Beyond the Reproductive Effect of Sex Steroids: Their Role During Immunity to Helminth Parasite Infections

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Abstract: During the helminth infections, the immune system tends to be modulated by host's sex hormones. Actually, many studies show the reciprocal relationship between sex steroids, the immune system and the elimination or establishment of helminth parasites. Is well known that innate immune response determines the type of adaptive immune response, so the effects in the innate immune response by hormones may affect subsequent adaptive immunity. The sex steroids as estrogens, progesterone and testosterone regulate growth, differentiation, survival and function of many cell types that could be involved in process like homeostasis and immunity, but also have a direct effect on the helminthes, that may probably be mediated by specific receptors on these parasites. Sex steroids, parasites and immunity are closely connected, and their interconnection is involved in the maintenance of elimination or establishment of helminthes in an immunocompetent host. For that reason, understanding the action's mechanisms of sex steroids on immune cells and its direct effect on helminth parasites is important for further progress in the development of novel therapies for chronic helminth diseases associated to immune dysregulation. In this review, we will describe the effects of sex steroids on the immune response during helminth infections as well as the direct effect in these parasites, and the possible implications of these effects on the incidence of several helminth infections.

Keywords: Sex steroids, immunity, parasites, helminthes, infections.

INTRODUCTION

For decades, the gonadal steroid hormones were thought of only playing a fundamental regulative role of behavior and brain physiology. Then, in the following years, it became apparent that they are essentially involved in the accurate development and differentiation of distinct mammalian neuronal systems, to name one. Over the years, different neuronal phenotypes, brain nuclei, neural circuitries, neurophysiological performances, immune response and parasite growth, establishment and reproduction, have been identified to be under the control of sex steroid hormones, at least at defined pre- and postnatal developmental periods. Furthermore, developmental sex-steroids effects are not confined to classical neuroendocrine systems in the hypothalamus and pituitary, but are also observed throughout the whole body systems cells. From these observations, we learned that ontogenetic effects of sex steroids, although sometimes only in a subtle and elusory way, influence a wide array of non-reproductive behaviors. Besides regulating neural network development and functional aspects of the CNS systems, sex steroid hormones have a well-documented impact as protective molecules during acute neurotoxic and neurodegenerative processes in the brain. Estrogens are probably the best-studied and most-convincing protective steroid hormones in the CNS, although there is ample evidence for an additional protective role of progesterone in the nervous system. Estrogens protect nerve cells against a variety of toxic events and have been proposed to be beneficial for a multiplicity of neuronal disorders including stroke, ischemia, Parkinson's and Alzheimer's disease. The cellular mechanisms underlying these guarding effects comprise classical nuclear signaling *via* estrogen receptor alpha and beta (ERα and ERβ, respectively) but also the direct modulation of signal transduction systems, neurotransmitter receptor function, and even anti-oxidant activities. Furthermore, sex steroids are able to regulate processes implicated in the immune response, including the maturation and selection of thymocytes, cellular transit, expression of molecules and receptors of the class II major histocompatibility complex, lymphocyte proliferation and cytokine production. These functions involve a large repertoire of highly specialized cells that perform different functions with precision and efficacy. Molecules secreted by components of the immune system delicately regulate these cells, but they are also susceptible to regulation by hormones, neurohormones and/or neurotransmitters, apparently distant from the immune system. Sex hormones apparently play an important role in the differences in susceptibility associated to sex in certain infections, particularly parasitic. A chart of the

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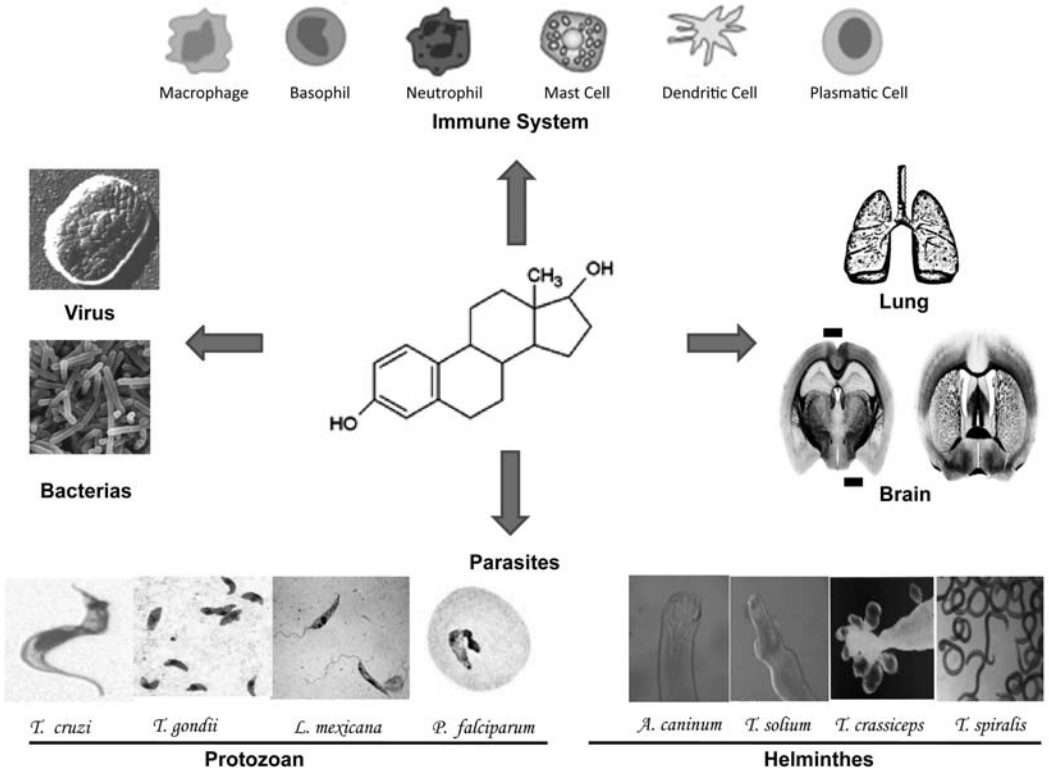

Fig. (1). Effects of sex steroids to cells from different host organs and parasite cells.

Besides their effects on sexual differentiation and reproduction, sex steroids (estradiol, progesterone, testosterone and dihydrotestoterone) can influence several systems and microorganisms by affecting differently many of the functions of virtually all cells types. For example, sex hormones regulate the innate immune response through their effects on macrophages (Mφ), monocytes, mast cells (MC), dendritic cells (DC), natural killer cells (NK) and granulocytes: neutrophils (neut), eosinophils (eos) and basophils. Also, their strong effects on virtually all neurons of the different brain areas, as well as the lung have been reported. Moreover, recently it has been shown that sex-steroids also regulate growth, differentiation and reproduction of several other organisms, such as bacteria, viruses, and parasites. The influence of sex steroids as important factors that affect the development of parasitic diseases has been demonstrated in several protozoa and in helminthes. Some of the specific actions of sex steroids on innate and adaptive immune cells, as well as in helminth parasites are discussed in the text.

different non-reproductive effects of sex steroids is depicted in Fig. (**1**).

On the other hand, parasites have developed diverse mechanisms of survival within the host, which facilitate the establishment of infection. These can be roughly grouped into two types: those in which the immune response is evaded by strategies such as antigenic variation and molecular mimicry [1, 2] and those in which the parasite exploits some system of the host to its benefit, and thus obtains an advantage such as establishment, growth or reproduction [3]. Thus *Naeglerai fowleria* is capable of internalizing antigen antibody complexes from their surface with the dual benefit of gaining the amino acids for their own metabolism and preventing the surface bound antibody from interfering with parasite host cell interactions [4]. Other pathogens, including *Coxiella burnetii* have developed molecules that directly interfere with antigen processing and presentation [5]. A striking example of exploitation of host molecules is the ability of a number of parasites to use host-synthesized cytokines as indirect growth factors for the parasite [3,4].

Recent experimental evidence [6-15] has led us to suggest a mechanism of host exploitation by the parasite. In this system of 'trans-regulation', the parasite benefits directly from host derived hormones or growth factors, to allow rapid establishment, increased growth and reproduction.

Trans-regulation phenomena in parasites have been scarcely explored. However, some evidence lends support to the notion that host-parasite regulation or trans-regulation is possible and has been described to date in at least eight parasitic infections caused by both protozoan and metazoans.

SEXUAL DIMORPHISM OF THE IMMUNE RESPONSE

As stated above, sex steroids regulate a variety of cellular and physiological functions of organisms such as growth, reproduction and differentiation [16, 17]. More recently, the ability of sex steroids to affect the immunological response directed against pathogenic agents has gained attention [18-21]. This is clearly evident during various parasitic diseases including malaria, schistosomiasis, toxoplasmosis, cysticer-

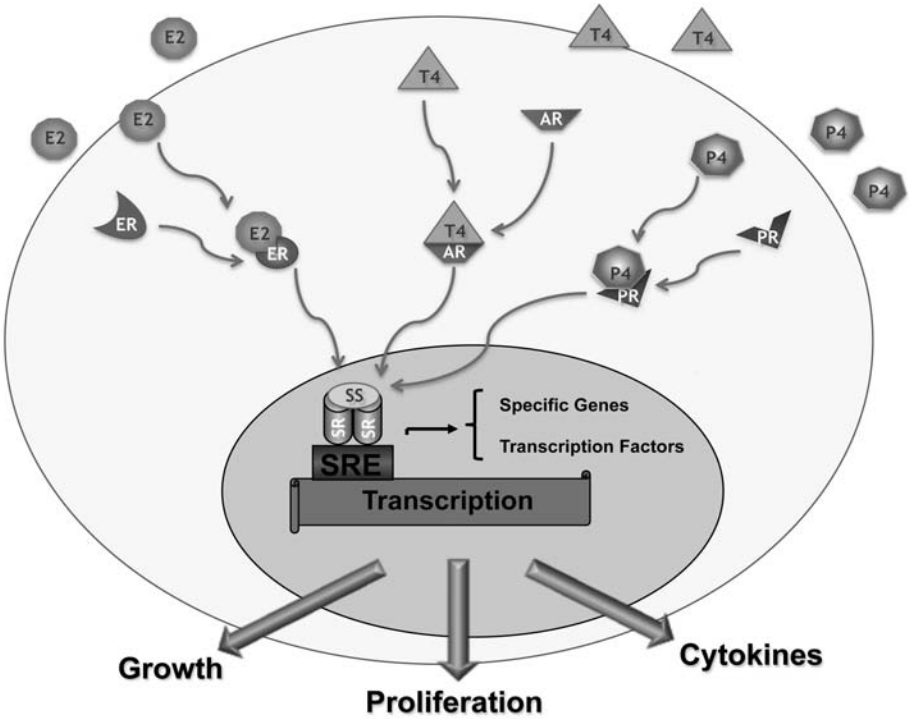

Fig. (2). Genomic action of sex steroid hormones on immune cells.

Estradiol (E2), progesterone (P4) and testosterone (T4) bind to their steroid receptors (ER, PR and AR, respectively). These nuclear receptors homodimerized in nucleus and bind to steroid response elements (SRE) and iniciate transcription of specifics genes involved on growth, proliferation or may be cytokines production. SS, sex steroid; SR, steroid receptor.

cosis, trypanosomiasis, leishmaniasis [22-26], among others, where strong hormonal regulation of the immune response has been described [27-32].

In many sexually dimorphic species the determination of the sexual genotype upon conception, followed by the organism's physiological and endocrinological development, brings about numerous and complex differences between males and females. Starting in infancy, and thereafter along reproductive life, these differences are based on the production, secretion, and circulating concentrations of estrogens, progesterone and testosterone, and caused mainly on the function and development of the hypothalamus-pituitary-gonad axis (HPG) [17]. The complex interaction between hormones produced by the HPG axis and other hormones, in addition to sex-independent gene products, determine the male and female phenotypes [33].

So we can infer that, in addition to the well studied effects of sex steroids regarding on sexual differentiation and reproduction, they also may determine differences in both sexes, specifically on their immune response to the same antigenic stimulus. For example, it has been demonstrated that females of different species produce higher levels of circulating immunoglobulins and display a more pronounced humoral response against infections [34]. In that way, it has been observed that following infection or vaccination, women generate vigorous antibody and cell-mediated immune responses in comparison with men [35]. Another clinical and epidemiological findings show that autoimmune diseases are more common in women of reproductive age, than men do, which suggest that sex steroids are crucial in determining these differences [36, 37]. In addition, the differences associated to host's sex are thought to be the principal cause of the female's susceptibility to autoimmune diseases (ie. multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE)) [38]. Now, regarding on infectious diseases it has been also observed differences associated to host's sex. These include sexual dimorphism of the immune response as well as dimorphism associated to infection parameters [39, 40].

As we mentioned, sex steroids (estradiol, progesterone and testosterone) can influence the immune system by affecting differently the functions of the immune cells types [35], and in consequence modulate a variety of phenomena which include: thymocyte maturation and selection, cellular transit, lymphocyte proliferation, expression of class II major histocompatibility complex molecules and receptors, and cytokine production [41, 42]. Indeed, the presence of both cytoplasmic or nuclear receptors for sex steroids on immune cells, [35] indicates that one mechanism by which these sex steroids may exert their biological effects (Fig. **2**). For these hormones to have an effect on immune system cells, the presence of hormone receptors is necessary. Although steroid hormones also exert effects by non-genomic mechanisms, by way of acting on cell surface receptors and

triggering signaling cascades. It is currently accepted, that the main route of biological activity occurs by means of specific nuclear receptors (NR) that function as transcription factors, and coordinate, after binding to their ligand, the expression of target genes. Between this NR we can mention the estrogen receptors (ER), ER-α, ER-β, which are encoded by individual genes and bind 17β-estradiol; the progesterone receptor A (PR-A) and progesterone receptor B (PR-B), which are generated for alternative splicing of the same gene and whose main ligand is progesterone; finally the androgen receptor (AR), encoded by a single gene and which is able to bind testosterone and dihydrotestosterone (DHT). Moreover, sex steroid effects are not only mediated by specific receptors localized in the cytoplasm and in the cellular membrane, [28, 29]. In fact, the binding between estradiol (E_2) and its membrane ER activates group I and II of the metabotropic glutamate receptor [43]. Interestingly, ER is able to bind to SRC kinases through the conserved SH2 domains, and that could change the phosphorylation pattern of ERK 1/2 and in consequence modify the effect of this transcription factor [44]. Nevertheless, there is few in formation on this type of mechanisms in lymphoid cells. For that reason is necessary to perform studies on these cellular and molecular mechanisms, which offer a good opportunity for drug design since the knowledge obtained on the metabolic pathways could provide specific potential targets (ie, enzymes, genes and transduction molecules) for therapeutic treatment exclusively present in the parasite cells (Fig. **3**). Recently, three new putative membrane progesterone receptors (mPRs), mPRα, mPRβ, and mPRγ have been described and detected also on T lymphocytes [45]. The mechanism of action of these membrane progesterone receptors is suggested to be through G_i-protein activation (Fig. **3**). Previous findings have also revealed unconventional non-genomic surface receptors for testosterone in rat T cells. These belong to the class of membrane receptors coupled to phospholipase C *via* a pertussis toxin-sensitive G-protein. Binding of testosterone to these cell surface receptors causes a rapid increase in intracellular free Ca^{2+} concentration ($[Ca^{2+}]i$) and an increased formation of inositol 1,4,5-triphosphate and diacylglycerol [46]. Preliminary evidence indicates that in murine T cells, testosterone also induces a rapid rise in $[Ca^{2+}]i$, presumably due to Ca^{2+} influx triggered by binding of testosterone to receptors on the outer surface of T cells (Fig. **3**).

SEX STEROIDS AND IMMUNE RESPONSE TO HELMINTH PARASITES

One interesting biological phenomenon very scarcely studied is the sexual dimorphism (SD) in parasitic infections. This phenomenon has a considerable significance for individual health, behavior, and lifestyles as well as for the evolution of species. Regarding of female supremacy paradigm on infectious diseases, it start to be consider a wrong concept, because in recent years there have been many notable exceptions to this rule of a favorable female bias in susceptibility to infection. The need to enrich the reductionist approach to complex biological issues, like SD, with more penetrating approaches to the study of cause-effect relationship is urgent. Particularly in the host's sexual differences to cystercosis infection, females are more likely to become infected, to carry larger parasite loads, to be more severely affected and more reticent to develop protective immunity to variable degrees that associate with their genetic backgrounds and times of infection. Mechanisms underlying sexual dimorphism in murine cysticercosis weave a complex network connecting the host's major sex steroids and their receptors and effectors in the immune and central nervous systems, interacting among them and with the parasite. Thus,

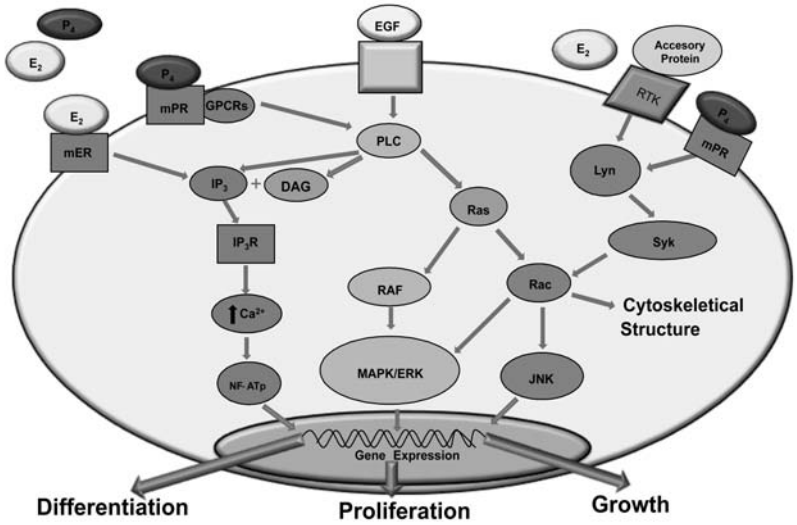

Fig. (3). Non-genomic action of sex steroids on immune cells. Sex steroid like progesterone binds to its membrane progesterone receptor (mPR), which is associated to G-proteins (G-protein coupled to receptors, GPCRs) and suggest to excert its action mechanism.

we earnestly encourage colleagues to carefully examine the usually neglected question of the role of the host's sex in their particular studies, promising exciting action and many surprising discoveries and possible applications. On immune system modulation, the cytokine secretion is a crucial aspect, because its secretion pattern determines the immune response that will confront a particular antigen. This pattern can be divided at least of two types: Th1 and Th2 pattern; the first one is effective to eliminate mainly intracellular pathogens, while the second one is crucial to eradicate extracellular pathogens. However, there are several immunological factors that affect the expression pattern of these molecules and also autoregulate the Th1/Th2 balance, but there are few evidences about effect of other protagonists of mammal's physiology. Moreover, it has been repeatedly shown that sex and its associated steroids, significantly influence various aspects of the immune system. A range of reports on the immune and the neuroendocrine system interactions indicate that hormones are capable of affecting immune functions [16, 17, 19, 33].

The importance of the interaction between the immune and endocrine systems becomes evident in particular circumstances of the lifespan of an organism, such as pregnancy, autoimmune diseases, and some time, it is also affected by infectious diseases. In all cases, the available evidence underscores the importance of sex steroids as immunoregulators [19].

The hormonal microenvironment and in particular the balance of male and female hormones may favor survival of certain parasites under certain circumstances. Predominance of a sex-distinctive steroid may directly induce reproduction, growth or differentiation of the parasite, and thus favor the establishment of infection. This represents a highly evolved host parasite relationship that places the parasite in an environment that, far from being hostile, endows it with growth factors that operate directly and positively on its growth and reproduction. This is independent of other elements such as the immune system. All of this allows to the parasite to exploite endocrine mechanism developed by the host for its own advantage.

Furthermore, certain parasites not only fair better in a host of a particular gender, but also a benefit in a specific developmental stage or physiological condition. For instance, some parasites have increased multiplication in pregnant females (for example, *Schistosoma mansoni* and *T. solium* in golden hamster and pig, respectively) [47-49]. Studies performed after this observation, have shown that progesterone plays a key role in parasite metabolism and infection [48, 49]. On the other hand, the prepuberty hormonal environment confers resistance of *S. mansoni* to humans at this developmental stage [50]. These effects could be explained by two possible mechanisms: 1) by modulation of the immune response to parasites by specific steroid hormones (not only sex, but also adrenal ones) and 2) by a direct effect of both type of hormones on the parasites.

It may thus be noted that the benefit of parasites to infect a host of a particular sex largely depends on the circulating steroid levels at the time of infection, and appears as the result of lengthy adaptive trials between host and parasite subjected to the same co-evolutionary process. We consider that the inclusion of the concepts of trans-regulation and sexual dimorphism among the arguments that intend to explain the complex evolutionary relationship between a parasitic and a parasitized organism will lead to a better understanding of the host-parasite relationship.

The mechanisms by which host hormones act on the parasite have recently been investigated and some parasite molecules, which involved in trans-regulation identified and characterized. These include receptors, transporters, steroidogenic pathway enzymes and second messengers, which are synthesized by parasites and allow them to exploit host hormones.

DIRECT EFFECTS OF SEX STEROIDS ON HELMINTHES

Current studies reveals that the sex steroids can influence the course of worm infection [51-55], as they do on infections caused by the cestodes *Taenia crassiceps* and *Taenia solium* [47, 56, 57]. *In vitro* experiments showed that 17-β-estradiol increases the reproduction of *T. crassiceps* parasites, while testosterone or dihydrotestosterone cause the opposite effect [15]. *In vivo* experiments performed with castrated mice and reconstituted with 17β-estradiol, showed that the number of parasites as well as their infective capacity increases up to 200% [31, 47]. Interestingly, castrated mice of both sexes and treated with progesterone has the opposite effect, that means, a decrease in the parasite loads of almost 100% [58]. The effects of progesterone and its antagonist RU486, on scolex evagination, which is the initial step in the development of the adult worm, have been recently shown. The progesterone treatment increased the scolex evagination and worm growth of *T. solium*, in a concentration-independent pattern. In an opposite way, the treatment with RU486, inhibited both scolex evagination and worm development. These results suggest that the progesterone directly acts upon *T. solium* cysticerci, possibly through its binding to a novel *T. solium* progesterone receptor (TsPR) [59] (Table **1**).

The parasite *Trichinella spiralis* is an intracellular nematode that infects striated muscles of mammalian. It is responsible for trichinellosis, a zoonosis caused by consumption of raw or undercooked meat from infected animals (e.g. pork, game animals) [60, 61]. Trichinellosis is regarded as an emerging or re-emerging disease in some parts of the World (particularly in Eastern Europe and Asia). Consistent with the level of co-evolution evident from parasite adaptation to the host, is the assumption that *T. spiralis* can exploit the hormonal microenvironments within the host [51]. Based on different reports on *Trichinella* infections in murine model of both sexes, a resistance/susceptibility has been suggested. For example, males are generally more susceptible than females to the infection, because mice males present more parasite burden at both intestinal and muscle level than females do [62-64]. Interestingly, when female rats are ovariectomized, the parasite burden in the small intestine and the skeletal muscle are increased compare with the intact females [53], suggesting that female hormones (estrogens and progesterone) are restrictive factors, while androgens are

Table 1. Direct Effects of Sex Steroids on Different Helminth Parasites

Parasite	Effect of Estrogens	Effects of Androgens	Refs
Ancyclostoma caninum	------	T4, increase reproduction	[74]
Echinoccocus granulosus	------	T4, increase development and reproduction	[77]
Mesocestoides cortii	------	T4, increase growth	[78]
Nematospiroides dubius	------	T4, increase viability	[75]
Nippostrongilus brasiliensis	------	------	[76]
Strongyloides sp	E2, decrease infectivity	T4; increase infectivity	[70]
Taenia solium	E2 and P4; increase growth. P4, promotes escólex evagination	T4, DHT: Inhibit growth	[57, 59]
Taenia crassiceps	E2, P4: Increase growth, reproduction, viability and infectivity.	T4, DHT: Decrease growth, reproduction, viability and infectivity.	[16]
Trichinella spiralis	E2 and P4; decrease molting rate	------	[68]

permissive factors for parasite establishment. In that way, sex differences on parasitemia can reflect the suppressive effects of testosterone and the increasing effects of estrogens in the immune system [67], principally on Th2 immune responses in females leading a higher production of interleukins (i.e, IL-4, -5, -6 and -10) [22]. On this regard, it has been reported resistance to *T. spiralis* infections in pregnant rats, which present high levels of progesterone. These infected rats presented less parasite loads in muscle compared to the parasite loads observed in virgin rats. Also, *in vitro* experiments using the sera of the pregnant rats was able to mediate death in newborn larvae (NBL) of *T. spiralis* in antibody-dependent cell cytotoxicity [66]. Moreover, effector peritoneal cells in culture can be activated by addition of progesterone to eliminate NBL in a rapid and antibody-independent manner [67].

Beside the intervention of the host's immune response in dealing with the parasite, the possibility of additional direct effects of sexual steroid hormones on the parasite's physiology should not be hastily discarded. The effects of sex steroids upon the molting process of *T. spiralis* larvae have also been observed [68]. *In vitro* experiments showed that estradiol and principally progesterone has a direct and marked inhibitory effect on molting process in the muscle larvae of this parasite, compared with controls. On the other hand, neither percent molting nor molting rate was modified for any testosterone concentrations. Furthermore, the motility and viability were not affected inpresence of these hormones [68]. Studies at molecular level about the expression of Ts-Cav-1 in the LM, one gene that is implicated in oocyte maturing [69], showed that both estradiol and progesterone decreased its expression level. This observation results important because suggests that the LM of *T. spiralis* could modify the expression of specific genes through steroid receptors similar to those found in other invertebrates [48, 70]. The two phenomenon described above could explain the resistance/susceptibility observed in this infection; first, the effect of the female sex steroids on the immune response generated against the parasite, and second, the direct effect of the female hormones in the parasite's physiology that could avoid the normal rate of molting process during the development of LM to adult parasite which in turn directly impacts in the potential of adult female that release NBL.

All together these findings may represent a new interesting approach on *Trichinella* infections, because if that sex-steroids can specifically down-regulate genes involved in the growth, development, fecundity and oogenesis of the parasite, we can propose the use of sex-steroid to inhibit the infection or even modulate the host's immune response to eliminate effectively the parasite.

There have been many reports showing that under the influence of androgens, there is an increased number of larval stage or adult worms in the gut or other systems of the vertebrate host. It has been shown that male mice are less resistant to nematodes like *Strongyloides* sp [71] than females; while administration of potent estrogenic compounds as estradiol increased resistance to the parasite [71-73]. For instance, *Ancyclostoma caninum* in the mouse gut has better growth and an increased number of eggs when the host is injected with testosterone [74]. *Nematospiroides dubius* augments the number of viable larvae in the gut of the rat in response to testosterone [75] and *Nippostrongilus brasiliensis* has the same response to androgens in the hamster gut [76]. Even the larval development of intestinal cestodes is accelerated by testosterone, as can be deduced from findings showing an increased number of hydatid cysts of *Echinoccocus granulosus* [77] and an enhanced growth of

tetrathyridial populations of *Mesocestoides cortii* in the mouse [78].

All these evidence appoint, that the direct effects of host's hormones upon helminth parasites (cestodes, nematodes and trematodes) are not unusual (Table **1**). Actually, some results suggest that parasites are not only are directly affected by hormones, but they have also developed strategies to exploit the host's endocrine microenvironment [3, 4, 79], which include: degradation of host proteins as an alternative source of aminoacids [6], development of parasitic-sex steroid receptors [7, 80], and cross-activation of signal transduction pathways [81-82].

STEROID RECEPTORS IN HELMINTH PARASITES

The study of parasite genomic mechanisms is very limited. However, more than one line of investigation is currently in progress to determine if parasites possess classical nuclear receptors and if these putative receptors have the capacity to bind host hormones to direct the downstream transcriptional events. In this context, a "specific retinol and retinoic acid-binding proteins" has been characterized in *Onchocerca volvulus, O. gibsoni, Dipetalonema vitae, Brugia pahangi* and *Dirofilaria immitis*. These proteins have the ability to bind host hormones and mediate the biological effects on parasites including growth, reproduction and differentiation [83]. Also, analysis on the genome of *O. volvulus* showed that this parasite has at least three classical nuclear receptors [84]. Two of these receptors named OvNR-1 and OvNR 2, are similar to the retinoid receptors characterized in vertebrates as well as to the *Drosophila melanogaster* protein EiP78c. Additional computer modeling analysis suggests that these molecules possess an appropriated molecular conformation on size and form capable of binding to a steroid [84-85]. In *S. mansoni,* was reported the presence of receptors capable of binding to 17β-estradiol [48], moreover, classical nuclear receptors to steroids, thyroid hormones and ecdisteroids have also been characterized [86]. Interestingly, the homology reported between these receptors and those described in *Drosophila*, mouse and human ranges from 70 to 95% [86]. In the case of the helminth parasite *Taenia crassiceps*, we have shown that cysticerci expressed a classic estrogen receptor, but there is no expression of progesterone receptor [15]. It appears that the direct *in vitro* effects of estrogens upon *T. crassiceps* reproduction are due to the binding of estradiol to its respective receptor. The small effects of progesterone observed in the apparent absence of its specific receptor could be due to non-conventional nuclear receptors, or merely reflect its transformation to estradiol as previously shown for androgens [87]. Binding of the ER to the classic estrogen-dependent elements could be responsible for the activation of AP-1 complex genes in the normal metabolism of *T. crassiceps* [88]. On the other hand, rapid action or non-genomic mechanisms have been explored more prolifically than mechanisms involving the presence of a classical nuclear receptor. However, this apparent advantage is only relative because the first reports indicating that host hormones may activate cascades of second messengers only appeared at the beginning of this century [6, 7, 9, 89]. The presence of a complete signaling cascade that corresponds to the Raf kinases has been determined in *Brugia malayi* [9]. Murine EGF increases transcription of Raf kinase and Ran, a nuclear GTPase in *B. malayi* and has been demonstrated to promote phosphorylation of some microfilarial proteins. Besides, physical interaction increases between Ran and other proteins yet to be defined and promotes phosphorylation of some proteins of microfilarial origin. The presence of a receptor (SmRTK-1) with tyrosine kinase activity in *S. mansoni* has been determined. Preferential localization of SmRTK-1 in sporocysts and oocysts could favor differentiation and growth processes in this parasite [90] considering that receptors with tyrosine kinase activity typically control metabolic, growth and development aspects. Recent studies show that *Schistosoma haematobium* synthesizes a protein of 28 kDa (Sh28GST) capable of binding to testosterone and facilitating transport, metabolism and physiological action of this hormone in the parasite [7].

CONCLUSIONS

Here, we describe different effects of sex steroids that probably have different action mechanisms during helminth infections: 1) by modulating the immune response to the parasites and 2) directly upon the parasite's physiology. These effects of sex steroids could explain, at least partially, the differences in parasite burdens observed on several helminthes infection between males and females, in pregnant and in non-pregnant hosts, and in other specific physiological conditions in which sex-steroids are involved. To our knowledge, this is the first review where sex-steroids effects are discussed upon helminth infections. These effects described for sex steroids open a promissory field in the design of new strategies that include the anti-hormone therapy for the control of several infection diseases caused by helminth parasites.

CONFLICT OF INTEREST

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

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