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The Role of Sex Steroids
in the Host-Parasite Interaction

Karen Nava-Castro[1], Romel Hernández-Bello[2],
Saé Muñiz-Hernández[3] and Jorge Morales-Montor[2]
*[1]Departamento de Infectología e Inmunología,
Instituto Nacional de Perinatología, Secretaria de Salud
[2]Departamento de Inmunología, Instituto de Investigaciones Biomédicas,
Universidad Nacional Autónoma de México
[3]Subdirección de Investigación Básica,
Instituto Nacional de Cancerología, Secretaria de Salud
México*

1. Introduction

In this Chapter, we intend to review and discuss the current literature, and the state of the art related to the role that sex steroids play in the complex host-parasite relationship, particularly during *Taenia crassiceps* and *Taenia solium* cysticercosis. It is well known that sex-steroids regulate a variety of cellular and physiological functions of organisms such as growth, reproduction and differentiation. More recently the ability of sex steroids to affect the immunological response directed against pathogenic agents, and importantly the direct effect of these molecules on these organisms, have gained attention. These effects are clearly evident during various parasitic diseases including malaria, schistosomiasis, toxoplasmosis, cysticercosis, trypanosomiasis and leishmaniasis, where strong steroid hormone regulation of the immune response, has been described (Remoué et al., 2001; do Prado et al., 1998; Satoskar & Alexander, 1995; Vargas-Villavicencio et al., 2006; Libonati et al., 2006; Liesenfield et al., 2001). For instance, sex steroids play a significant role in regulating the parasite load in experimental intraperitoneal *Taenia crassiceps* cysticercosis of male and female Balbc/anN mice. Briefly, estrogens increase parasite loads and androgens decrease them (1) by acting directly on the parasite, favoring or hindering its reproduction, respectively, and (2) by biasing the hosts' immune response towards a parasite-permissive Th2 or a parasite-restrictive Th1 response. Recent experimental evidence, suggests that either steroids hormones may exert their effects directly upon the parasite, which may be able to exploit the host hormonal microenvironment for its exclusive benefit. The fact that steroids can directly influence parasites has been described in at least 17 different species of helminths and protozoan with medical and veterinary relevance. Briefly, we detail some of the most important experimental evidence about direct effects of steroid upon parasites. In fact, the hormonal microenvironment inside an immunocompetent host is so important, that experimental evidence suggests that an inadequate hormonal environment may lead to apoptosis of crucial parasite cells, as has been proposed in some parasites (e.g., retinoic acid

has been shown to affect female *Litomosoides carinii* and microfilariae of *L. carinii, Brugia malayi, B. pahangi* and *Acanthocheilonema viteae*) (Zahner et al., 1989). In the same sense, *in vitro* experiments have shown that testosterone negatively affects fecundity in *Schistosoma. haematobium* adult worms (Remoué et al., 2002). Interestingly, this hormonal microenvironment also modulates the gene expression of female and male *S. mansoni* adult parasites. This finding may represent an interesting approach, because if we know that sex-steroids can specifically down-regulate genes involved in the fecundity and oviposition of *S. mansoni* and *S. haematobium*, we can propose the use of sex-steroid analogues to modulate this effect (Barrabes et al., 1979). Finally, parasites have developed diverse mechanisms of survival within the host, which facilitate the establishment of infection. These can be grouped into two types: those in which the immune response is evaded by strategies such as antigenic variation and molecular mimicry 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. 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 (Shibayama et al., 2003). Other pathogens, including *Chlamydia trachomatis* and *Coxiella burnetii* have developed molecules that directly of interfere with antigen processing and presentation (Brodsky et al., 1999). 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. Recent experimental evidence 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.

In view of this evidence, it is clear that the endocrine system, particularly sex steroids, not only influences the course of parasitic infection by the modulation of the immune system, but can also be directly exploited by parasites. In this way host hormones, by means of genomic and non-genomic mechanisms, regulate important parasite processes such as growth, differentiation and reproduction, through a mechanism described as trans-regulation. This mechanism allows the parasite to accomplish a more successful infection.

Comprehension of these concepts, as well as the study of sex steroid receptors and of those that regulate the activity of various second messenger cascades in parasites opens interesting research perspectives in the complex host-parasite evolutionary relationship. Reports on nuclear receptors in parasites are extremely scarce and to date have only been described in six parasites. However as more parasite genome projects reach completion, evidence for these receptors in other parasites is likely to grow. The ability of a parasite to differentially affect a female or a male of the same species (sexual dimorphism of an infection) can be due to hormonal regulation of the immune response or direct hormonal affects on the parasite. Understanding the contribution of each of these and characterization of the parasite molecules involved may facilitate the development of drugs that counteract the effects of hormones on the immune system or the parasite.

The relationship between parasites (P), particularly helminthes, and their hosts (H) implies biochemical co-evolution and communication between their complex physiological and metabolic systems among themselves and with the environment, at all levels of biological organization. Hormones are known to regulate a variety of cellular and physiological functions of organisms such as growth, reproduction and differentiation (Verthelyi, 2001).

Hormones and immune actors are prominent in H-P relationships (Klein, 2004). The comparatively sophisticated immune systems of vertebrates add complexity to H-P interactions. Mammals sense and react with their innate and acquired immunological systems to the presence of a parasite and the parasite is also sensitive and reactive to the host's immune systems effectors. Host's hormones are also involved in the modulation of the immune system's protective or pathogenic functions and also on the parasite's metabolism and reproduction (Roberts et al., 2001; Escobedo et al., 2005). Host's adrenal hormones are well known immune modulators (Tait et al., 2008), whilst sex steroids (estradiol, progesterone and testosterone) are progressively being recognized to also significantly affect the immune system's functions (Bouman et al., 2005; Verthelyi, 2001). More recently the ability of hormones to affect, the immunological response directed against pathogenic agents has gained attention (Roberts et al., 2001).

2. 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 (Derijk & Berkenbosh, 1991; Grossman et al., 1991). More recently the ability of sex steroids to affect the immunological response directed against pathogenic agents has gained attention (Klein, 2004; Roberts et al., 2001; Escobedo et al., 2005). This is clearly evident during various parasitic diseases including malaria, schistosomiasis, toxoplasmosis, cysticercosis, trypanosomiasis and leishmaniasis where strong hormonal regulation of the immune response has been described (Remoue et al., 2001; do Prado et al., 1998; Satoskar & Alexander, 1995; Vargas-Villavicencio et al., 2006; Libonati et al., 2006; Liesenfield et al., 2001). 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) (Angioni et al., 1991). 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 (Besedovsky & del Rey, 2002).

It may thus be inferred that, in addition to their effects on sexual differentiation and reproduction, sex hormones may also determine the differences between the sexes regarding their immune response to the same antigenic stimulus. These differences include sexual dimorphism of the immune response as well as dimorphism associated to infection parameters (Bouman et al., 2005; Morales-Montor et al., 2002b; Zuk & McKean, 1996).

Besides their effects on sexual differentiation and reproduction, sex steroids (estradiol, progesterone and testosterone) can influence the immune system by affecting differently many of the functions of virtually all-immune cells types (Muñoz-Cruz et al., 2011). In fact, sexual hormones modulate a large variety of phenomena involved in the immune response, including thymocyte maturation and selection, cellular transit, lymphocyte proliferation, expression of class II major histocompatibility complex molecules and receptors, and cytokine production (Bebo et al., 2001; Da Silva, 1999). Furthermore, the presence of sex steroid receptors on immune cells (Muñoz-Cruz et al., 2011) indicates that one mechanism

by which sex steroids may exert their biological effects involves interactions with either cytoplasmic or nuclear receptors. For these hormones to have an effect on immune system cells, the presence of hormone receptors in these cells is necessary. Although steroid hormones also exert effects by non-genomic mechanisms by 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. The following NR are mediators of these effects: estrogen receptors (ER) and androgen receptor (AR); the estrogen receptors ER-α and ER-β, each coded for by an individual gene, whose predominating ligand is 17β-estradiol; progesterone receptor (PR), which has variants A and B generated from the same gene by alternative splicing, and whose main ligand is progesterone. Androgen receptors (AR), coded for by a single gene and its ligands being testosterone and dehydrotestosterone (DHT). In fact, the binding between estradiol (E_2) and its membrane ER activates group I and II of the metabotropic glutamate receptor (Boulware et al., 2005). It should here be mentioned that ER is able to bind to Src kinases through their highly conserved SH2 domains, which could considerably modify the effect of ERK 1/2 on the phosphorylation pattern of this transcription factor (Auricchio et al., 2008). Recently, three new putative membrane progesterone receptors (mPRs), mPRα, mPRβ, and mPRγ have been described and detected also on T lymphocytes (Dosiou et al., 2008). The mechanism of action of these membrane progesterone receptors is suggested to be through G_i-protein activation. 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 (PLC) 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 (Benten et al., 1999). 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.

3. Sex steroids and immune response to helminthes parasites

Sexual dimorphism (SD) in parasitic infections it is a scarcely studied biological phenomenon of considerable significance for individual health as well as for the evolution of species. Most of the poor knowledge about this topic is related to the wrong concept of the female supremacy in infectious diseases. However, there are many notable exceptions to this rule of a favorable female bias in susceptibility to infection. 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. 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 (Verthelyi, 2001).

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 amounts to the parasite exploiting endocrine mechanism developed by the host for its own advantage. 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.

4. The case of Cestodes

Cestoda is the class of parasitic flatworms, commonly called tapeworms that live in the digestive tract of vertebrates as adults and often in the bodies of various animals as juveniles. There are two subclasses in class Cestoda, the Cestodaria and the Eucestoda. By far the most common and widespread are the Eucestoda, with only a few species of unusual worms in subclass Cestodaria. The cyclophyllideans are the most important to humans because they infect people and livestock. Two important tapeworms are the pork tapeworm, *Taenia solium*, and the beef tapeworms, *T. saginata* (Morales-Montor et al., 2004). Taennids, particularly *Taenia solium* (causal agent of porcine cysticercosis and human neurocysticercosis) and *Taenia crassiceps* (causal agent of murine cysticercosis) are highly evolved parasites that have developed diverse mechanisms of survival that facilitate their establishment in the hosts. Taennids can also exploit the hormonal microenvironment within the host in their favor (Escobedo et al., 2005; Locksley, 1997). Taennids have evolved structures similar to the steroid and protein hormone receptors expressed in upper vertebrates, with binding properties and terminal effects similar to the hormonal metabolites synthesized by the host (Damian, 1989; Salzet et al., 2000). In the next paragraphs, we summarize the findings on the role of sex steroids in two cestodes: *Taenia crassiceps* and *Taenia solium*.

4.1 Experimental *T. solium* Taeniosis/cysticercosis

T. solium is an ancient parasite that still threatens public health and porcine husbandry in Latin America, Africa and Asia, and is re-emerging in developed countries on account of the massive human migrations of modern times (Hoberg, 2002; DeGiorgio et al., 2005; Sorvillo et al., 2011). Cysticercosis results from the ingestion of the *T. solium* eggs by intermediate hosts (humans and pigs, principally), to then hatch in the intestines liberating motile oncospheres that penetrate the circulation and distribute in the organism. Oncospheres may establish in muscles, subcutaneous connective tissue, central nervous system, liver, and other organs of the host, where they develop into cysticerci, the larvae of *T. solium* contained within a vesicular translucent structure of about one cm in size (Sciutto et al., 2000). Once developed, many cysticerci die leaving scar tissue or nodular calcifications, while others live-on causing chronic and severe organic malfunction because of space-occupation and/or local inflammation, especially when located in the brain of the human intermediate host. Humans are also the only definitive hosts of the intestinal adult tapeworm, the stage in which the parasite is capable of sexual reproduction and of massive egg production. Pigs are nowadays the preferred intermediary host for the *T. solium*'s larval stage (i.e., cysticercus), a necessary

stage in the parasite´s life cycle before its eventual transformation into an adult tapeworm upon their ingestion by humans in infected and uncooked pork meat.

Host's sexual dimorphism in *Taenia solium* infections is much less obvious than that of experimental *Taenia crassiceps* cysticercosis in laboratory mice. Nonetheless, there are various hints pointing in that direction and several speculations as to the reasons behind such low profiles of sexual differences in cysticercotic pigs and humans. Human's immunological contact with any of *T. solium*'s developmental forms is likely to induce an immune response. The high mean prevalence of seropositive individuals in the open population of Mexico (~1%) (Larralde et al., 1992), when compared with the presumed prevalence of neurocysticercosis (~0.1 to 10%) (Fleury et al., 2003; 2006), is taken to indicate that very few of the contacts result in the establishment of the cysticercus in the tissues of humans and less so in their brains. In view of the many weaknesses of such numbers and assumptions lacking the objective finding of the parasite in the suspected human cases it's somewhat adventurous to interpret them as signs of sexual dimophism in human disease, even if significant differences in serological prevalence favor women over men in Mexico (Larralde et al., 1992). The more so if no credible prevalence differences of neurocysticercosis were supported by necropsy studies (Rabiela et al., 1982). Nonetheless, there are other findings indicating to sexual dimorphism among human neurocyticercotic patients. Women develop more frequently generalized encephalitis than men and, when bearing subarchnoidal and ventricular vesicular parasites, women show higher inflammatory profiles in their cerebral spinal fluid than men (Del Brutto et al., 1988; Fleury et al., 2004). However, in those same patients there were no other immunological signs of sexual dimorphism (Chavarria et al., 2005). Also, in Peru, it was reported that subjects included a newly devised anti-helminth treatment protocol were mostly women highly suspected of carrying an adult *T. solium* in their intestines. Likewise, women were recently reported to harbor more single cysticercotic calcified lesions in their right cerebral hemisphere than in the left. Presumably, lateralization of calcified cysticerci reflects the differential immunological abilities between the cerebral hemispheres (Meador et al., 2004). Although no sexual differences in these cerebral abilities have been notified, cysticercus lateralization is not found in male neurocysticercotic patients. Gender discriminatory practices in health services also throw shadows upon morbidity and mortality differences between women and men in Mexico: men request more frequently medical attention at hospitals than women do, yet they have similar mortality rates in the many diseases not in close association with genital organs, including infections. It would then follow that Mexican women more frequently resort to informal consult and therapy of their ailments than men do, thus defaulting from morbidity data and appearing for consult in the final stages of disease. Notwithstanding the many sex and gender associated biological and social biases involved, the findings of sexual dimorphism in cysticercotic humans should not be confidently dismissed.

Sex steroids play an important role during *T. solium* infection, particularly progesterone has been proposed as a key immunomodulatory hormone involved in susceptibility to human taeniosis in woman and cysticercosis in pregnant pigs. Then, we evaluated the effect of progesterone administration upon experimental taeniosis in hamsters (*Mesocricetus auratus*). Intact female adult hamsters were randomly divided into 3 groups: progesterone-subcutaneously treated; olive oil-treated, as the vehicle group; and untreated controls. Animals were treated every other day during 4 weeks. After 2 weeks of treatment, all hamsters were orally infected with 4 viable *T. solium* cysticerci. After 2 weeks post infection, progesterone-treated hamsters showed reduction in adult worm recovery by 80%, compared

to both vehicle-treated and non-manipulated infected animals. In contrast to control and vehicle groups, progesterone diminished tapeworm length by 75% and increased proliferation rate of leukocytes from spleen and mesenteric lymph nodes of infected hamsters by 5-fold. IL-4, IL-6 and TNF-α expression at the duodenal mucosa, promoted local exacerbation of inflammatory infiltrate.

The issue of sexual dimorphism in naturally acquired porcine cysticercosis is a bit stronger than it is in human cysticercosis. Male rural pigs castrated 4 months before sacrifice show a cysticercosis prevalence double that of non-castrated male pigs, and so do pregnant sows (Morales et al., 2002; 2006). There is, however, an exposure catch obscuring the reason of such associations: castrated pigs flock around a dominant female that effectively search for foodstus in the open fields whilst sexually active boars are almost wild creatures, roaming around marginally to any flock and are thus presumed to be less well nurtured and less exposed to consuming human feces and becoming infected. Anyways, research is in progress to ascertain if any endocrinological changes in the sex steroids of rural pigs associate with cysticercosis. Moreover, frequency of *T. solium* pig cysticercosis is increased during pregnancy, when there is a significant increase in progesterone levels (Morales et al., 2002; Peña et al., 2007). It has also been demonstrated that castration in naturally infected male boars, induces an increase in the prevalence of cysticercosis, which highlights the possible role of host androgens to restrict parasite establishment and estrogens to facilitate it (Morales et al., 2002).

4.2 Sexual steroids directly act upon *Taenia solium*

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 demonstrated (Escobedo, et al, 2010). Interestingly, progesterone increased *T. solium* scolex evagination and worm growth, in a concentration-independent pattern. Progesterone effects could be mediated by a novel *T. solium* progesterone receptor (TsPR), since RU486 inhibits both scolex evagination and worm development induced by progesterone. By using RT-PCR and western blot, sequences related to progesterone receptor were detected in the parasite. A phylogenetic analysis reveals that TsPR is highly related to fish and amphibian progesterone receptors, whereas it has a distant relation with birds and mammals. Conclusively, progesterone directly acts upon *T. solium* cysticerci, possibly through its binding to a progesterone receptor synthesized by the parasite (Escobedo et al, 2010).

4.3 Experimental *Taenia crassiceps* murine cysticercosis

Due to the intrinsic difficulties in working with the natural hosts (pigs and humans) of *T. solium* or because of the high costs of sufficient pigs plus the slowness in data retrieval, we have used an experimental cysticercosis approach to gain knowledge of the complex host (H) parasite (P) relationship in cysticercosis. Murine intraperitoneal cysticercosis is caused by the taenid *Taenia crassiceps* and it has been useful to explore the physiological host factors associated with porcine cysticercosis, and to some degree, with human neurocysticercosis (Sciutto et al., 2011). Intraperitoneal *T. crassiceps* cysticercosis of mice lends itself well to controlled and reproducible experimentation, generating numerical data of parasite loads in individual mice in a matter of weeks after infection. Its general representation of other forms of cysticercosis has later been strengthened by similar results in other mouse and parasite strains, by the parasite's extensive sharing of antigens with other taennids and cestodes and

by the DNA homology between *T. crassiceps and T. solium* (Rishi & McManus, 1988). These characteristics have made murine cysticercosis a convenient instrument to test vaccine candidates and new drugs or treatments against cysticercosis (Vargas-Villavicencio). Several features of natural cysticercotic disease have been found by extrapolation from experimental murine cysticercosis (Morales-Montor et al., 2008).

4.4 Role of sex steroids in cysticercosis

In *T. crassiceps* cysticercosis, females of all strains of mice studied sustain larger intensities of infection than males, but during chronic infection (more than 4 weeks) this difference disappears and the males of BALB/c strain show a feminization process, characterized by high serum estrogens levels (200 times the normal values) whilst those of testosterone are 90% decreased. The target organs for testosterone action, testes and seminal vesicles, have a 50% weight reduction (Larralde et al., 1995). At the same time, the cellular immune response (Th1) is markedly diminished in both sexes, and the humoral (Th2) response is enhanced (Terrazas et al., 1998). Estradiol is involved in the immunoendocrine regulation of murine *T. crassiceps* cysticercosis as a major protagonist in promoting cysticercus growth interfering with the thymus dependent cellular immune mechanisms that obstruct parasite growth (Terrazas et al., 1994). Gonadectomy alters this resistance pattern and makes intensities equal in both sexes by increasing that of males and diminishing it in females (Huerta et al., 1992), whilst the serum sex steroids level are not detectable in these animals. However, the absence of estrogens does not prevent parasite growth in both genders, demonstrating that although estradiol favours *Taenia crassiceps* development, it is not indispensable for rapid parasite growth (Larralde et al., 1995).

5. Immuno-endocrine interactions in the host

The mechanisms by which sex steroids act upon *T. crassiceps* cysticercus asexual reproduction are two: A) through the host's immune system mediation or/and B) directly through the parasites own physiological systems.

The changes in steroid production of infected male mice were found to associate with an increase in *c-fos* mRNA content in all tissues studied, whereas the *c-jun* mRNA content was increased only in the thymus. The p53 mRNA content was markedly reduced in all tissues of the parasitized animals analyzed, whereas bcl-2 gene expression was abolished only in the thymus (Morales-Montor et al., 1998).

On the other hand, thymic cell analysis performed by flow cytometry showed a diminution in the percent of CD3+CD4+, and CD3+CD8+ subpopulations in the infected mice, suggesting that the increase in estradiol levels of the host could change the expression pattern of several genes that participate in apoptosis regulation in the thymus of male mice during chronic infection with *T. crassiceps* cysticerci, and that estrogens could inhibit the specific cellular immune response to the parasite (Morales-Montor et al., 1998). Previous immunological experiments had led to suspect that estradiol positively regulates parasite reproduction in hosts of both sexes, presumably by interfering with the thymus-dependent cellular immune mechanisms that obstruct parasite growth (Th1) and favoring those that facilitate it (Th2) (Terrazas et al., 1998; Bojalil et al., 1993). A specific shift from Th1 to Th2 immune response in the course of infection was found that coincided with the initial low rate of reproduction that accelerates at later times of infection. The shift is characterized by a marked decrease of

IL-2 and IFN-γ in both sexes, while the secretion of cytokines involved in the specific humoral response (IL-6, IL-10 and IL-4) is enhanced (Terrazas et al., 1998, 1999). Thus, striking differences in susceptibility to cysticercosis between male and female mice may involve the joint action of the immune system and the gonads, both driven by a parasite that is able to change the parasite's restrictive male normal hormonal milieu during chronic infection to a more parasite's permissive female environment.

To strengthen the above notions and in an effort to identify the sex steroids involved we studied the effects of testosterone, dihydrotestosterone, and 17β-estradiol in castrated mice of both sexes infected with *Taenia crassiceps* cysticerci (Morales-Montor et al., 2002a). In this study, we found that castration and treatment with either testosterone or dihydrotestosterone before infection markedly decreased parasite loads in both gender mice, while the treatment with 17β-estradiol increased it in both genders (Morales-Montor et al., 2002a). The specific splenocyte cell proliferation and IL-2 and IFN-γ production were depressed in infected-castrated mice of both genders, while treatment with testosterone or dihydrotestosterone produced a significant cell proliferation recovery and enhanced production of IL-2 and IFN-γ (Morales-Montor et al., 2002a). An opposite effect of the same sex steroids was found on the humoral response: it was unaffected with testosterone or dihydrotestosterone restitution, while the treatment with estradiol in both genders augmented the levels of anti-cysticerci IgG, as well as IL-6 and IL-10 production. These results suggest androgens mediate immune functions, which protect mice from cysticercosis, possibly through the stimulation of the specific cellular immunity of the host (Morales-Montor et al., 2002a).

Immunoendocrine interactions during cysticercosis are the cornerstone of the feminization of male mice. When the infected male mice have an intact immune system, there is an increase in serum estradiol levels and a decrease of those of testosterone and DHT. However, when the immune system is knocked down by total irradiation or neonatal thymectomy, there is no change in the levels of serum steroids in chronically infected male mice, and the levels remain steady between infected and uninfected male mice (Morales-Montor et al., 2001).

The importance of sex-hormones driving the specific immune response during cysticercosis was assessed by administration of Fadrozole (a P450-aromatase inhibitor) in male and female mice to suppress the production of 17β-estradiol (Morales-Montor et al., 2002b). A reduction was found in parasite loads (~70%) in infected mice treated with Fadrozole. The protective effect of the P450-aromatase inhibitor was associated in male mice with a recovery of the specific cellular immune response. Furthermore, it has also been demonstrated that administration of Tamoxifen (an anti-estrogen) produced an 80% parasite load reduction in female mice, and had a weaker effect of 50% in male mice. This protective effect was associated in both sexes with an increase in the mRNA levels of IL-2 (a cytokine associated to protection against cysticerci) and IL-4 (innocuos against infection). Tamoxifen treatment modified 17β-estradiol production in females, while serum testosterone was not affected. However, the expression of the two types of estrogen receptor, ER-α and ER-β, in the spleen of infected mice of both sexes, was decreased by Tamoxifen treatment (Vargas-Villavicencio et al., 2007). The *in vitro* treatment of *T. crassiceps* with Tamoxifen, reduced reproduction and induced loss of motility in the parasite. These results indicate that Tamoxifen treatment is a new therapeutic possibility to treat cysticercosis, since it can act at both senses of the host-parasite relationship: increasing the cellular immune response protective against the parasite and acting directly upon the parasite, reducing its

reproduction and increasing its mortality (Vargas-Villavicencio et al., 2007). Another steroid that was recently tested and found to be implicated in the regulation of the parasite loads during murine cysticercosis is progesterone (P_4). P_4 treatment has a dichotomic effect: if mice of both sexes are non-gonadectomized (intact), P_4 treatment increased parasite loads, possibly through manipulation of the specific cellular immune response, besides the steroid's promotion of parasite reproduction (Vargas-Villavicencio et al., 2005). However, if mice are gonadectomized, P_4 completely decreases parasite loads, an impressive and unprecedented cysticidal effect, the likes of which are absent from other preventive or therapeutic measures (Vargas-Villavicencio et al., 2006). These two experiments suggests that, in intact hosts, progesterone is metabolized to estradiol, that is permissive for parasite reproduction, while in castrated animals, there is an active metabolism of progesterone in the adrenal glands to androgens, resulting in a toxic effect in the parasite growth (Vargas-Villavicencio et al., 2005, 2006). The major steroid produced by the adrenal gland is the androgen dehydroepiandrosterone (DHEA). So, another set of experiments showed DHEA effect on male and female infected mice. DHEA treatment reduced parasite loads by 70 and 80% respectively. In contrast with the common assumption of DHEA as an immuno-stimulatory hormone, the immune responses of our mice was not affected by DHEA treatment (Vargas-Villavicencio et al., 2008). *In vitro*, treatment of *T. crassiceps* cysticerci with DHEA induced an 80% reduction in parasite reproduction, which may partially explain the reduction of parasite loads observed *in vivo* a partial effect suggesting the involvement of other unknown factors in the *in vivo* regulation of parasite loads (Vargas-Villavicencio et al., 2008).

6. Sexual steroids directly act upon *Taenia crassiceps*

Not only do sex steroids regulate parasite loads through the immune response modulation of the host, but also they directly act upon cysticerci reproduction. For instance, it has been shown that E_2 and P_4 *in vitro* treatment stimulates *T. crassiceps* reproduction, while *in vitro* treatment with T or DHT inhibit and even exert a slight toxic effect on the parasite (Escobedo et al., 2004). The possible molecular mechanisms by which sex-steroids affect *Taenia crassiceps* reproduction, imply the presence of estrogen receptors (both α and β isoforms) and androgen receptors, but no progesterone receptors. In addition, once host's E_2 has bound to its parasite estrogen receptor, the active, ligand bound complex would activate the transcription of several *Taenia crassiceps* proliferative genes, such as *c-fos, c-jun* and cyclin D1, and in that way up-regulate parasite growth and reproduction. All this hypothetical molecular mechanism could be interrupted *in vitro* by means of using tamoxifen that is well known for its anti-estrogenic effects (Vargas-Villavicencio et al., 2007), which strongly suggests a genomic action mechanism for 17-β estradiol on the parasite. On the other hand, action mechanism of the androgen is likely different from the found for estrogens and progesterone. Testosterone and DHT likely directly affect parasitic DNA integrity by activating apoptotic mechanism in the cysticercus cells. This experimental finding is not dependent of a nuclear receptor, because flutamide (a well studied and used anti-androgen) did not have effects upon parasite reproduction *in vitro* (Escobedo et al., 2004). These results demonstrate that sex steroids act directly upon parasite reproduction perhaps by binding to receptors closely resembling classic and specific sex-steroid vertebrate receptors (Escobedo et al., 2004) (64).

7. Concluding remarks

The evidence presented above illustrates the complexity and importance of neuroimmunoendocrine interactions during helminth infections, and provides clues to the many other possible mechanisms of parasite establishment, growth and reproduction in an immunocompetent host. Further, strong neuroimmunoendocrine interactions may have implications in the control of transmission and treatment of several parasitic diseases, but particularly in those produced by helminth parasites, in animals and humans. In practical importance, the complexity of the helminth-host relationship suggests that all physiological factors (i.e., sex, age) should be taken into account in the design of vaccines and new drugs. The differential response of helminthes to sex steroids may also be involved in their ability to grow faster in female or male hosts. Host and parasite sex-associated biases may be combined to favour their evolution towards a mutually acceptable relationship. Also, the strong immune-endocrine interactions observed during *Taenia crassiceps* and *Taenia solium* cysticercosis, could give ways to possible new mechanisms of parasite establishment, growth and reproduction in an immunocompetent host.

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9. References

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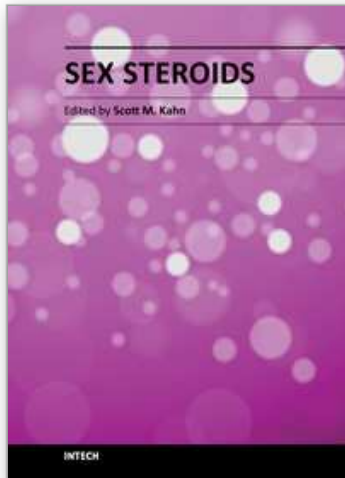
This book, entitled "Sex Steroids", features a valuable collection of reviews and research articles written by experts in signal transduction, cellular biology, diseases and disorders. "Sex Steroids" is comprised of four sections, "The Biology of Sex Steroids", "Sex Steroids, Memory, and the Brain", "Sex Steroids and the Immune Response", and "Therapy"; individual chapters address a broad range of recognized and predicted functions and applications of sex steroids. "Sex Steroids" is intended to provide seasoned veterans as well as newcomers to this area of research with informative, resourceful, and provocative insights. Readers of "Sex Steroids" should emerge with an appreciation and understanding of the multitude and complexity of biologic processes attributed to these important hormones, and possible future directions of research in this fascinating and ever evolving field.

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