Parasite Immunology, 2006, **28**, 667–674 DOI: 10.1111/j.1365-3024.2006.00906.x

Gonadectomy and progesterone treatment induce protection in murine cysticercosis

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SUMMARY

The effects of progesterone on castrated mice of both sexes infected with Taenia crassiceps *cysticerci were studied. Gonadectomy and treatment with progesterone before infection decreased parasite loads by 100% compared with intact uninfected mice. mRNA levels of IFN-γ and IL-2 (typically associated to Th1-like profiles) were markedly decreased in infected gonadectomized (Gx) mice, whereas progesterone treatment of infected Gx mice did not affected its expression. mRNA levels of IL-4, and IL-10 (typically associated with Th2-like profiles) were reduced by gonadectomy, whereas restitution with progesterone did not affected this pattern in infected Gx progesterone-treated mice. Infection markedly induced expression of progesterone receptor isoform A in splenocytes of Gx mice (5-fold), whereas isoform B had no changes. Progesterone metabolism to dehydroepiandrosterone (DHEA) in Gx animals was increased 3-fold only in infected progesterone-treated uninfecteds of both sexes, but was not detectable in infected Gx progesterone-treated mice. Conversely, DHEA levels increased 100-fold in infected Gx progesterone-treated mice. However, androgen receptor expression in splenocytes of male mice showed a reduction by gonadectomy, and by infection, whereas in females AR expression showed no changes in the different mouse groups. These results suggest that progesterone, through its metabolism to DHEA, negatively affects the establishment, growth, and reproduction of* Taenia crassiceps, *by a mechanism that does not implicate a classic genomic pathway involving a nuclear androgen receptor.*

Keywords *cysticercosis, DHEA, immunoendocrine, metabolism, progesterone*, Taenia

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Received: 30 January 2006
Accepted for publication: 1 June 2006

INTRODUCTION

The reciprocal endocrinological interactions between host and parasite are receiving increased attention (1). Specifically, the course of murine and porcine cysticercosis is shown to be influenced by the function of the neuroendocrine system of the host (2). It was previously thought that the parasite simply defended itself in the face of a hostile host environment. However, new understandings implicate the host–parasite interaction in a more dynamic interplay, wherein the parasite exploits host homeostatic mechanisms for survival, maturity, and transmission. These homeostatic mechanisms involve the complex interaction of the endocrine and immune systems (3).

Experimental intraperitoneal murine cysticercosis is also well known as a source of cross-reacting antigens useful in immunodiagnosis of human cestode disease (4,5,6), and as a practical model to test candidate vaccines against porcine *Taenia solium* cysticercosis (7,8,9). It is also a manageable experimental system designed to explore the role of biological factors involved in host susceptibility (10,11,12). Murine cysticercosis has progressively revealed the complexities of the interactive network between the immunological and endocrinological systems of the host and of the parasite in regulating infection (13,14).

For a brief period, a notably significant sex-associated susceptibility to *T. crassiceps* cysticercosis occurs in mice where females of various strains bear larger parasite loads than males during early infections (15). After 4 weeks of infection, the parasite loads of males increase progressively and approach the massive levels of females in a few months (16). Concomitantly, a feminization process ensues in the chronically infected male mice: serum 17β-estradiol (E_2) levels increase to reach those of females, while testosterone (T) drops to 10–15% of its normal levels (13,16,17).

The feminization process also coincides with a specific shift from TH1 (protective) to TH2 (innocuous) immune responses in the infected host, 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 is enhanced (IL-10 and IL-4) (18). Castration and treatment

with either testosterone or dihydrotestosterone before infection markedly decreases parasite loads in both genders, whereas treatment with 17β-estradiol increases it in both genders. Specific splenocyte cell proliferation and IL-2 and IFN-γ production are depressed in infected-castrated mice of both genders, whereas treatment with testosterone or dihydrotestosterone produces significant cell proliferation recovery and enhanced production of IL-2 and IFN-γ. The humoral response has an opposite effect. It is unaffected by testosterone or dihydrotestosterone restitution, whereas treatment with estradiol of both genders increases the levels of anti-cysticercus IgG, and of IL-6 and IL-10 production (19,20).

Based upon these studies, it is clear that sex steroids can regulate parasite loads mechanistically through their reciprocal interactions with immune mechanisms, but in addition, they can also act directly upon the cysticercus. Thus, it has been previously reported that estradiol, and progesterone to a lesser extent, stimulate *in vitro T. crassiceps* bud production, DNA synthesis and ^{3}H-thymidine uptake. Conversely, testosterone and dihydrotestosterone (DHT) are slightly inhibitory and even exert a pathogenic effect on the parasites (21).

Most studies, including those in *T. crassiceps*, have examined the effect of sex hormones (oestrogens and androgens) on the establishment of helminths in the host and little information is available regarding other hormonal influences (22). Typically, increased concentrations of progesterone down-regulate immune cell functions, whereas reduced progesterone concentrations up-regulate them (23). It has been demonstrated that progesterone treatment in intact mice, through its metabolism to estradiol, positively affects establishment, growth and reproduction of the helminth parasite *T. crassiceps* (24). However, in this study the effects of progesterone were masked because host gonads bio-converted progesterone to estradiol, and parasite load encumberment was attributed to estradiol, not progesterone.

To investigate the effect of progesterone solely, we castrated animals of both sexes, treated them with progesterone, and investigated how whole parasite counts relate to the host humoral and cellular immune response, to the expression of sex hormone receptors in splenocytes, and to the host's hormonal status in infected gonadectomized mice. Interestingly, although these infected mice have no gonadal tissue, our results point to a positive control of the infection by progesterone metabolism to DHEA in the adrenal glands.

MATERIALS AND METHODS

Mice and experimental infections

Six-week-old BALB/c AnN mice of both sexes were used in this study. They were fed with Purina Diet 5015 and water *ad libitum*, and the light–dark cycle was set at 14 h light: 10 h dark. The fast growing ORF strain of *Taenia crassiceps* isolated by Freeman in 1962 (25) was used to infect the mice of all experiments. Larvae for experimental infection were obtained from female donor mice infected 3–6 months earlier. Ten small (approximately 2 mm diameter) non-budding *Taenia crassiceps* larvae were suspended in 0·3 mL of PBS (0·15 M NaCl, 0·01 M sodium phosphate buffer, pH 7·2) and injected intraperitoneally into 42-day-old mice using a 0·25 gauge needle. After an 8-week period of infection, mice were sacrificed by cervical dislocation after deep pentobarbital anaesthesia, and all cysticerci found inside the peritoneal cavity were counted. A complete parasite count was obtained visually from each mouse after sacrifice and subsequently parasites were collected after thoroughly rinsing with PBS. Parasites were never found outside the peritoneal cavity.

Animal care and experimentation practices at our institute are frequently evaluated by the University Animal Care and Use Committee and by governmental agencies to ensure compliance with established international regulations and guidelines.

Hormonal treatments

Subcutaneous 60-day-release progesterone pellets (5·0 mg) or vehicle (5·0 mg) were introduced using a precision trochar (10 gauge needle; Innovative Research of America, Toledo, Ohio). After a week of steroid treatment, mice were infected as described above. The effects of progesterone upon parasite loads and immunological parameters were measured 8 weeks after infection.

Gonadectomy and hormonal treatments

Four-week-old mice of both sexes were Gx under pentobarbital anaesthesia (100 μL of pentobarbital plus 900 μL of PBS), as previously reported (20). Mice were then allowed a one-week recovery period before progesterone treatment. After another week of steroid treatment, mice were infected as described above. The effects of progesterone upon parasite load were then recorded as described.

Serum steroid levels

Blood for steroid determinations was collected by cardiac puncture, performed in mice under deep anaesthesia. After incubation for 5 h at room temperature, and 18 h at 4°C, the blood clot was centrifuged and serum was obtained. Steroids were ether-extracted and solubilized in buffer and then used for immunoassay. Progesterone, and dihydrotestosterone sulphate (DHEA-S) concentrations were determined by

liquid-phase kinetics enzyme immunoassay kits (Diagnostics Laboratory Inc., Webster, TX), according to the manufacturer's instructions. After reactions were developed, the samples were read at 450 nm in an ELISA reader.

RNA extraction

Total RNA was isolated from testes, uterus (positive expression uninfected tissues for sex steroid receptors) and splenocytes of uninfected, infected, vehicle Gx uninfecteds, vehicle infected Gx, infected Gx and Gx progesterone-treated *T. crassiceps*-infected mice by the extraction method using TRIzol reagent (Gibco-BRL, NY, USA). Briefly, each tissue was removed and immediately disrupted in TRIzol reagent (1 mL/0·1 g tissue), and 0·2 mL of chloroform were added per ml of TRIzol. The aqueous phase was recovered after 15 min centrifugation at 2500 *g* RNA was precipitated with isopropyl alcohol, washed with 75% ethanol, and re-dissolved in RNAse-free water. RNA concentration was determined by absorbance at 260/280 nm and its purity was verified after electrophoresis in 1·0% denaturing agarose gel in the presence of 2·2 M formaldehyde. Total RNA from all extracted tissues was reverse transcribed followed by specific PCR amplification of the IL-2, IL-4, IL-10, IFN-γ, PR-A, PR-B, AR and β-actin gene sequences.

IL-2, IL-4, IL-10, IFN-γ, PR (A and B) and AR expression in splenocytes

Nucleotide sequences of the primers used for amplification have been previously reported (24). Briefly, 5 μg of total RNA from each tissue was incubated at 37°C for 1 h with 400 units of M-MLV reverse transcriptase (Applied Biosystems, Boston MA) in 1·25 μg of reaction volume containing 50 mM of each dNTP and 0·05 μg oligo (dt) primer (Gibco, NY). Ten μL of the cDNA reaction were subjected to PCR in order to amplify specific sequences of the specified genes. The 50 μL PCR reaction included 5 μL of previously synthesized cDNA, 25 μL of 10x PCR-buffer (Biotecnologías Universitarias, México), 1 mM MgCl, 0·2 mM of each dNTP, 0·05 μM of each primer, and 2·5 units of Taq DNA polymerase (Biotecnologías Universitarias, México). Twenty μL of the total PCR reaction products of each sample were electrophoresed on 2% agarose gel. PCR products were visualized by staining with ethidium bromide. A single band was detected in all cases, as expected. In order to determine if all amplified genes as well as the constitutively expressed uninfected gene (β-actin) were in the exponential phase of amplification, and to make sure that changes in expression were not artifactual (such as β-actin being in the stationary phase), we obtained RNA, cycling and temperature curves for each analysed gene.

Densitometric analysis

Hybridization signals were quantified by densitometric scanning of multiple autoradiograms of various exposures and represented as the ratio of the signal from the analysed gene relative to the expression of β-actin, a constitutively expressed gene used as internal uninfected (relative expression). We used the software 'Scion Imagen for windows' (Scion Corp. Release: Alpha 4·0·3·2)

Experimental design and statistical analysis

The experimental design is a four-factorial experiment. The independent variables were (a) treatment: (two levels: progesterone or vehicle) (b) gender (two levels: male, female) (c) infection (two levels: Yes, No) and (d) gonadectomy (two levels: Yes, No). The dependent variables were the number of parasites, serum sex steroids and the expression of PR-A, PR-B, AR and, IL-2, IL-4, IL-10 and IFN-γ in the tissue sample, as measured by the optical density (OD) of the corresponding gel divided by the OD of β-actin in the same tissue sample in the same gel, used as the uninfected gene for amplification technology. The complete design was repeated twice and the tissues used in each experiment at each time of infection were those pooled from five normal or infected mice. Statistical analysis of variance components was performed in the software Prism 2·01 (GraphPad Software Incorporated). When applied, *post hoc* individual contrasts of group means by the ANOVA test used the sum of the residual and four factor interactions variance to test for significant differences.

RESULTS

Parasite growth

Because of the extremely high variation in parasite loads found in murine *T. crassiceps* cysticercosis, we plotted individual parasite burdens found in each mouse after each treatment. Figure 1 shows the individual data of parasite burdens obtained after progesterone treatment in infected Gx mice of both sexes. Although individual variation was noted in the number of parasites, statistical analysis demonstrated that differences were significant when treatments were compared. In uninfected mice, female mice were more susceptible to the infection ($^{**}P < 0{\cdot}01$) than male mice. Progesterone treatment in intact males tripled the number of parasites (from $35{\cdot}8 \pm 16{\cdot}3$ to $122{\cdot}1 \pm 17{\cdot}3$), whereas in intact females the effect was slighter, because it increased parasite load nearly two-fold (from $247{\cdot}1 \pm 97{\cdot}6$ to $394{\cdot}9 \pm 84{\cdot}7$) ($^{**}P < 0{\cdot}01$). Gonadectomy equalized host sex-susceptibility, because both genders harboured a similar number of parasites;

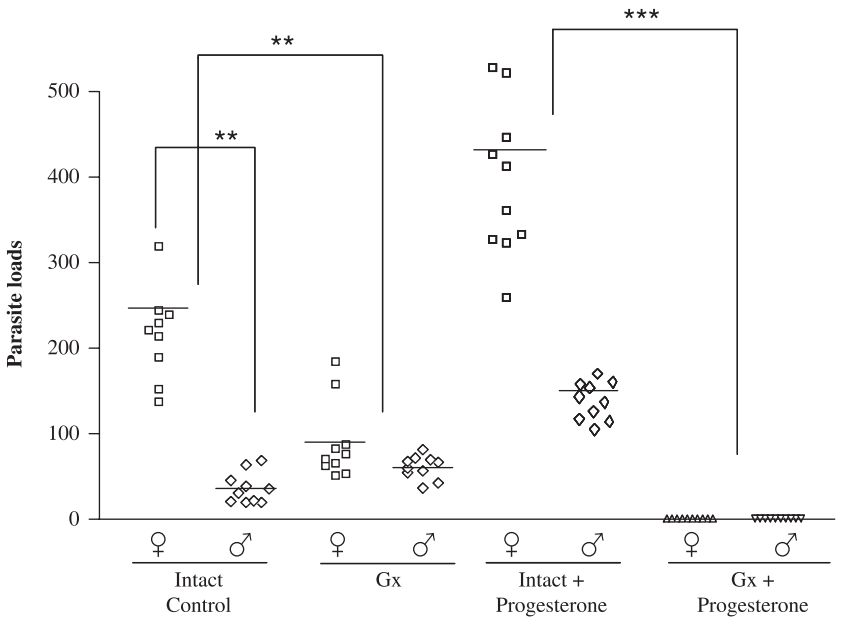

Figure 1 Number of *Taenia crassiceps* cysticerci obtained from the peritoneal cavity of BALB/c AnN mice of both genders after different experimental treatments. Each point represents individual parasite loads of a total of 10 mice. $^{**}P < 0{\cdot}01$ compared with uninfected mice, for both genders. $^{***}P < 0{\cdot}001$ compared with infected and vehicle groups, for both genders.

however, Gx animals treated with progesterone had zero parasites in all animals from either gender (Figure 1).

Serum steroid levels

To create a sex steroid profile, the individual murine levels of progesterone, and DHEA obtained after the different treatments are presented in Figure 2. Progesterone levels decreased by 50% only in female infected mice ($2{\cdot}39 \pm 1{\cdot}07$, $^{***}P < 0{\cdot}001$) compared to uninfected matching uninfecteds ($5{\cdot}20 \pm 1{\cdot}37$). There was no change in the levels of progesterone between uninfected ($0{\cdot}18 \pm 0{\cdot}02$ ng/mL) and infected male mice ($0{\cdot}16 \pm 0{\cdot}05$ ng/mL), both of which had very low circulating levels of progesterone. However, when infected mice of both genders were treated with progesterone, serum levels dramatically increased to reach similar levels in mice of both genders ($4{\cdot}32 \pm 1{\cdot}33$ in females and $4{\cdot}78 \pm 1{\cdot}11$ in males). Interestingly, levels of DHEA in infected Gx progesterone-treated mice also increased three-fold with respect to uninfected Gx and infected Gx mice ($^{***}P < 0{\cdot}001$). Vehicle-treated groups showed similar progesterone and DHEA levels to infected groups (not shown).

IL-4 and IL-10 expression

The profile of the Th1 and Th2 immune responses in infected animals treated with progesterone was measured. Figure 3 shows the splenocyte relative expression of IL-4 and IL-10 obtained from mice of both genders in response to different treatments. IL-4 and IL-10 mRNA levels were markedly decreased in both sexes in response to castration, compared with intact uninfecteds ($^{***}P < 0{\cdot}001$). Progesterone treatment in infected mice of both sexes did not affect the pattern expression of these cytokines. Again, vehicle-treated groups behaved similarly to the infected group.

IL-2 and IFN-γ expression

Figure 4 shows the data obtained for the Th1-type immunity mRNA cytokine profile, associated with protection against infection. Notably, IL-2 mRNA was induced after gonadectomy, because there were no detectable levels of IL-2 in uninfected mice. There were no significant differences in the expression of this cytokine between splenocytes obtained from male and female mice in response to infection, vehicle or progesterone treatment.

Sex steroid receptors expression pattern

In order to amplify classic sex hormone receptors (SHR), we amplified the expression of PR-A and PR-B in splenocytes of normal, Gx, vehicle and infected Gx progesterone-treated mice of both genders. The expression of β-actin was used as internal uninfected. Figure 5 shows the quantification by the OD of PR-A and PR-B expression in male and female mice exposed to different treatments. The OD quotient for PR-A/B/β-actin was calculated for each gender and treatment in relation to uninfecteds for background variation in PCR amplifications at each different experiment replication. The graphs in Figure 5 strongly suggest that the PR-A/β-actin quotient is similar between uninfected, uninfected Gx and progesterone-infected Gx mice of both sexes. However, there

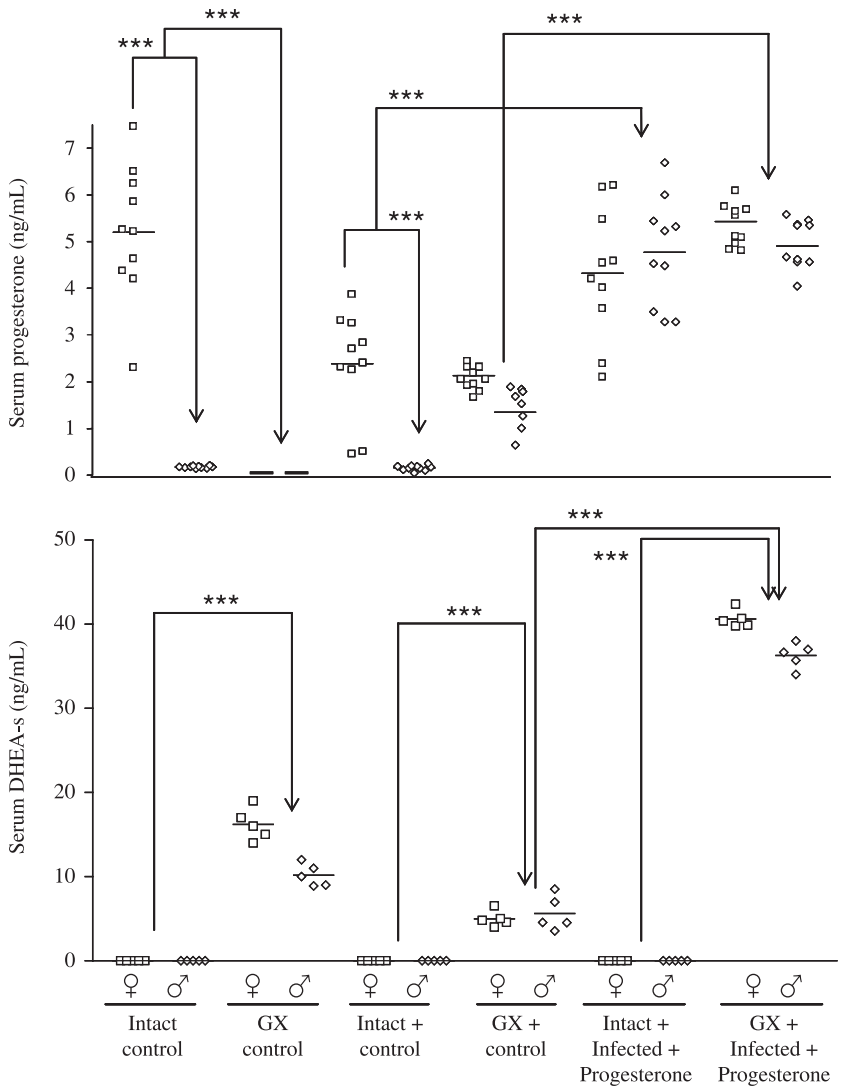

Figure 2 DHEA and progesterone levels throughout the infection course in both genders, compared to differently treated mice. Each serum sample was determined in duplicate of for each mouse. ***$P < 0{\cdot}001$, compared with uninfected mice, for both genders.

is a twofold increase in female and male infected Gx mice compared to all other groups of mice ($P < 0{\cdot}001$). In contrast, in males, PR-B expression showed an increase when both mice genders were gonadectomized, infected and treated with progesterone (Figure 5).

AR expression pattern

The spleen, ovary, uterus, and testes were collected from mice at necropsy, and AR expression was assessed by RT-PCR. The expression of β-actin as internal uninfected was also measured, and found to be constant in all mice, in all studied tissues. Densitometric analysis of the RT-PCR is shown in Figure 6. Relative expression of AR mRNA was higher in splenocytes of male mice ($P < 0{\cdot}01$), but AR mRNA was also expressed in female mice. Castration and infection of both genders decreased the expression of AR in male mice by 50%, while female AR pattern expression remained unaffected. Castrated and infected mice of both genders, as well as infected Gx and progesterone-treated mice of both genders, showed a similar expression pattern for AR mRNA to the Gx-uninfected group. Vehicle-treated groups behaved similarly to the infected group.

DISCUSSION

Experiments involving gonadectomy, thymectomy and whole body irradiation have demonstrated that both the endocrine and the immune systems of mice are involved in parasite load differences between the host sexes (11,13,16). In the present corroborative study, we have found that progesterone treatment in castrated host mice of both sexes protects

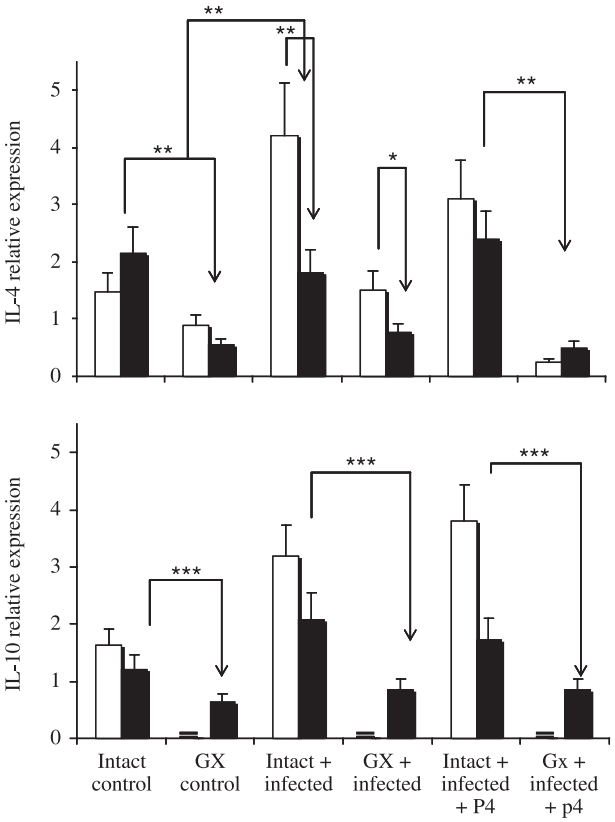

Figure 3 Effect of gonadectomy, infection and progesterone treatment in the expression of IL-4 and IL-10 in splenocytes of mice of both genders infected with *Taenia crassiceps* cysticerci. Data are represented as the mean ± SD of two different experiments ($n = 5$). Each splenocyte culture was performed in triplicate, after an 8-week infection period. $*P < 0{\cdot}05$, $**P < 0{\cdot}01$, $***P < 0{\cdot}001$, all compared to the vehicle group. Open bars represent female mice, while black bars represent male mice.

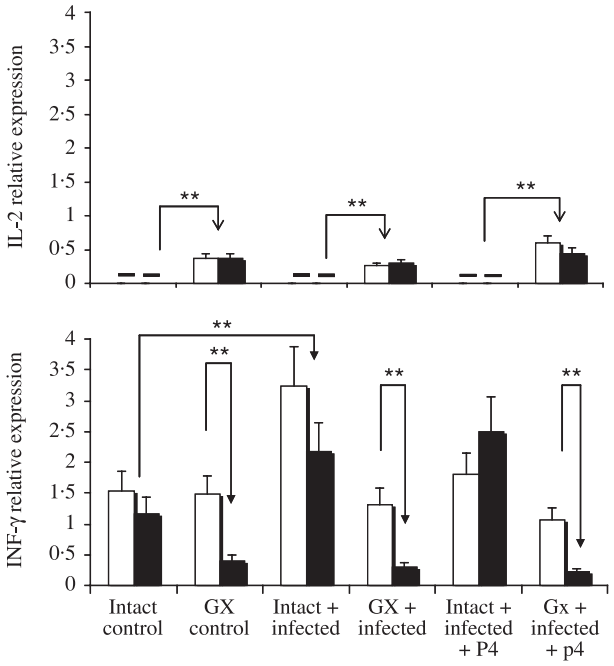

Figure 4 Effect of castration infection and progesterone treatment on the expression of IL-2 and IFN-γ in splenocytes of mice of both genders infected with cysticerci of *Taenia crassiceps*. Data are represented as the mean ± SD of two different experiments ($n = 5$). Each splenocyte culture was performed in triplicate, after an 8-week infection period. $**P < 0{\cdot}01$, both compared to the uninfected group. Open bars represent female mice, while black bars represent male mice.

against infection with *T. crassiceps* cysticerci. Our results demonstrated that castrated male and female mice treated with progesterone were completely protected from parasite burden by comparison to uninfected-infected, infected Gx and vehicle-treated infected mice. These results showed protective levels higher than any yet reported in the literature, including vaccination. Notably, no variation was observed in this experimental system, which otherwise showed large differences in parasite numbers among mice.

The fact that progesterone was being metabolized to DHEA further supports our data that measured progesterone levels were not as high as expected and, by contrast, DHEA levels were greatly increased. Thus, it seems that the observed effects were the result of adrenal conversion of progesterone metabolism to DHEA.

The notion that sex steroids are important biological factors of the host that affect the course of infection has also been previously demonstrated in natural diseases in pigs infected with *Taenia solium*. Recently, it was shown that castration of males doubles the prevalence of naturally acquired *T. solium* pig-cysticercosis from about 25 to 50% (19). This observation suggests an important role for androgens in the susceptibility of pigs to *T. solium* infection. Collectively, these findings support our contention that sex steroids act upon parasite reproduction through an immune interaction with the host. Specifically, androgens (testicular and adrenal) hinder parasite reproduction and estradiol favours the parasite-permissive Th2 immune response which, in turn, down-regulates the parasite-hindering Th1 responses.

The carefully orchestrated events that result in a protective immune response are coordinated to a large extent by cytokines produced by Th1 and Th2 cell subsets. Th1 cells preferentially produce IL-2 and IFN-γ, resulting in a cellular response that helps to eliminate *T. crassiceps* cysticerci. In contrast, Th2 cells produce IL-4 and IL-10, stimulating an Ab response that is not important eliminating this parasite. In cysticercosis, because the influence of gender on immune responsiveness usually becomes apparent after sexual maturity, a crucial role in this process has been attributed to sex

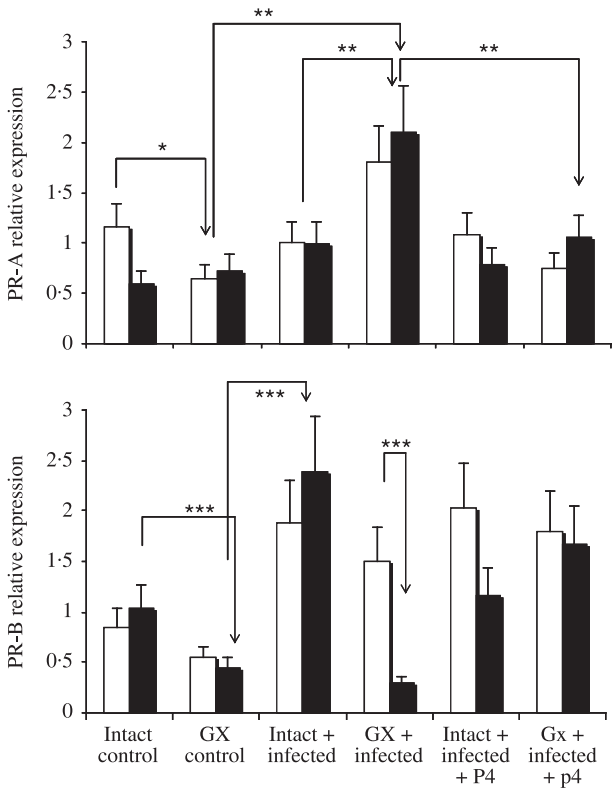

Figure 5 Progesterone receptor A and B gene expression during infection with *T. crassiceps*. The results of gene expression are reported as densitometric data of the autoradiographic signal. The relative expression was obtained by correcting the expression of PR-A/B to that of β-actin. Data represent five mice, and each experiment was performed in duplicate. Values are mean ± SD. $*P < 0{\cdot}05$, $**P < 0{\cdot}01$, $***P < 0{\cdot}001$, compared to the uninfected group. Open bars represent female mice, while black bars represent male mice.

steroid hormones, such as oestrogens and androgens. This fact, may be the reason why the pattern of expression of splenocytes in normal males and females, as well as in gonadectomized males and females, showed a very particular pattern: IFN-γ, IL-4 and IL-10 expression were markedly reduced by gonadectomy only in males, but not females. In contrast, it is very interesting to note that IL-2 was only detectable in Gx mice, irrespective of infection and P4 treatment. Because the other cytokine genes showed no difference when males or females were castrated, this suggests that they may have an imprinting. This is because gonadectomy in both sexes did not alter the pattern of gene expression, whereas IFN-γ, IL-4 and IL-10 may be genes up-modulated by androgens, while the opposite could be for IL-2 genes: because the lack of them induced its expression. The presence of a sex-steroid response element in the promoters of these genes could explain why their expression is affected by castration. To our knowledge, this is the first report that shows a sex-associated pattern of expression of cytokine genes at the transciptional level during a parasitic infection. These results support significant hormonal regulation of the immune system and may have therapeutic implications in several diseases, in addition to cysticercosis.

Because many mechanisms are present by which sex steroids could affect the immune system function, we decided to amplify classic receptors in the spleen of all experimental animals, and were able to show that they expressed both isoforms of the progesterone receptor (A and B), as well as the androgen receptor. Interestingly, we demonstrated that only one isoform of the classic progesterone receptor (B) was down- or up-regulated by progesterone treatment in infected mice of both sexes; however, the androgen receptor showed a marked decrease only in Gx and in infected male mice, whereas in females there were no changes in the differentially treated mice, which suggests that DHEA is probably acting differentially in male or female mice. Perhaps, in female mice, DHEA is acting through other mechanisms that do not involve a classical nuclear receptor.

Because there were no apparent changes in the specific immune response against the parasite, the DHEA inhibitory effect could possibly be acting directly on the parasites' physiology. In fact, we previously showed that androgens can act directly upon *T. crassiceps* cysticerci proliferation and

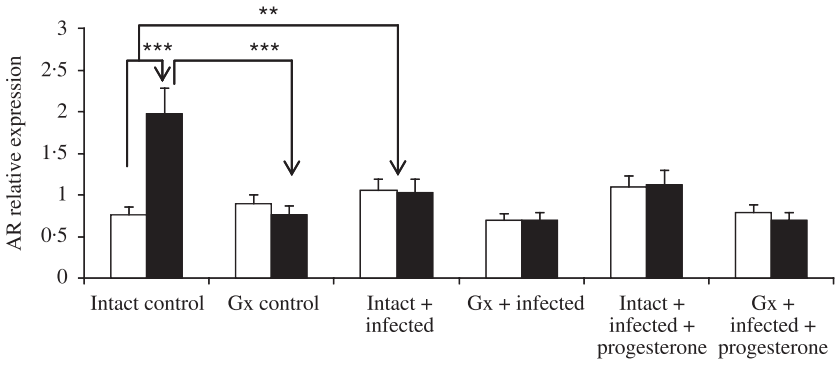

Figure 6 AR mRNA pattern expression in the spleen of mice of both genders castrated, infected with *T. crassiceps* and treated with progesterone. Results of gene expression are reported as densitometric data of the autoradiographic signal. Data represent pools of five mice, and each experiment was performed in triplicate. Values are mean ± SD. $**P < 0{\cdot}01$, $***P < 0{\cdot}001$with respect to the uninfected group. Open bars represent female mice, while black bars represent male mice.

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viability, without need for the host's participation. DHEA could thus significantly inhibit and/or abrogate parasite proliferation. Indeed, we have illustrated that androgens directly affect *T. crassiceps* reproduction *in vitro*, and found that these effects depend both on hormone concentration and on the exposure period: DHT was more drastic in its deleterious effects on cysticerci than testosterone (21). A similar effect of DHEA has also been supported in the compromising of *Schistosoma mansoni* cercariae, schistosomula, and adult worms viability *in vitro* (26). In this study, we have shown that progesterone negatively interfered with the development of *T. crassiceps* cysticerci, possibly through its conversion to DHEA. These data merit further exploration for future vaccination or chemotherapeutical development initiatives.

ACKNOWLEDGEMENTS

Financial support: Grant no. 40072-Q from the Consejo Nacional de Ciencia y Tecnología (CONACYT) de México, and grant no. IN-208103 from the Programa de Apoyo a Proyectos de Investigación e Inovación Tecnológica (PAPIIT) from the Dirección General de Asuntos del Personal Académico (DGAPA), U.N.A.M., both to J. M.-M. José A. Vargas-Villavicencio, who has a doctoral scholarship from CONACYT. Isabel Pérez Montfort corrected the English version of the manuscript.

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