrations augment Th2 responses and humoral immunity [41]. The splenic lymphocytes and T cells purified from mice treated with E2 show upregulation of the transcription factor T-bet, and this causes IFN-γ production and Th1 cell migration (Table 1) [42]. In several models, increased IL-4 expression from Th2 cells positively correlates with cyclical variations in estrogen levels in humans [43]. Moreover, mice treated with high doses of estrogen have decreased IL-17 production by Th17 cells [44]. Treg cell frequency increases in pregnant mice exposed to E2 through the transcriptional induction of Foxp3, IL-10, and PD-1 overexpression in both lymphoid organs and blood compared to non-estrogen treated or non- pregnant mice (Table 1) [45,46]. In other mouse models, long-term exposure to exogenous high doses of E2 enhances polyclonal B cell activation [47]. Physiological concentrations of E2 stimulate B antibody production by B lymphocytes in the genital tract and systemic lymphoid tissues of normal cycling female macaques during the menstrual cycle periovulatory period [48]. In male and female humans, E2 enhances IgG and IgM production by peripheral blood mononuclear cells (PBMCs) without altering cell viability, proliferation, or non-specific differentiation (Table 1) [49].

Hormones	Immune cells	Effect	References
Estradiol (E2)	Neutrophils	Regulate the number and function Decrease chemotaxis by altering the expression of ICAM-1 Decrease superoxide anion production Produce cytokines TNF-α, IL-6, and IL-1beta	[28-31]
	Macrophages	Increase macrophage phagocytic activity Increase CD14, LBP and TLR42	[32,33]
	Dendritic cells	Promote functional differentiation Increase the expression of MHC II, CD14, CD40, CD80, CD86, CXCL8 and CCL2 Induce IKDCs and increase nitric oxide	[34-36]
	NK cells	Decrease cytotoxicity Upregulate the number of cells and expression of CD69, NKp46, NKG2DL, CD244, granzyme B and FasL	[39,40]
	Lymphocytes	Upregulate T-bet expression (Th1 and proinflammatory cytokines) Increase IL-4 production from CD4+ T cells Decrease production of IL-17 Upregulate Treg cells (expression of Foxp3, IL-10 and PD-L1) Stimulate antibody production	[42-49]
Progesterone (P4)	Macrophages	Inhibition classical pathway activation (iNOS and arginase activity)	[61]
	Dendritic cells	Inhibit the activity of mature DCs Down-regulate TNF-α, IL-1β, MHC II, CD80 Inhibit DC-stimulated proliferation of T cells	[62]
	NK cells	Regulate differentiation (Hox-A10) Reduce in cytotoxicity (HLA-G) Inhibit of perforin release (PIBF) Th2 differentiation and cytokine production (PIBF)	[13,14,63,66]
	Lymphocytes	Promote differentiation of Th2 Induce migration of Treg cells to the pregnant uterus	[13,181]
Testosterone (T4)	Macrophages	Inhibit the function of macrophages	[12]
		Reduce TLR4 expression Inhibit NO production	
	APC's	Down-regulate IL-1β, IL-6 and TNF-α	[70]
	Lymphocytes	Reduce Th1 cytokine release Induce Th2 profile Maintain Treg cells	[72,73]
DHEA	Neutrophil	Increase superoxide generation	[75]
	Dendritic cells	Induce mature DCs	[76]
	Lymphocytes	Enhance IL-2 secretion of Th1 cells and cytotoxicity function of T cells Induce apoptosis pathway Fas/Fas-L	[77,78]

Table 1: Effects of steroids hormones on immune response.

One remarkable effect that E2 can exert (concentration-dependent) is a proinflammatory or anti-inflammatory response. Low levels of E2 induce TNF-α, IL-6, and IL-1β. E2 also inhibits Th2-type cytokines and increases leukocyte migration to sites of inflammation [41]. However, at high levels, E2 inhibits cell-mediated immunity and decreases the expression of activation markers [50,51]. E2 inhibits TNF-α, IL-1β, and IL-6 production by T cells, macrophages, and DCs. Conversely, E2 induces Th2-type cytokines, such as IL-4, IL-10, and TGF-β, that results in anti-inflammatory effects [52]. E2 peak levels reduce Th1-type cytokine production (TNF-α and IFN-γ) by T cells, macrophages, and DCs [41,53,54]. E2 also enhances antibody production by enhancing IL-10 in human peripheral blood mononuclear cells (Table 1) [49]. In the female genital tract, E2 elevates IgG, IgA, and SC levels in ovariectomized rat uterus [55,56]. However, E2 action on cervicovaginal IgA, IgG, and SC is independent of the uterine influence because the E2 treatment of rats with ligated uterocervical junctions had decreased cervicovaginal IgA and SC levels. This is an important finding if the uterus is the main antibody source in genital tract secretions. After hysterectomy, the levels of IgG are reduced by one half and the levels of IgA are decreased by 15-fold [56]. E2 also affects lymphocytes, macrophages, NK cells and the migration and infiltration of other cells into the female genital tract. Additionally, E2 inhibits MCP-1 expression in endometrial stromal cells by controlling endometrial macrophage migration [57]. Furthermore, high E2 levels decrease macrophage and inflammatory T cell recruitment through ICAM-1, E-selectin, and VCAM-1 downregulation [58]. In contrast, E2 increases CD56+ NK cell recruitment to human endometrium by CXCL10 and CXCL11 chemokine upregulation [59]. Finally, E2-mediates the inhibition of antigen presentation and CTL activity in the female reproductive tract through the induction of TGF-β production by the uterine epithelial cells (Table 1) [60].

Progesterone: The hormone progesterone (P4) is secreted by the *corpus luteum* in the ovary and placenta. Principally, P4 is involved in the regulation of the female menstrual cycle and in pregnancy and embryogenesis of humans and other species. During early pregnancy, P4 recruits macrophages into the endometrium. The macrophages contribute to embryo implantation and pregnancy initiation by altering the remodeling process, uterine decidual response and placental trophoblast invasion. In mice, P4 negatively regulates macrophage activation of innate and classical pathways associated with NO and IL-12 production by down regulating inducible nitric oxide synthase 2 (iNOS) and arginase (Table 1) [61].

DCs derived from LPS-activated rat bone marrow cells treated with P4 have suppressed pro-inflammatory cytokine secretion (TNF-α, IL-1β). Additionally, the expression of activation markers, such as MHC class II and CD80, are downregulated. This causes reduced stimulation and T lymphocyte proliferation (Table 1) [62]. Moreover, P4 suppresses several innate immune responses including macrophage and NK cell activity and NF-κB signal transduction [63]. Activated lymphocytes express P4 receptors during pregnancy and high levels can stimulate the synthesis of progesterone-induced binding factor (PIBF) [14]. P4 also increases Th2 type cytokine production by IL-4 receptor stimulation and subsequent activation of the Jak/STAT pathway (Table 1) [13]. This activation results in inflammatory Th1 responses both at the maternal fetal interface and systemically [64,65].

Previous studies have demonstrated that P4 exerts a strong immunosuppressive effect on the production and transepithelial transport of IgG and IgA [56]. Studies of ovariectomized rats treated with P4 showed a significant decline in IgA and IgG cervicovaginal expression. In monocytes, P4 inhibits NK cell activity and FcγR expression and reduces antibody-dependent cell cytotoxicity mediated by the progesterone-induced blocking factor (PIBF) [66]. Finally, membrane-associated and intracellular progesterone receptors are expressed by a number of immune cells including macrophages, NK cells, and γδ-T cells [62,67].

Testosterone: Testosterone (T4) is the main androgen secreted by testicular Leydig cells in males. It is also produced in small quantities by ovarian theca cells in females in response to the luteinizing hormone [68]. T4 inhibits histamine and serotonin release by mast cells after stimulation by compound 48/80 or neuropeptide P [69]. *In vitro* studies with macrophage (RAW 264.7 cells) cell lines treated with T4 showed decreased TLR-4 expression and TLR-4 specific ligand sensitivity. Furthermore, orchidectomized mice are more susceptible to lethal LPS challenge *in vivo*. Interestingly, significantly higher TLR-4 cell surface expression was observed in macrophages isolated from these animals (Table 1) [12]. Moreover, treating a group of diabetic men with T4 decreased IL-1β, IL-6, and TNF-α production *ex vivo* by APCs (Table 1) [70]. Further evidence of the role for T4 in regulating immunity is obtained from studies of male medical castration, which decreases Treg cell levels. In contrast, androgen therapy replenishes the Treg cell numbers (Table 1) [71].

Female *SJL* mice are more susceptible than males to experimental autoimmune encephalomyelitis (EAE) induced by myelin basic protein (MBP) specific T lymphocytes. However, the females implanted with dihydrotestosterone exhibited a significantly less severe EAE course (Table 1) [72]. Finally, T4 inhibits immunoglobulin IgM and IgG production. A recent study using human peripheral blood mononuclear cells (PBMC) demonstrated this effect is mediated indirectly by T4 inhibition of monocyte-derived IL-6 production (Table 1) [73].

Dehydroepiandrosterone: Dehydroepiandrosterone (DHEA) is a pregnenolone-derived C-19 steroid that is predominantly synthesized in the adrenal cortex cells [74]. DHEA sulfate ester (DHEAS) activates recombinant protein kinase C-beta (PKC-beta), which results in amplified phosphorylation of p47 (phox). Phosphorylated p47 is an active component of the reduced nicotinamide adenine dinucleotide phosphate complex responsible for neutrophil superoxide generation (Table 1) [75]. Additionally, DHEAS synergizes with GM-CSF and IL-4 to generate mature DCs from monocytes (Table 1) [76]. Moreover, DHEAS regulates cytokine production by both myeloid and lymphoid cells. Thus, most reports suggest this steroid is a potent inducer of IL-2 secretion by Th1 cells and human T cell cytotoxic function (Table 1) [77]. Finally, DHEA enhances Fas and Fas-L expression to induce thymocyte apoptosis [78].

Hormones, immune response and parasitic infection

In helminths infections: Protective immunity against helminth parasites is generally dependent on the development of a strong Th2 response involving IL-4 and IL-13. In general, females are more resistant than males. This is particularly true for gut parasitic helminth infections. There are many examples (*Strongyloides ratti*) where gonadectomy significantly reduces worm burdens in male rats but ovariectomy has no effect on parasite burdens in females [79]. Thus, increased male susceptibility to gut parasitic nematodes may be a direct result of androgenic as opposed to estrogenic influences on immunity. As a result, ovariectomy of females has no effect, but injection of testosterone into females or males increases gut worm burdens [79]. *Nippostrongylus brasiliensis* infection of Indian soft-furred rats reveals that males are more susceptible to infection since parasite burdens are higher in males

than in females after 4 weeks of infection [80]. According to this, orchidectomy reduced parasite burdens in males while ovariectomy had no effect in females [80]. The intestinal parasite *Trichuris muris* is a significant example illustrating how sex hormones influence mast cell activity in female mice by favoring gut parasitic nematode expulsion [81]. Studies utilizing cytokine deficient mice might reveal underlying mechanisms modulating sex hormone influences on immunity and outcomes of parasite infection. Female C57BL/6, BALB/c IL-4 -/- and BALB/c mice showed *T. muris* infection resistance; however, male C57BL/6, IL-4 -/- and BALB/c are susceptible. This observation reflects the female ability to generate IL-13 [82,83]. In experimental assays, the administration of recombinant IL-13 to male BALB/c IL-4 -/- induces worm expulsion, while IL-13 neutralization in BALB/c IL-4 -/- inhibited expulsion [82,83]. These results suggest there is a possible link between E2 and the ability to produce IL-13 or IL-4 as mediators of resistance against this parasite and the infection susceptibility is a consequence of inadequate TH2 cells production [82,83].

In the case of the intracellular parasite *Trichinella spiralis*, estrogens can increase the resistance of male CD1 mice to parasites, as measured both by adult worm burdens and tissue larvae [84]. Gonadectomy also increases male resistance and T4 treatment increases female susceptibility. Consequently, both T4 and E2 influence *T. spiralis* control in a reciprocal manner, and this control is Th2 dependent [84]. Mast cells also play a crucial role in worm expulsion as in the case of *T. muris* [85]. These results suggest that sex hormones influence the Th2 response during gut parasitic infections and demonstrate the invariable female resistance to helminthic parasites (including filarial nematodes, in which Th2 responses promote resistance to infection). *Litomosoides sigmodontis* filarial survival is reduced in males compared to female BALB/c mice and the microfilariae prevalence and density are higher in females [86]. The susceptibility of BALB/c mice to *L. sigmodontis* is caused by the generation of potent regulatory T cell responses that overcome Th2 effector functions and permit survival of the adult parasite [87]. It is important to emphasize that E2 at physiological levels expands $CD4^+CD25^+FoxP3^+$ regulatory T cells expressing IL-10 [87,88] and that IL-10 is essential for microfilariae persistence [89].

Several groups have demonstrated that *in vitro* culture of *Taenia solium* cysticerci in the presence of sex steroid (P4) induces evagination in 100% of treated cysticerci [90]. In contrast, T4 and DHEA induce the opposite effect and inhibits 85% to 90% of evagination events [5]. The use of the P4 competitive antagonist RU486 inhibits the evagination process in cysticerci, and this effect is mediated by a classical steroid receptor that is able to block the transcription of some genes [90]. The use of flutamide (androgen antagonist) does not reverse the T4 and the DHEA effect [5]. These results suggest the cysticerci evagination process could be mediated by a specific P4-receptor present on the parasite (Figure 1) [90]. In contrast, host treatment with P4 reduces the number of parasitic worms [91]. The effect of E2 on *T. crassiceps* cysticerci showed that the hormone is able to induce budding and increase the parasite infective capacity to 200% [5]. The effect could be mediated through a specific estrogen receptor that promotes the expression of *c-fos* and *c-jun* (AP-1 transcriptional complex) and suggests that E2 has proliferative effects on the parasite [92]. Our laboratory also demonstrates that exposure of T. *crassiceps* cysticerci to E2 and P4 induced differential protein expression patterns regarding to changes in actin, tubulin and myosin expression altering flame cells at the level of the ciliary tuft [93]. In contrast T4 and DHT induced 90% of mortality caused by an alteration in the function of flame cells, without changes in actin, tubulin or myosin expression [94].

DHEA has been shown to affect different stages of *Schistosoma mansoni in vitro*. The treatment with DHEA decreases adult worm oviposition and increases the cercariae mortality rate to 100% [95]. In mouse models of *S. mansoni* infection, the sex difference is reversed and the female mice are more susceptible to infection because they develop higher inflammatory responses as measured by organ weights and delayed type hypersensitivity responses [96]. In mice, adrenalectomy exacerbates disease, as measured by worm burden and host mortality following inoculation with *S. mansoni* parasites [97]. In contrast, human males are more susceptible to *S. mansoni* infection than females [98]. In the case of *Schistosoma hematobium,* the treatment with T4 decreases the adult parasite reproductive capacity and reduces its fecundity through sexual hormone interaction with a glutathione S-tranferase (Sh28GST) to inhibit parasite metabolism [99]. A stimulant effect of murine epidermal growth factor (EGF) has been found on *Brugia malayi* microfilariae *in vitro*. EGF induces overexpression of *Raf* and *Ran* transcriptional levels and causes microfilariae growth and differentiation [100]. These experimental reports suggest that some human helminth and nematode parasites have molecular structures analogous to the classic hormone receptors. These receptors have similar functions as in mammals (Figure 1) [4,5,101].

In protozoa infections: In parasitic protozoa, some hormonal effects have also been reported on different morphologic stages. In *Toxoplasma gondii* murine infection models, females develop severe brain inflammation and are more likely to die following infection than males [102]. Male mice produce higher concentrations of TNF-α, IL-12, and IFN-γ than females during acute infection [102,103]. In female mice, ovariectomy reduces and administration of E2 exacerbates tissue cyst development caused by *T. gondii* infection [104,105]. The ovariectomized female mice treated with pharmacological doses of potent E2 compounds including 17β-estradiol, diethylstilbestrol, or alpha-dienestrol, renders mice more susceptible to disease as measured by brain cyst formation [105]. The host treatment with T4 reduces the parasite number and pathology [104,106]. *T. gondii* infection in rodents results in pronounced behavioral alterations including increased exploratory behavior and aggression. These changes may make the infected animal more conspicuous to and reduces definitive host fear (the cat) [107,108]. However, different studies with genetically engineered mice have shown that *T. gondii* stimulates the innate immune response during the initial parasite establishment and growth. During chronic infection, the disease state can be maintained directly by adaptive immune responses to control and benefit both host and parasite survival [109]. To achieve this outcome, *T. gondii* express a number of TLR ligands, including GPI-anchors [110], HSP70 [111,112] and profilin [113]. The parasite also induces IL-12 production through CCR5 receptor ligation [114]. These processes result in the activation of macrophages, DCs, and NK cells that produce IL-12, TNF-α, and IFN-γ. The production of cytokines can control parasite growth, induce Th1 cell expansion and facilitate the cytotoxic $CD8^+$ T cell development [115,116]. *Plasmodium sp.* infection is similar between males and females [117], however, previous studies suggested that males have higher parasitic burdens [118,119], but females have higher mortality rates [120]. It has been observed that cortisol treatment *in vitro* in *P. falciparum* merozoites increases the size and number of gametocytes produced. E2 treatment increases parasite growth and reproduction [121,122]. In contrast, prolactin can mediate lethal effects on various parasite stages [123]. In diseased rodent models using *Plasmodium chabaudi* female C57BL/10 [119,120] and C57BL/6 [124] mice, there was less
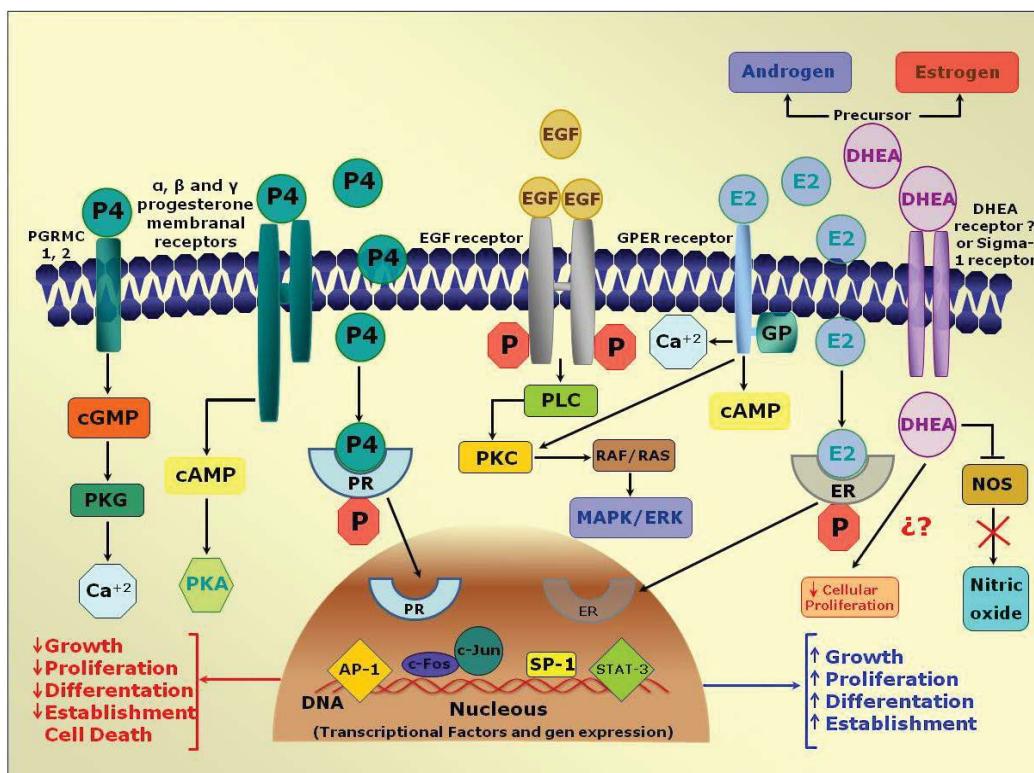
Figure 1. Signaling pathways and positive or negative effects of different hormones on the growth, differentiation, proliferation and establishment of parasitic cells. Some hormone signals are involved in the expression of transcription factors in the cell nucleus (genomic effects). These factors regulate the gene expression or the second messenger expression (no genomic effects), which results in the activation and/or inhibition of signaling cascades. DHEA: dehydroepiandrosterone; P4: Progesterone; EGF: murine epidermal growth factor; E2: 17-β-Estradiol.

parasitic induced mortality compared with male mice. Moreover, during *P. chabaudi* infection, T4 is a key modulator in the sexual dimorphism exhibited. Hormonal treatment in females can prevent self-healing, whereas male castration leads to self-healing [125,126]. Interestingly, in this disease model T4 is not signaling through classical androgen or estrogen receptor [125-128]. *In vivo* assays showed that female C57BL/10 mice orally administered T4 had increased mortality rates and death was associated with a decreased peritoneal cell generation of reactive oxygen species [129]. However, in *P. falciparum* T4 and DHEA increase the growth and parasite reproduction [123]. Finally, T4 treatment of females results in CD8$^+$ T cell increases in the spleen and decreases in numbers of overall splenocytes [130]. Conversely, P4 treatment in mice increases growth and reproduction and favored parasite establishment [122]. Recent data showed that gonadectomy of increased T and B splenic cells in both sexes, increased macrophages cells and decreased the NK subpopulation only in male mice infected with *Plasmodium berghei ANKA*. Gonadectomy also induced an increase in the synthesis of IgG1, IgG2b, IgG3, and total IgG; the pro-inflammatory cytokines TNF-α and IL-6 and induced higher levesl of NO only in female mice. This suggest that female sex hormones have anti-inflammatory properties in malaria [131,132].

The intestinal protozoans *Entamoeba sp.* and *Giardia sp.* are transmitted fecal-orally and cause amoebiasis and giardiasis, respectively. During infection neutrophils play an important role in both diseases. For example, the alpha-defensins secreted by neutrophils *in vitro* have anti-giardial properties [133] and neutrophil-

depleted mice have more severe amoebic liver abscess (ALA) and intestinal amoebiasis [134]. Macrophages produced NO is involved in protection of invasive amoebiasis [135]. Additionally, mast cells play a critical role in controlling giardiasis [136]. Studies performed using C57BL/6 mice infected with *Giardia muris* showed that male mice have higher parasite burdens in their gut [137,138], and more prolonged disaccharidase deficiency [138] than females. Moreover, infected female C57BL/6 mice had elevated levels of parasite-specific IgG and stronger IgG2b and IgG3 responses than males [139]. In *E. histolytica* human infection the invasive disease predominates in males compared to females [140]. Studies in mice have demonstrate that females show a significantly early IFN-γ production and the presence of Natural Killer T-cells (NKT) cells compared with male mice, which have higher levels of IL-4-producing cells. This cytokine and NKT cells seem to be important in the control of the disease since the use of IFN-gamma-neutralizing monoclonal antibodies or NKT-deficient female mice showed an exacerbated amoebic liver absses (ALA) [141]. *In vitro* exposure to DHEA and cortisol increase *E. histolytica* trophozoite proliferation and DNA synthesis. DHEA also induces a progressive loss of adherence capacity, which is crucial during intestinal infection [134] (Figure 1). In contrast, during intestinal infection treatment with testosterone (T 4) stimulated trophozoites migration from intestine to liver and increased ALA infections [141].

Trypanosoma spp. is the causal agent to Chagas´ disease in America and sleeping sickness in Africa. Chagas´ disease consists of acute and chronic phases. Although the role of the immune system during

disease clearance and pathogenesis is not well understood, studies have shown sex hormones play a role in disease modulation. It is well documented that male mice and rats are more susceptible to disease than females in *T. cruzi* experimental infection [142-145]. In addition, males are clinically more likely to develop severe cardiomyopathies [146] and exhibit abnormal electrocardiograms more often than females [147]. Data indicates that EGF induces an increase in the growth, metabolic activity, and DNA synthesis of *Trypanosoma cruzi* trypomastigotes *in vitro*. Additionally, EGF induces the expression of receptors with tyrosine kinase activity, protein kinase C (PKC), and mitogen-activated protein kinases (MAPK) [148]. Susceptibility and/or resistance could be directly linked to the presence of female sex hormones, and ovariectomized females are more susceptible to disease [142,145,148]. However, a role for male sex hormones in mediating susceptibility is less clear, and gonadectomized males are reported to have reduced parasite burdens [145] and unaltered parasitemia and mortality [142]. Interestingly, female mice treated with high pharmacological doses of 17β-estradiol increases parasitemia and mortality. The low physiological doses have either no effect or reduced parasite burden and death [143]. DHEA administration after *T. cruzi* infection plays an essential role in enhancing host resistance. The macrophages infected with *T. cruzi* express different hormonal receptors and secrete more TNF-α, IL-12 and NO after treatment with DHEA. This cytokine secretion results in a decreased trypomastigote load in blood and suggests its protective role is a result of potent immunoregulatory actions during infection [149,150].

In the sleeping sickness caused by *T. brucei spp.*, the disease is characterized by two distinct stages; an early hemolytic stage followed by a late meningoencephalitic stage. This last phase is characterized by leukocyte infiltration into the central nervous system, astrocyte and microglial activation, and acute neuroinflammation that ultimately results in coma and death [151]. African trypanosomes have developed many mechanisms to evade host immune response. However, most important is their ability to switch immunodominant variant surface glycoprotein (VSG´s), exchange the antigen surface and always avoid the immune response [152,153]. In this case, sex hormones play a role in modulating immunity to African trypanosomes. Researchers have found that female mice have lower parasitemia and survive longer than their male counterparts [154]. During human disease, males have trypanosomes in their cerebral spinal fluid more often than females and males have more relapses following treatment [155]. Unfortunately, no further research has determined the roles of specific sex hormones during disease. It has been shown that infection can result in hypogonadism and decreased T4 and E2 levels in both clinical and experimental studies [156-159].

Human babesiosis is caused by the intraerythrocytic protozoan parasite called *Babesia microti*. Researchers studying this infection have found that male mice are more susceptible to disease [160]. However, studies of WA1-type babesial report that female mice are more susceptible [160]. While the mechanisms behind female susceptibility to WA1-type babesial are unclear, research into male susceptibility to *B. microti* indicates that T4 causes longer and more severe infections in mice that have been castrated and implanted with T4 compared to mice castrated and implanted with inert oil [161,162]. Additionally, higher-ranking mice within a home cage have higher T4 higher levels, and these higher levels are associated with depressed levels of serum immunoglobulin and reduced resistance to infection with *B. microti* [163]. Interestingly, ixodidae ticks preferentially attach to rodents with high T4 levels [162]. Although T4 exacerbates disease, E2 does not confer resistance to *B. microti* disease [164]. More research is required

to examine both the basic immune responses against *Babesia* parasites and the role that sex hormones play during disease. Additional studies investigating differences between parasite species and mouse strains are also needed.

The sexually transmitted parasite *Trichomonas vaginalis* is an extracellular mucosal protozoan with a progressive growth. Several studies show that *T. vaginalis* has androgen and estrogen receptors on its cell surface (Figure 1) [165]. Interestingly, to study *T. vaginalis* in the laboratory, female mice must receive estrogen treatments to establish disease [166,167]. Similarly, in clinical studies, female volunteers also require estrogen treatment to establish the disease [168]. Furthermore, conditions associated with high levels of estrogen, such as menses and pregnancy, can exacerbate *T. vaginalis* infections [169]. 17β-estradiol enhances the *in vitro* growth of parasites, whereas T4 and P4 inhibit growth at early phases. Other studies using euthymic and athymic BALB/c mice found that females are more susceptible than males at developing abscesses following subcutaneous injections of *T. vaginalis* [170]. Conversely, some *in vitro* studies have found that E2 inhibits *T. vaginalis* growth [171] and both virulence factor and cell-detaching factor, which are correlated with disease severity [172].

Leishmania spp. is an obligate intracellular protozoan parasite transmitted by the bite of certain sandfly species. In humans infected with *L. mexicana,* females generally have increased Th1 responses, as measured by DTH reactions and decreased Th2 responses and IgE production compared to males [173]. In *L. major* infections, gonadectomy increases male resistance and T4 implants increase female susceptibility [174]. Similarly, E2 promotes macrophage mediated killing of *L. mexicana* at physiological levels through increased NO production independent of proinflammatory cytokine expression [175]. During *L. donovani* infection, T4 regulates murine bone marrow-derived macrophage p38 MAPK activation in a negative manner, and this promotes parasite survival [176]. *L. mexicana* infection is more severe than *L. major infection* because virulence is based on downregulation of macrophage function and IFN-γ induced Jak1, Jak2, and STAT1 activation [177,178]. E2 upregulates IFN-γ mRNA expression by T cells [39] whereas T4 inhibits production of this cytokine [71]. The IL-10 cellular sources are potentially subject to sex hormone control [179]. Thus, the Th1/Th2 paradigm of resistance/susceptibility to intracellular parasites is a gross oversimplification of a far more complicated network of regulatory/counter-regulatory interactions that are also subject to further modulation by sex hormones.

Conclusion

As previously mentioned, during many parasitic infections, there is a reciprocal relationship amongst sex steroids, the immune system, and the eventual elimination or establishment of the parasites in humans. In certain cases, hormones can regulate the innate immune response and the subsequent adaptive immune response [180].

The hormonal microenvironment may favor or inhibit the survival of parasites differentially between the sexes. This result may represent a highly evolved host-parasite relationship in which certain hormones appear to serve as proliferation or death factors that influence the establishment of infection and are independent of the host immune response. All of to the data suggest the parasites exploit endocrine mechanisms developed by the host for its own advantage.

The elucidation of neuroimmunoendocrine interactions during parasite infections is fundamental to understand the mechanisms involved in parasite establishment, growth, and reproduction in human

hosts. A deeper comprehension of this complex relationship could have implications in the control and treatment of various infections throughout the world. The physiologic elements that are essential in the network of neuroimmunoendocrine interactions during parasite infection could have a deep biological and physiopathological impact. Thus, a better understanding could be extremely valuable in designing vaccines and new antiparasitic drugs and in controlling various human and veterinary parasitosis. It may also lead to the development of new therapies for autoimmune diseases.

Acknowledgements

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