Chapter

Hormones and Parasites, Their Role in *Taenia solium* and *Taenia crassiceps* Physiology and Development

Marta C. Romano, Ricardo A. Valdez, Martin Patricio, Alejandra Aceves-Ramos, Alex I. Sánchez, Arlet Veloz, Pedro Jiménez and Raúl J. Bobes

Abstract

The host's hormonal environment determines the susceptibility, the course, and severity of several parasite infections. In most cases the infection disturbs the host environment, and activates immune responses that end up affecting the endocrine system. In the other hand, a number of reports indicate that parasites have reproductive systems, and some others have shown that these organisms synthetize sex steroid hormones. We have shown that cysticerci, the larval stage of *Taenia solium and Taenia crassiceps* ORF and WFU, synthesize steroid hormones. This capacity was modified by drugs that act inhibiting the steroid synthesizing enzymes, or blocking the parasite's hormone receptors. We have also shown that the cysticerci of *T. crassiceps* WFU and *T. solium* have the capacity to synthesize corticosteroids as deoxicorticosterone and corticosterone. We also reviewed the effects of insulin on these parasites, and the receptors found for this hormone. A deep knowledge of the parasite's endocrine properties will contribute to understand their reproduction and the reciprocal interactions with the host. Likewise, may also help designing tools to combat the infection in clinical situations.

Keywords: Parasites, *Taenia*, cysticerci, hormones, steroids

1. Introduction

Corticosteroids and sex steroids are crucial in vertebrate reproduction, metabolism and immune response, but their role in invertebrates had received a reduced attention, similarly happen with the influence of peptides and protein hormones in parasite's development. Therefore, we review here the parasite-endocrine system interplays.

The interaction between parasites and the host defines the intensity of parasite infections. In many cases, the presence of parasites in the host changes its endocrine equilibrium due to the activation of the immune system response, which finally affects the host endocrine system through the influence of cytokines and growth factors released by the immune cells. These changes sometimes control the

infection, but in many cases the immune system of the host cannot reject the parasite invasion and thereafter the organisms succeed, and rapidly multiply in the host. A role for 17-beta-estradiol in immunoendocrine regulation of murine cysticercosis by *Taenia crassiceps* was verified [1].

Some parasite infections disrupt the host endocrine system, to this regards we recently reported that the chronic infection of female mice with *T. crassiceps* WFU disrupted the ovarian folliculogenesis, causing a significant increase in follicle atresia, and a reduction in the number of corpora lutea (**Figure 1**) [2]. We also showed in that study that *T. crassiceps* cysticerci infection increased the female mice serum estrogen concentrations, an effect that augmented with the infection time, and that the infection increases the ovarian expression of the steroidogenic enzymes P450-aromatase and P450-Cyp19 [2]. We and collaborators also shown that the nervous system infection with *T. solium* cysticerci (neurocysticercosis) caused endocrine alterations in male and female patients [3], and Sacerdote et al. [4] showed that brain cysticerci images reduced or disappeared after treatment with raloxifene in a patient diagnosed with neurocysticecosis.

In some cases, the parasite's infection affects the host reproductive behavior, for example, changes in reproductive behavior occurred in *Taenia crassiceps* ORF infected male mice [5].

1.1 Sex steroids effects

Several reports indicate the host hormonal environment determines the susceptibility, the course, and severity of many parasite infections. Supporting this fact, a clear dichotomy in infection susceptibility between males and females had been observed in some parasitic infections. For example, the rich estrogen environment provided by female mice facilitates *T. crassiceps* ORF cysticerci proliferation [6].

In addition, steroids may directly influence the growth and proliferation of parasites. For example, *T. crassiceps* ORF and WFU cysticerci cell proliferation and metabolism evaluated by ^{3}H-thymidine and MTT incorporation was increased by the addition of physiological concentrations of testosterone, and 17β-estradiol to the culture media [7] and enhance proliferation of *T. crassiceps* ORF cysticerci, a progesterone like receptor was found in these parasites [8].

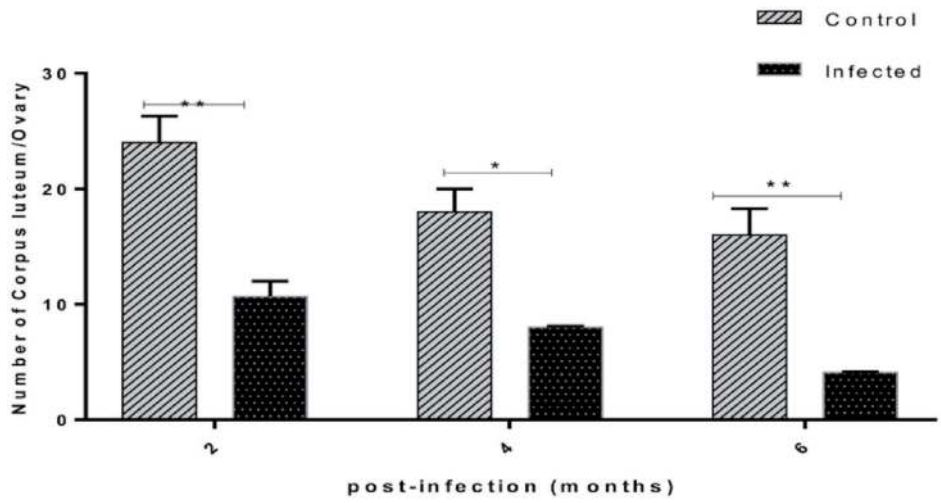

Figure 1.
The infection with Taenia crassiceps *WFU decreased the ovarian corpora lutea of female mice. The number of corpora lutea diminished when the infection progresses.*

Particularly estrogens are important for *T. crassiceps* and *T. solium* cysticerci development. Estrogen synthesis is the result of the transformation of androgens to estrogens by the steroidogenic enzyme P450-Aromatase (Arom) that transforms androstendione and testosterone to the estrogens 17β-estradiol and estrone. Interventions that reduced estrogen synthesis, or affected the binding to its receptors affect the cysticerci proliferation. For instance, the administration of fadrozole, a drug that inhibits Arom, to *T. crassiceps* ORF female infected mice reduced the parasite's load [9].

The presence of steroid receptors in parasites have been documented [10], hence the blockage of steroids receptors might mitigate the effect of these hormones. For example, the expression of an estrogen binding protein similar to nuclear estrogen receptor was shown in *T. crassicpes* ORF cysticerci [11].

Interventions on the sex steroid receptors affect the *T. crassiceps* cysticerci parasite charge. That is the case for the administration of tamoxifen, a competitive antagonist of the estrogen receptor alfa that reduced *in vitro* the proliferation and viability of *T. crassiceps* ORF cysticerci [12] and *in vivo* reduced parasite's load. Likewise, we have shown that the administration of flutamide, an androgen receptor competitor, reduced the parasite proliferation [7].

1.2 Corticosteroids are key hormones in the host-parasite interplay

Corticosteroids are synthesized in the adrenal cortex and are classified as glucocorticoids, mineralocorticoids and adrenal androgens. Cortisol and corticosterone are the main glucocorticoids and are involved in glucose, lipid and protein metabolism. Aldosterone and dexycorticosterone (DOC) are classified as mineralocorticoids because they participate in the hydro-electrolytic balance, whereas adrenal androgens as dehydroepiandrosterone (DHEA) take part in the pubertal process. DHEA is an estrogen precursor that can be transformed to potent androgens in the testis and is an important immune regulator [13].

Cortisol and corticosterone are key hormones in the physiological stress response (in example exercise), and in non-physiological stress situations, such as social isolation, persecution, infections, etc., all circumstances that increase serum corticosteroids levels. It is now generally accepted that prolonged stress conducts to impairment of the immune response.

1.2.1 Corticosteroid use in neurocysticercosis

Corticosteroids are employed to prevent or modulate the brain inflammation that follows anthelmintic treatment of parasitic cysts with cysticidal drugs as albendazole or praziquantel [14–16]. The absence of corticosteroids administration in the cysticidal treatment initiates an acute immune response to the parasite that conducts to serious clinical symptoms as seizures, brain edema, and death. These side effects are caused by neuroinflammation and are effectively managed with corticosteroids. On the other side, the administration of dexamethasone plus albendazol to Balb/c mice reduced the cysticidal effect of albendazole [17].

1.2.2 In vitro *effects of glucocorticoids on parasite growth and viability*

It had been shown that corticosteroids may directly influence parasite's proliferation and metabolism. For instance, we had shown that corticosterone and dexamethasone increase the capacity of *T. crassiceps* WFU cysticerci to synthesize androgens and estrogens, hormones that favor the parasite reproduction [18].

1.3 *Taenia solium* and *crassicpes* synthesize steroid hormones

1.3.1 Sex steroids and corticosteroids

The adult worm of *T. solium* and *T. crassiceps* WFU remain attached to the host gut with hooks placed in their head, and develop reproductive units called proglottids, where testis and ovaries gradually differentiate, and finally contain spermatocytes and infective eggs [19]. As stated elsewhere *T. solium* cysticerci is the larval stage of the parasite and is found in the brain or muscle of humans and pigs, whereas *T. crassiceps* WFU cysticerci constitute a useful laboratory model due to their reproduction by budding in the peritoneal cavity of mice. In the last years we have been investigating if *T. solium* and *T. crassiceps* ORF and WFU cysticerci and tapeworms synthesize sex steroids *in vitro.* We found that *T. solium* and *T. crassiceps* ORF cysticerci transform steroid precursors such as progesterone, DHEA, and androstenedione to androgens and estrogens, the capacity to transform precursors to testosterone was related to the developmental stage of the larvae (**Table 1**) [20–22]. These findings demonstrated that *Taenids* are steroidogenic organisms.

Our group have also examined the capacity of *T. solium* and *T. crassiceps* WFU to synthesize corticosteroids. Thereafter, we had incubated *T. crassiceps* cysticerci in the presence of ^{3}H-progesterone and found an important transformation into DOC, a steroid that has mineralocorticoid functions in vertebrates [23, 24]. The addition to the culture medium of metyrapone, a drug used for the medical control of hypercortisolism in Cushing's syndrome, reduced the cysticerci corticosteroid synthesis [23]. In addition, the parasites synthesized corticosterone, which was measured by radioimmunoassay in the culture media. More recently, we found corticosteroid-like synthesis in *T. solium* and *T. crassiceps* tapeworms [24, 25]. To note, the steroidogenic capacity of *T. crassiceps* is related to the development of the parasite [24]. Besides their effects on the own parasite development and differentiation, the cysticerci and tapeworm's steroidogenic capacity might play a role in the permanence of the parasites in the host tissues and organs, by disturbing the host immune cell response.

1.3.2 Taenia solium *and* Taenia crassiceps *and steroidogenic enzymes. Repurposed drugs affect the capacity of parasites to synthesize hormones*

Tritiated androstenediol and testosterone were recovered from the culture media of *T. crassiceps* incubated with ^{3}H-DHEA indicating the presence and activity of enzymes from the Δ5 steroid pathway in these tapeworms [26].

The effect of enzyme inhibitors on the steroid synthesis by *T. crassiceps* WFU cysticerci was investigated by [27]. This study demonstrated that fadrozole, a drug that inhibits P450-aromatase, reduced the transformation of 3H-androstenedione to 17β-estradiol (**Figure 2**), while danazol that inhibits 3β-hydroxysteroid dehydrogenase and 17β-hydroxisteroid dehydrogenase, reduced the transformation of 3H-DHEA to androstendiol, testosterone and 17βestradiol. The incubation of cysticerci with tritiated progesterone as a precursor and different concentrations of ketoconazole that inhibits 11β-hydroxilase, 17α-hydroxilase and 17-20 lyase, resulted in the reduction of the synthesis of tritiated 3H-DOC [27].

We have recently shown that *Taenia solium* cysticerci express the enzyme 17β-HSD that belongs to the short chain dehydrogenases/reductase family [28]. Transient transfection of HEK293T cells with Tsol17β-HSD-pcDNA3.1 (+) induced expression of Tsol17β-HSD that transformed ^{3}H-androstenedione into testosterone (**Figure 3**). In contrast, ^{3}H-estrone was not significantly transformed into estradiol. Therefore, *T. solium* cysticerci express a 17β-HSD that catalyzes the androgen reduction and belongs to the short chain dehydrogenases/reductase (SDR) protein

Radioactive precursor metaboliteS	**Transformation rate evaluated in two developmental stages of *Taenia crassiceps* WFU cysticerci**	
^{3}H-A$_4$/Testosterone	Invaginated cysticerci	Evaginated cysticerci
6 hours	9.6 ± 2.1	22.9 ± 1.9**
24 hours	71.4 ± 7.6	75.5 ± 4.5
43 hours	75.0 ± 4.7	74.1 ± 5.3
^{3}H-A$_4$/Estradiol		
6 hours	7.7 ± 2.7	5.3 ± 3.3
24 hours	4.7 ± 2.7	3.8 ± 4.3
43 hours	3.1 ± 2.5	0.1 ± 0.5

$^{**}p < 0.01$.

Table 1.
Synthesis of sex steroids by Taenia crassiceps *WFU cysticerci. The parasites were incubated by different periods in the presence of ^{3}H-androstenedione, the culture media was analyzed by TLC. The synthesized steroids are express as percent transformation of the tritiated precursor.*

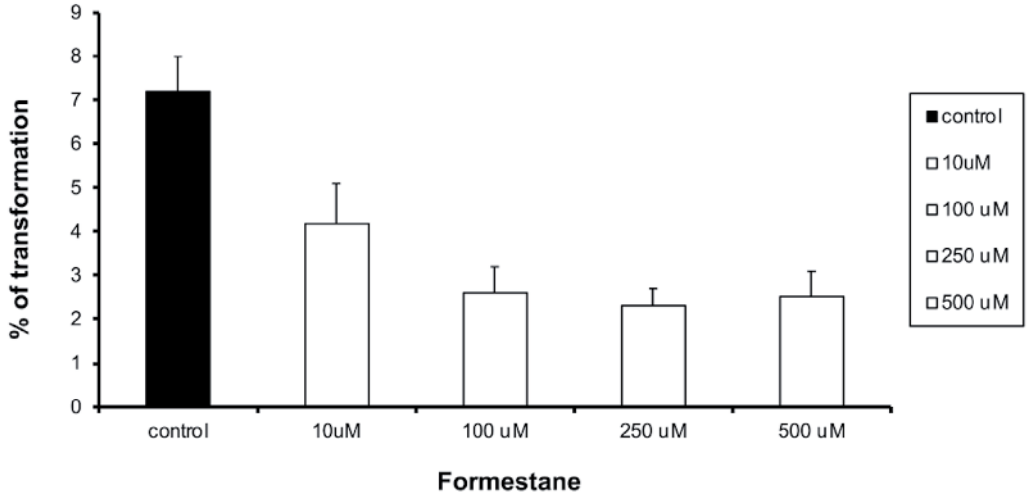

Figure 2.
Effect of formestane, an inhibitor of P450-aromatase, on the synthesis of 17β-estradiol by T. Crassiceps *WFU cysticerci. The parasites were incubated with ^{3}H-androstenedione for 24 h. The percent of tritiated 17β-estradiol synthesized was determined by TLC.*

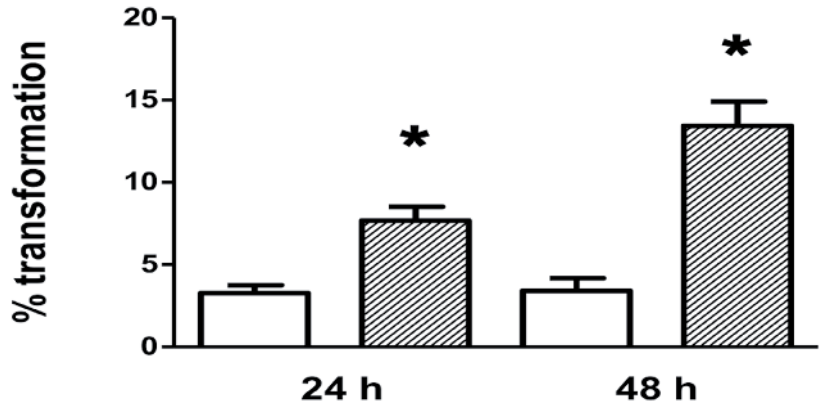

Figure 3.
Testosterone production by HEK293T cells transfected with Tsol-17βHSD-pcDNA3.1(+). After 24 h of transfection with Tsol-17βHSD-pcDNA3.1(+) (white bars) or with pcDNA3.1(+) (black bars), cells were incubated with ^{3}H-androstenedioned for 24 or 48 h. The percent of tritiated testosterone was determined by TLC.

superfamily [28]. A sequence with an identity of 84% with Tsol-17βHSD and a total coverage has been described for *E. multilocularis*, suggesting the presence of 17β-HSD enzymes in these parasites [29]. However, the expression level and enzyme activity of this species has not been yet investigated.

1.4 Additional hormones studied in *T. solium* and *Taenia crassiceps*

Insulin is a potent metabolic hormone that exerts a wide variety of effects. The main metabolic effect of insulin is to stimulate glucose uptake and utilization in muscle and fat tissue, but this hormone also increases lipogenesis, and even acts on protein synthesis. Insulin signaling through insulin receptors (IR) is an ancient and well conserved pathway in metazoan cells organized as transmembrane proteins with tyrosine kinase activity. To note, the uptake and metabolism of glucose is crucial for *T. solium* and *crassiceps* survival.

We have shown that incubation of *T. crassiceps* cysticerci with insulin increased the reproduction of the parasites and also found that female mice exposed to insulin had larger parasite loads than control mice inoculated with vehicle [30]. In the same study an insulin-like receptor present in *T. solium* and *T. crassiceps* was amplified by reverse transcriptase-polymerase chain reaction.

Using genome-wide screening Wang et al. [31] identified putative insulin-like peptides in several parasitic platyhelmths as *T. solium*. Furthermore, two insulin receptor genes were identified and characterized in *T. solium*. The receptors were found in diverse zones of the parasite and are involved in the uptake of glucose, that is crucial for these parasites [32].

The effect of human chorionic gonadotropin (hCG) on the growth and proliferation of larval stages of *T. crassiceps* (WFU strain) and *T. solium,* and the presence of receptors for this hormone in different developmental phases of both cultured parasites was reported [33, 34].

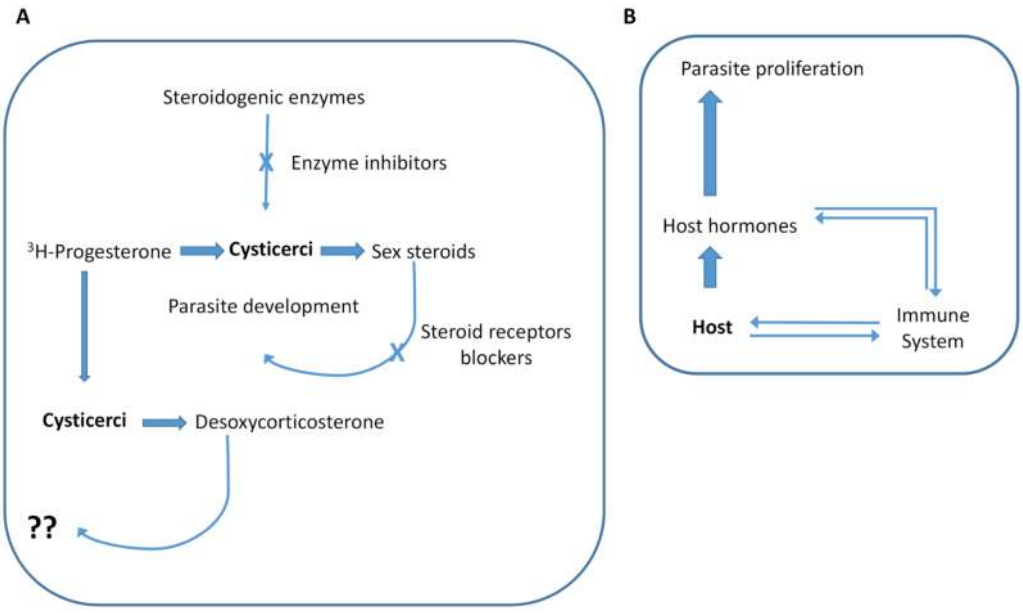

Figure 4.
A. Synthesis of steroids by cysticerci. The larval stage of Taenia solium *and* Taenia crassiceps *synthesize sex steroids and corticosteroids from tritiated precursors. Sex steroids influence the cysticerci development. The addition of steroidogenic enzymes or receptor blockers to the culture media reduced the steroid synthesis by the parasites. B. The host-parasite interplay, and the immune-endrocrine interactions influence the course of the parasite infections.*

2. Conclusions

The interaction between parasites and the host defines the intensity of parasite infections. Steroid hormones play an important role in this interplay. Sex steroids and corticosteroids modify *in vitro* the proliferation of *T. solium* and *T. crassiceps* ORF and WFU cysticerci. Cysticerci and worms have the capacity to synthesize corticosteroids and sex steroids from tritiated precursors, a fact that suggested they have several active steroidogenic enzymes. One of these enzymes, 17β-hydroxysteroid dehydrogenase like was characterized and cloned in *T. solium* cysticerci. The steroidogenic capacity of these parasites was modified with repurposed drugs that affects steroidogenic enzymes as formestane that acts on P450-aromatase, danazol and ketoconazol (**Figure 4**). Insulin modifies the proliferation of cysticerci, and receptors for insulin had been found in parasites. Steroidogenic enzymes inhibitors, and receptors blockers might be used as therapeutic tools for the control of parasitic infections

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Conflict of interest

The authors declare that they have no known conflict of interests or personal relationships that could have appeared to influence the work reported in this chapter.

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