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Chapter 2

Neuroimmunoendocrine Interactions in Murine Cysticercosis: From the Lab Bench Work to Its Possible Applications in Controlling Porcine Cysticercosis and Human Neurocysticercosis

Karen Nava-Castro, Romel Hernández-Bello,
Saé Muñiz-Hernández, Lorena López-Griego,
Jhonatan A. Hernández-Valdés, Valeria López-Salazar,
Nelly Tiempos-Guzmán and Jorge Morales-Montor

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1. Introduction

The immune and neuroendocrine systems are interconnected by a network in which hormones, antigens, receptors, cytokines, antibodies and neuropeptides modulate immune response in connection with neuroendocrine changes while maintaining homeostasis (Besedovsky & del Rey, 1996). Two of the main components of this network are the hypothalamic-pituitary-adrenocortical (HPA) and the hypothalamic-pituitary-gonadal axes (HPG) (Besedovsky & del Rey, 2000; Rivier & Rivest, 1993).

Interactions between the immune system and both the HPA and HPG axes are characterized by their activation and starting of the stress response, which, in turn, has immunomodulating activities that are important in preventing excessive immune responses (Chikanza & Grossman, 2000; Morales-Montor *et al.*, 2004b). Furthermore, the important functions of both axes have been shown for adaptation and maintenance of homeostasis during critical illness and viral, bacterial, parasitic and autoimmune diseases (Besedovsky & del Rey, 1996). An important aspect of cell communication that has emerged as a result of studying neuro-endocrine-immune interactions is the redundancy of the use of some chemical messengers to communicate among them. As an example, neurotrophins are chemical messengers first identified and characterized in the nervous system. Members of this protein family are also expressed and secreted by immune and endocrine cells, and have immunological and endocrinological functions (Haddad *et al.*, 2002).

Thus, the lack ubiquitous use of some cellular messengers by different organic systems might be a rule, rather than an exception. Although strong evidence supports that neurons, endocrine and immune cells produce hormones, while neural, endocrine and immune cells synthesize and secrete neuroactive messengers (Ferone *et al.*, 2006), it remains somewhat controversial whether this network is involved in the final outcome of parasitic diseases, and, particularly in cysticercosis (natural and experimental) (Morales-Montor & Larralde, 2005).

Taeniids, particularly *Taenia solium*, the porcine cysticercosis (CC) and human neurocysticercosis (NCC) causal agent; and *Taenia crassiceps*, murine cysticercosis causal agent, are highly evolved parasites that have developed diverse mechanisms of survival that facilitate their establishment in the host. These mechanisms can be roughly grouped into two types: 1) evasion of the immune response by molecular mimicry or by inactivating effector immune processes (i.e, complement inhibition) (Baig *et al.*, 2005; Laclette *et al.*, 1989); and 2) by exploiting the host system to allow its establishment, growth or reproduction (Escobedo *et al.*, 2004). This exploitation mechanism provides parasites with a dual benefit: first, obtaining amino acids for metabolism, and second preventing the surface-bound antibody from interfering with cytotoxic cells interacting with the parasite (Damian, 1989; Locksley, 1997). A striking example of host's molecules exploitation is the ability of several taeniids to use host-synthesized cytokines as indirect growth factors for themselves and also exploit the hormonal microenvironment within the host in their favor (Escobedo *et al.*, 2005). Taeniids 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 (Gomez *et al.*, 2000). Such cross regulation from host to parasite has been described in at least eight parasitic infections that are caused by parasitic cestodes, like schistosomiasis (LoVerde *et al.*, 1985), filariasis (Rajan *et al.*, 2005), hydatid disease (Brehm *et al.*, 2003) and murine cysticercosis (Escobedo *et al.*, 2004).

Understanding how the host's endocrine system can favor the establishment of taeniids under certain circumstances, led us to explore the parasite's hormone receptors that might be involved, designing hormonal analogs and drugs to specifically affect the parasite (Escobedo *et al.*, 2004). This review is focused on the literature concerning sex-steroids, adrenal steroids and other hormones and neurohormones that have been studied in regard to control parasite loads in experimental murine cysticercosis.

1.1. Experimental murine cysticercosis

Due to the intrinsic difficulties in working with the natural hosts (pigs and humans) of *T. solium* and the high costs of enough 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 CC. Murine intraperitoneal cysticercosis is caused by the taeniid *T. crassiceps* and it has been useful to explore the physiological host factors associated with porcine cysticercosis, and to some degree, with human NCC (Larralde *et al.*, 1990). Intraperitoneal *T. crassiceps* cysticercosis of mice (Huerta *et al.*, 1992; Larralde *et al.*, 1990; Smith *et al.*, 1972) 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 (Larralde *et al.*, 1986), by the parasite's extensive sharing of antigens with other taeniids and cestodes and by the DNA homology between *T. crassiceps and T. solium* (Larralde *et al.*, 1986; Larralde *et al.*, 1990). These characteristics have made murine cysticercosis a convenient instrument to test vaccine candidates (Sciutto *et al.*, 1990) and new drugs or treatments against CC. Several features of natural cysticercotic disease have been found by extrapolation from experimental murine cysticercosis (Morales-Montor *et al.*, 2002a; Sciutto *et al.*, 2007).

1.2. Immuno-endocrine interactions in the host

In order to figure out the effect of infection on the immune system, on the feminized male mice, thymic cell analysis performed by flow cytometry showed a diminution in the content of CD3+, CD4+, and CD8+ subpopulations in the infected mice. This suggest 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, by inhibiting the 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 genders, presumably by interfering with the thymus-dependent cellular immune mechanisms that obstruct parasite growth (Th_1) and favoring those that facilitate it (Th_2) (Bojalil *et al.*, 1993; Terrazas *et al.*, 1994). A specific shift from Th_1 to Th_2 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 genders, while the secretion of cytokines involved in the specific humoral response (IL-6, IL-10 and IL-4) is enhanced (Terrazas *et al.*, 1998; Terrazas *et al.*, 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, which 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 (T_4), dihydrotestosterone (DHT), and 17β-estradiol (E_2) in castrated mice of both genders infected with *T. crassiceps* cysticerci (Morales-Montor *et al.*, 2002a). In this study, we found that castration and treatment with either T_4 or DHT before infection markedly decreased parasite loads in both gender mice, while the treatment with E_2 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 T_4 or DHT 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 T_4 or DHT restitution, while the treatment with E_2 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 T_4 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). Interleukin-6 (IL-6) was demonstrated a key factor in this puzzle: IL-$6^{-/-}$ (KO) infected mice do not develop the feminization process, while the restitution with IL-6 again allows the feminization. The expression of IL-6 gene in the testes of parasitized mice was enhanced, a fact that can explain the primordial role of the testes in the feminization process produced by cysticercosis (Morales-Montor *et al.*, 2002a; Morales-Montor *et al.*, 2001). Thus, IL-6 activates aromatase expression in the testes of the cysticercotic mice and produces active aromatization from androgens to estrogens. The increased serum levels of follicle stimulating hormone (FSH), the natural activator of aromatase expression, found in the chronically infected mice, supports the notion that FSH could be also a factor involved in the feminization process in the male mouse (Morales-Montor *et al.*, 2001). Actually, macrophage-migration inhibitory factor (MIF) is known to be involved in immunoendocrinological processes during sex-associated susceptibility in cysticercosis. Thus, to determine the role of IL-6 and MIF during infection, knockout (KO) mice were used, and the number of parasites and serum sex-steroid levels were measured. It was found that IL-6 and MIF KO mice of both genders infected with *T. crassiceps* cysticerci harbor similar numbers of parasites, with no change in sex-hormone levels. However, in wild-type strains, the sex-associated susceptibility to infection is observed, concomitantly with the feminization process in the chronically infected mice (Morales-Montor *et al.*, 2002b). These results suggest a role for both IL-6 and MIF genes in sex-associated susceptibility in murine *T. crassiceps* cysticercosis.

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 E_2 (Morales-Montor *et al.*, 2002c). 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. IL-6 serum levels, and its production by splenocytes were dramatically augmented, together with an increase in its expression in the testes of infected male mice. Fadrozole treatment returned these levels to baseline values. These results suggest that P450-ase and IL-6 are key molecules in feminization undergone by infected male mice and in regulating parasite loads. Fadrozole treatment appears as a possible new therapeutic approach to control murine cysticercosis (Morales-Montor *et al.*, 2002c) and perhaps other parasites with active asexual reproduction in intermediate hosts.

Progesterone (P_4) was recently tested and implicated in the regulation of the parasite loads during murine cysticercosis. P_4 treatment has a dichotomic effect: in non-gonadectomized

(intact) of both genders, P_4 treatment increased parasite loads, while gonadectomized mice, P_4 completely decreases parasite loads, an impressive and unprecedented cysticidal effect. In the first case, the effect of P_4 is possibly associated to the manipulation of the specific cellular immune response, besides the steroid's promotion of parasite reproduction (Vargas-Villavicencio *et al.*, 2006). In a second analysis, it was demonstrated that infected mice that received P_4 treatment increased estrogen levels two-fold compared to infected control mice. (Vargas-Villavicencio *et al.*, 2005; Vargas-Villavicencio *et al.*, 2006). A flow chart of the main immunoendocrinological effects of *T. crassiceps* infection in male and female mice is depicted in Figure 1.

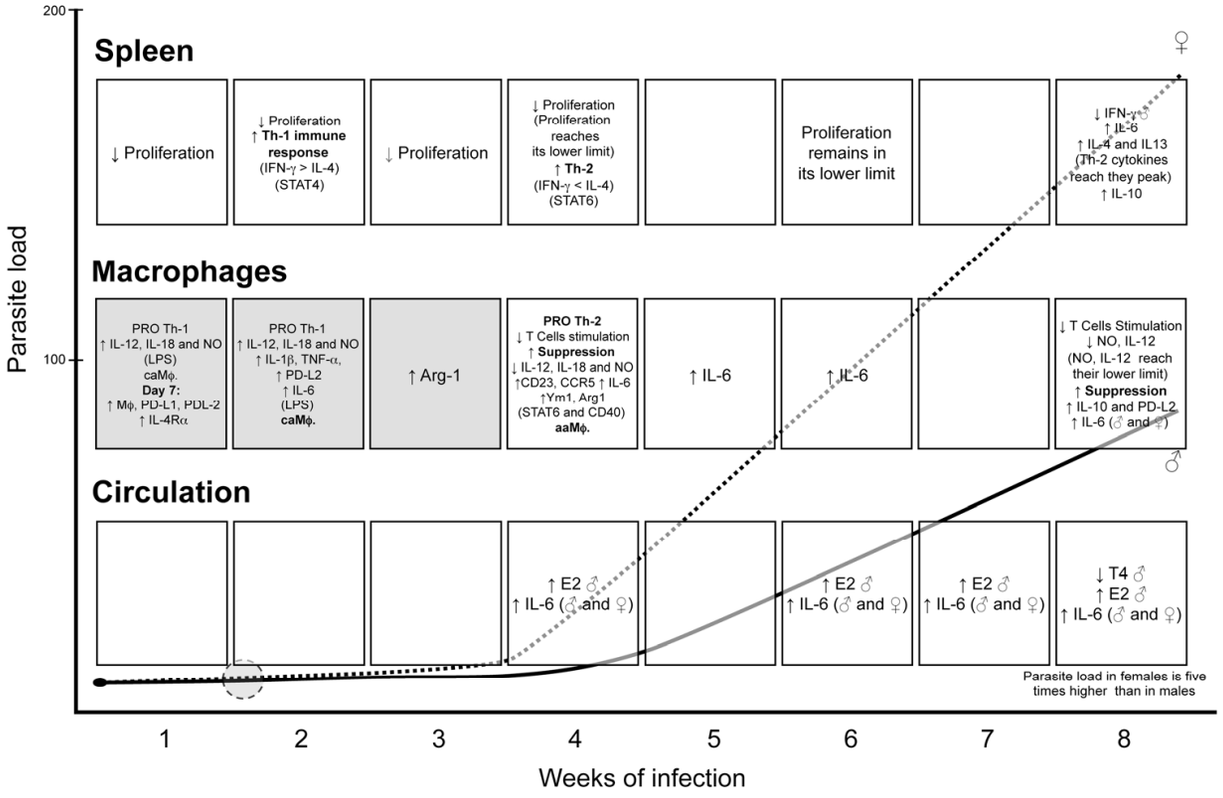

Figure 1. Early immune events during murine cysticercosis. During murine cysticercosis, there is a marked sexual dimorfism in parasite loads, having females, higher parasite loads than males, because of the effect of E_2 and T_4. These hormones also regulate immune responses. During the second week post infection, there is a clear Th1 response characterized by the expression of STAT4, high levels of IFN-γ and reduced levels of IL-4. After 4 weeks post-infection, immune response polarizes to a Th2 profile, in which STAT6, high levels of IL-4 and reduced levels of IFN-γ are observed. All these changes correlate to an overproduction of E_2. IL-6 levels are also increased as infection takes place. High levels of this cytokine are associated to a feminization process, as observed by the low levels of T_4. Doted line: Female parasitic load. Solid line: Male parasitic load. Signs (↑ and ↓) denote increase or decrease phenomena.

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 immune-stimulatory hormone, the immune responses of our mice, characterized by the expression of IL-2, IFN-γ, IL-4 or IL-10, was not affected by DHEA treatment (Vargas-Villavicencio *et al.*, 2008). *In vitro*, treatment of *T. crassiceps* cysticerci with DHEA induced 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). In addition, the use of 16α-bromoepiandrosterone (EpiBr), a DHEA analog without significant androgenic activity, inhibited proliferation of cysticerci in vitro and decreased the *T. crassiceps* cysticerci load up to 50% in the peritoneal cavity of Balb/c mice (Carrero *et al.*, 2010).

1.3. Behavioral changes in the infected host

The hormonal changes in cysticercotic mice, profoundly affect their behavior, such as sexual activity (Morales *et al.*, 1996), aggressiveness (Gourbal *et al.*, 2001), social status (Gourbal *et al.*, 2002) prey/predator defense responses, and also cognitive functions. Male mice infected with *T. crassiceps* show remarkable changes in sexual behavior, characterized by a complete loss of the ejaculation response early at the infection (six weeks), followed by a gradual decrease in the number of mounts and intromissions, and their latencies increased, until none of the parasitized mice showed any sexual response toward female mice (Morales *et al.*, 1996). Moreover, it was demonstrated that changes in sexual behavior were due to the change in the normal production of sex-steroids by the mouse, since there was a complete restoration of their sexual behavior after T_4 or DHT restitution of the infected male mice (Gourbal *et al.*, 2001). Since *c-fos* and progesterone receptor gene (PGR), both are key E_2-regulated genes involved in the regulation of sexual behavior, we studied possible changes of *c-fos* and PGR expression in the central nervous system (CNS) of infected male mice. Indeed, *c-fos* and PGR expression oscillated with time of infection and to different magnitudes in hypothalamus, brain cortex and preoptic area but neither in other areas of the brain nor in several other organs of the host (Morales-Montor *et al.*, 2004a; Rodriguez-Dorantes *et al.*, 2007).

Furthermore, infection disrupts the dominant-subordinate status (Gourbal *et al.*, 2002). In infected male mice strong perturbations in territorial behavior and aggressiveness were found. In addition, during confrontation between naive infected and healthy mice, infected animals more often assumed a subordinate status than healthy ones. The effects of the infection by *T. crassiceps* were more likely to prevent adult male mice from becoming behaviorally dominant than to reverse existing dominance relationships (Gourbal *et al.*, 2001).

Significant CNS changes in *c-fos*, and PR expression during infection signifies the brain senses the infection episode and may be involved in the ensuing behavioral changes of the infected mice, as well as, through its connectivity, extend the effects of infection to other physiological systems under its influence. That these changes in CNS are beneficial to the host or parasite remains speculative (Klein, 2000). One could argue that feminization of male hosts favors the parasite by allowing reproduction in otherwise restrictive male mice, but equally arguable would be to consider feminization of the male host as deleterious to the parasite's completion of its cycle by reducing male exposure to its predators, the definitive

hosts. Other similar mutually conflicting statements may be elaborated with the above premises, the true ones remain to be identified and could perhaps vary with each different host-parasite relationship.

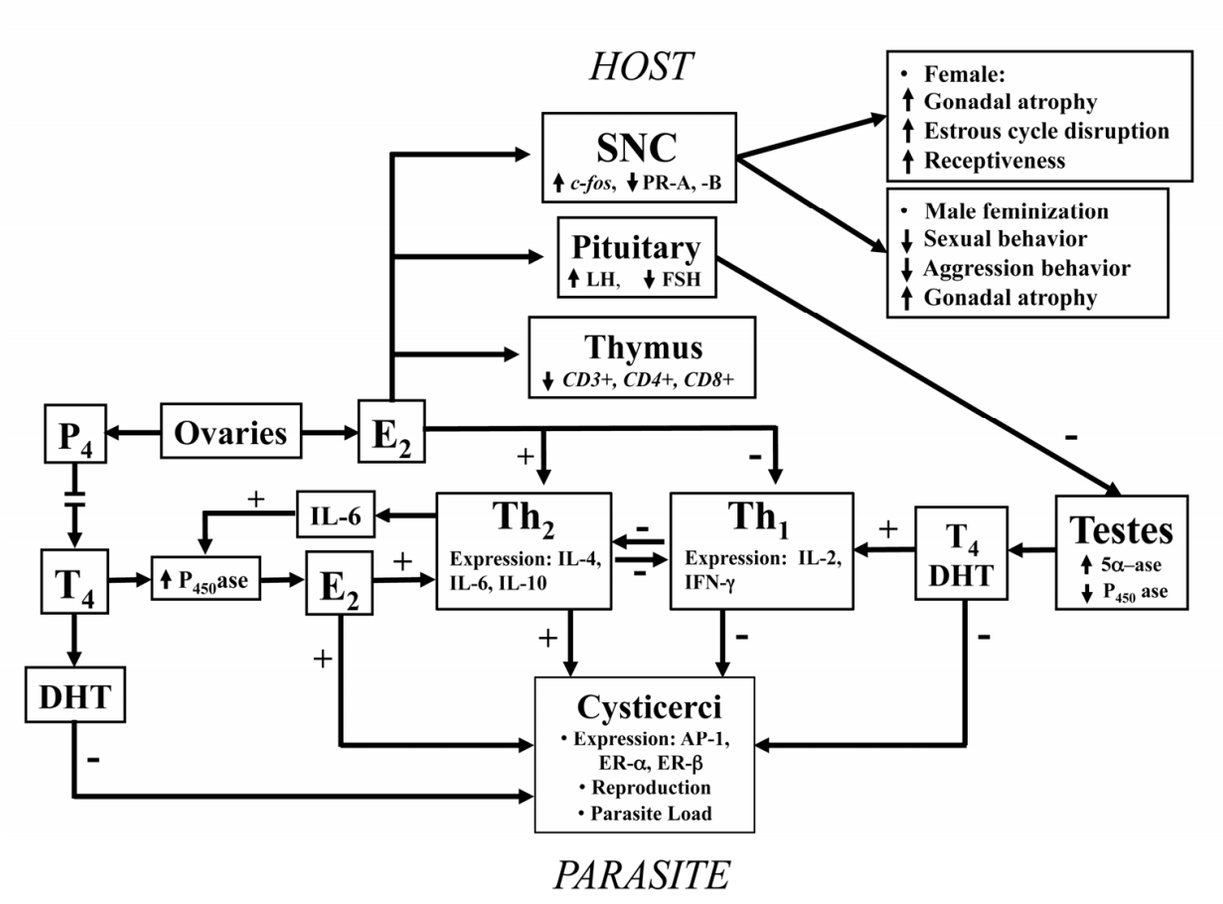

Figure 2. Neuroimmunoendocrine changes in host during murine cysticercosis. Infection with *Taenia sp*, leads to a Th2 response with high levels of IL-6 activating the P450-aromatase, which convert T_4 into E_2 increasing its level in the host. Estrogens are permissive for the infection while androgens (T_4, DHT) inhibit parasite reproduction and reduce parasite load. E_2 overproduction induces behavioral changes in male and female. Signs (+ and -) means induction and inhibition respectively; signs ($\uparrow$ and $\downarrow$) denote increase or decrease phenomena.

However, not only male mice are behaviorally affected by CC, female mice also suffer perturbations in their sexual behavior. Infected females were less receptive to the male at 6 weeks post infection (p.i.) and until 12 weeks p.i.; and there was also an interruption in the estrous cycle that was clearly starting at 12 weeks of infection and remained until the 16th weeks. These changes were associated to the low levels of serum E_2 that were comparable to those found during the diestrus stage of control mice (Arteaga-Silva *et al.*, 2009). That sex steroids, particularly E_2 is very important to the host-parasite relationship in CC, was recently demonstrated by Guzman, *et al* (Guzman *et al.*, 2009). A single injection of E_2 administered to 4-day-old male and female mice increased the cellular immune response and induced resistance to *T. crassiceps* cysticercosis. At the same time, there are changes in

the expression pattern of PR and estrogen receptor (ER) isoforms in the brain and splenocytes. Regardless of gender, when treated mice reached adulthood, they were highly resistant to infection. Female mice presented early vaginal opening and altered estrous cycles. In male and female mice, the expression of the PR and ER isoforms in the brain was differentially regulated after neonatal exposure to estradiol. Moreover, an increase in the expression of IL-4 and IFN-γ was found in the serum of experimentally infected neonatally estrogenized animals, which correlated with the observed protection against *T. crassiceps* infection. In conclusion, early exposure to E_2 permanently modifies immune system activity and sex steroid hormone receptors in the brain, and causes profound changes in sex-associated susceptibility, leading to resistance to helminthic infection (Guzman *et al.*, 2009). A chart of all neuroimmunoendocrine changes during murine cysticercosis is depicted in Figure 2.

1.4. *Taenia solium* cysticercosis, neurocysticercosis and taeniosis

As described for the mouse model of CC, host's biological factors such as genetic background, the innate and acquired immunity and gender can lead to resistance and/or susceptibility to cysticercosis/taeniosis by *Taenia solium*. It has been shown that sexual hormones play an important role in porcine CC. For instance, castrated male pigs increased by 30% the prevalence of naturally acquired CC, while pregnant sows doubled the prevalence, compared to non castrated males and non-pregnant sows (Morales *et al.*, 2002). Another interesting finding, was found when in experiments designed to explore the hormonal profiles of sex steroids, as well as DHEA in serum of boars that had naturally acquired CC, it was observed a significant reduction in the T_4 levels, change that was independent of the heterogeneous genetic background and large range of ages. These findings suggest that sex steroids can be associated to *T. solium* susceptibility and transmission dynamics of this parasite in natural conditions (Pena *et al.*, 2007).

Interestingly, sex steroids are not the unique hormones that can be useful to this parasite. It has been recently described that the *in vitro* culture of *T. crassiceps* with insulin stimulates parasite reproduction by two-fold and increased the average of the bud diameter. However, this hormone had no effect on *T. solium* cysticerci culture (Escobedo *et al.*, 2009). On the other hand, hamsters treated with P_4 and experimentally infected with *T. solium* showed an 80% reduction of anchored-*T. solium* tapeworms, a reduced growth of these parasites and a down-regulation of the PR expression in 50% duodenum associated tapeworms. Immune response of P_4 treated hamsters showed an increase in IL-4, IL-6 and TNF-α cytokines and an exacerbated inflammatory infiltrate located along the lamina propria, compared to infected non-progesterone treated controls (Escobedo *et al.*, 2011). These results clearly support the fact that P_4 protects against the *T. solium* adult tapeworm establishment by improving the immune system.

The studies in mice and pigs have already been scaled to the natural human disease. A recent study on human NCC, caused by larvae of *T. solium* infiltration in the CNS demonstrated a strong correlation between the endocrine, immune systems, gender and age during the clinical manifestation and susceptibility to the disease. Cardenas, *et. al,* designed a clinical study to evaluate the hormonal changes associated with NCC and the relationships

between disease heterogeneity, endocrine and immunological status. Since the proper diagnostic of the disease was fundamental in this study, a precise clinical and radiological description of the disease and a complete hormonal and immunological profile was performed to 50 patients and 22 healthy subjects. Patients had lower DHEA levels compared to healthy subjects. Concerning to gender, male patients showed a clear decrease in 17β-estradiol serum levels and high levels of Luteinizing Hormone (LH), while female patients with clinically severe disease showed lower levels of progesterone and androstenedione. Higher concentrations of follicle stimulating hormone (FSH) and lower concentrations of testosterone (similar to those reported previously during murine cysticercosis) were found in male patients with severe disease, when compared with the less clinically severe patients. Significant correlations were found between E_2 and IL-10 in male patients, and between DHEA and IL-1β, and androstenedione and IL-17 in female patients, suggesting a possible immunoendocrine interaction. The study by Cardenas, *et. al.* in neurocysticercotic patients constitutes the first demonstration that the presence of *T. solium* larvae in the central nervous system, can modify the host environment by the induction of endocrine and immunological changes. As the authors point out, these results provide a stimulating background to analyze the repercussions of the hormonal changes during the course of disease and on patient reproductive health (Cardenas *et al.*, 2012). Taken together, the above-presented evidence open up the possibility of the use analogues of hormones, as novel anti-cysticercotic agents.

1.5. Direct effect of sex steroids on *Taenia crassiceps* and *Taenia solium* cysticercy

As described before, hormones play a significant role in murine *T. crassiceps* cysticercosis and participate in the susceptibility to *T. solium* cysticercosis. However, this effect is not only due to the regulation of the immune response by sex steroids, but also by acting directly upon cysticerci reproduction. For instance, it has been shown that *in vitro* treatment with E_2 and P_4 stimulates *T. crassiceps* reproduction. In contrast, T_4 or DHT inhibit and even exert a toxic effect on the parasite (Escobedo *et al.*, 2004). The possible molecular mechanisms by which sex-steroids affect *T. crassiceps* reproduction imply the presence of sex hormone receptors, since the use of tamoxifen, an anti-estrogenic compound (Escobedo *et al.*, 2005), decreases parasite reproduction *in vitro* and parasite loads *in vivo*, as described before (Vargas-Villavicencio *et al.*, 2007), we look for a estrogen receptor expressed by parasitic cells. As described by Ibarra, *et. al.* there is a molecule similar to the estrogen receptor alpha (ERα) identified by diverse methods such as western blot and PCR. This receptor is expressed exclusively by parasitic cells, as identified by the expression of a parasite-specific protein, paramyosin (Ibarra-Coronado *et al.*, 2011). Parasite cells expressing the ER-like protein were located by confocal microscopy in the subtegumental tissue exclusively. Sequencing of the spot produced a small fragment of protein similar to the mammalian nuclear ER. In addition to, once host's E_2 has bound to its parasite estrogen receptor, the dimeric complex would activate the transcription of several *T. crassiceps* proliferative genes, such as *c-fos*, *c-jun* and cyclin D1, directly or through the activation of the MAPK family of serine/threonine

kinase, such as ERK, which has been also recently described in this parasite (Escobedo *et al.*, 2010). Since this hypothetical molecular mechanism could be *in vitro* interrupted by using tamoxifen, we suggest a genomic action mechanism for E_2 on the parasite.

On the other hand, the androgen mechanism might be different from the found for estrogens and progesterone. T_4 and DHT directly affect parasitic DNA integrity probably 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.*, 2005). 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.*, 2005).

Furthermore, it has been shown that T. crassiceps cysticerci are able to metabolize sex steroids in vitro and, and that it possibly uses hosts hormones as positive or negative factors for its own reproduction (Gomez *et al.*, 2000). *T. solium* cysticercosis is a health problem in underdeveloped and developed countries. Sex hormones are involved in cysticercosis prevalence in female and male pigs. Interestingly, progesterone increased *T. solium* scolex evagination and worm growth, in a concentration-independent pattern. This effect could be mediated by the expression of a novel *T. solium* progesterone receptor (TsPR) since RU486 inhibits both scolex evagination and worm development induced by progesterone (Figure 3).

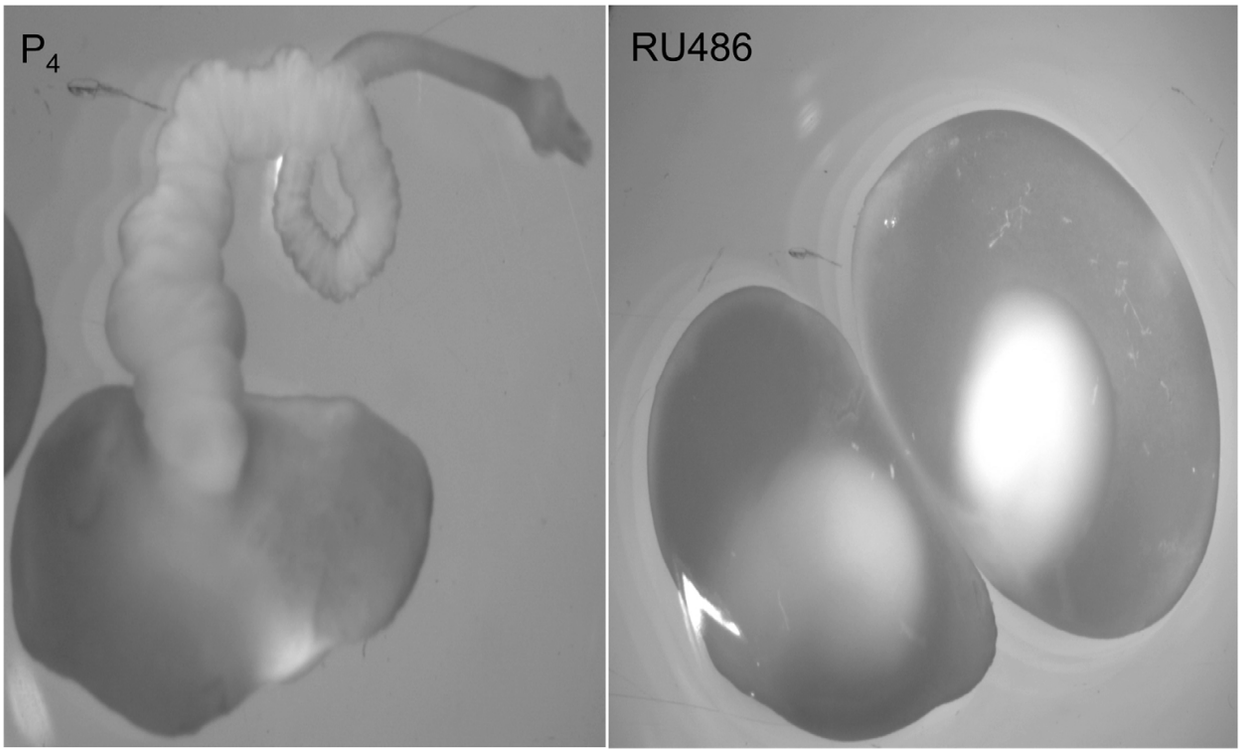

Figure 3. Effect of progesterone (P_4) and RU486 (progesterone analogue) in cultured cysts of *T. solium*. Progesterone promotes scolex evagination and worm growth while RU486 inhibit scolex evagination.

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 by binding to a progesterone receptor synthesized by the parasite. The strong effects of sex steroids upon cysticercosis open new avenues for its control. In Table 1, there is a list of some hormone receptors reported in helminth parasites to date.

Hormone Receptor	Parasite	Ref/AC
Epidermal Growth Factor	*Schistosoma mansonii* *Echinococcus multilocularis*	(Ramachandran *et al.*, 1996) (Spiliotis *et al.*, 2003)
Insulin Receptor	*Schistosoma mansonii* *Schistosoma japonicum* *Echinococcus multilocularis*	(Khayath *et al.*, 2007) (You *et al.*, 2010) (Konrad *et al.*, 2003)
Retinoid X receptor	*Schistosomamansonii* *Brugia malayi*	(Freebern *et al.*, 1999) (Tzertzinis *et al.*, 2010)
Transforming growth factor-β	*Brugia pahangi*	(Gomez-Escobar *et al.*, 1997)
Retinoic acid-binding protein	*Onchocerca volvulus* *Onchocerca gibsoni,* *Dipetalonemaviteae* *Brugia pahangi* *Dirofilaria immitis*	(Sani *et al.*, 1985)
Estrogen Receptor	*Taenia crassiceps*	(Ibarra-Coronado *et al.*, 2011)
Constitutive androstane Receptor	*Schistosoma mansonii*	(Hu *et al.*, 2006)
Estrogen-related receptor-β	*Schistosoma japonicum*	(Wu *et al.*, 2012)
Putative Follicle-stimulating hormone receptor	*Trichinella spiralis*	XP_003375811
Ecdysone receptor	*Brugia malayi* *Dirofilaria immitis*	(Tzertzinis *et al.*, 2010) (Shea *et al.*, 2010)
Nuclear Hormone Receptors	*Brugia malayi* *Dirofilaria immitis* *Onchocerca volvulus* *Echinococcus multilocularis*	(Crossgrove *et al.*, 2002) (Crossgrove *et al.*, 2008) (Unnasch *et al.*, 1999) (Forster *et al.*, 2011)

Table 1. Principal hormonal receptors in parasites reported to date.

In vitro effects of human chorionic gonadotropin (hCG) on the larval stages of *T. crassiceps* (WFU strain) and *T. solium* have also been reported. As a matter of fact, these effects were correlated to the presence of receptors for hCG in different developmental phases of both cultured parasites. Authors argued that direct effect of hCG can be recognized as a factor contributing to the growth and development of *T. crassiceps* and *T. solium* cysticerci (Castellanos-Sanchez *et al.*, 2009). *T. crassiceps* and *T. solium* cysticerci have the ability to

metabolize exogenous androstenedione to T_4, using different hormonal precursors (Jimenez *et al.*, 2006). A chart of all the immunoendocrine effects during *T. solium* cysticercosis is presented in Figure 2.

Finally, both *T. crassiceps* and *T. solium* expressed the insulin receptor, although insulin had effects only on *T. crassiceps.* Thus, insulin may be recognized by *T. crassiceps* cysticercus cells as a mitogenic factor, and contribute to parasite proliferation inside the host. This phenomenon has not been reported for cysticercosis caused by *T. solium*, which could, in part, be related to the poor effect of insulin upon the human parasite (Escobedo *et al.*, 2009).

1.6. Therapeutic applications of hormones in cysticercosis/taeniosis

The study and evaluation of new substances of hormonal nature and its analogues has emerged with great importance to develop a new generation of anti-parasitic drugs. In the case of *T. crassiceps*, the reconstitution and substitution (depending the host and hormone used) with sex steroids showed that T_4 or DHT treatment before infection decreased parasite loads by 50 and 70% respectively, suggesting a protective role for androgens (Morales-Montor *et al.*, 2002a). In contrast the treatment with E_2 increased it by three times in both genders as compared with controls. Even more, castrated mice of both genders treated with progesterone before infection, decreased parasite loads by 100% compared with intact uninfected mice. However the negative effects in the establishment, growth and reproduction of *T. crassiceps* was mediated by the metabolism of progesterone to DHEA in the adrenal gland of castrated animals (Vargas-Villavicencio *et al.*, 2006). To strength out the notion of DHEA as a protective agent, we designed experiments to test this hypothesis, by incubating *in vitro T. crassiceps* cysticerci with increasing concentrations of DHEA, and by *in vivo* treating male and female mice with DHEA and infecting them with *T. crassiceps* cysticerci. *In vitro*, DHEA has a strong cysticidal effect, being dose-dependent in physiological and pharmacological conditions. *In vivo* assays showed that DHEA reduce the viability of cysticerci in both male and female mice (Carrero *et al.*, 2006; Carrero *et al.*, 2010).

The use of EpiBr (analogue of DHEA) reduced the parasitic load in a major proportion in both male and female infected with *T. crassicepps* (Freilich *et al.*, 2000). Tamoxifen is an antiestrogen compound belonging to the group of Selective Estrogen Receptor Moduladors (SERM). Administration of tamoxifen in infected mice of both genders produced an 80% parasite load reduction in female mice, and a weaker effect of 50% in male mice. This protective effect was associated in both genders, with an increase in the mRNA levels of IL-2 (a cytokine associated with protection against cysticerci) and IL-4 (no effect on infection). Tamoxifen treatment modified E_2 production on females, whereas serum testosterone was not affected. However, the expression of the 2 types of ER, i.e., ER-α and ER-β in the spleen of infected mice of both genders, was decreased by tamoxifen treatment. *In vitro*, treatment of *T. crassiceps* with tamoxifen reduced reproduction and loss of motility. These results indicate that tamoxifen treatment is a new therapeutic possibility to treat CC, because it can act at both ends of the host–parasite relationship, i.e., by increasing the cellular immune response protective against the parasite and by directly affecting the parasite's reproduction

and survival (Vargas-Villavicencio *et al.*, 2007). Table 2 has a summary of the above-mentioned therapeutic use of hormone analogue in *T. crassiceps* cysticercosis.

Compound	Infection	Reference
DHEA / DHEAS	*Cryptosporidium parvum*	(Rasmussen & Healey, 1992)
	Plasmodium falciparum	(Kurtis *et al.*, 2001)
	Entamoeba histolytica	(Carrero *et al.*, 2006)
	Schistosoma mansoni	(Fallon *et al.*, 1998)
	Trypanosoma cruzi	(dos Santos *et al.*, 2005)
16α-bromoepiandrosterone (EpiBr or HE2000)	*Taenia crassiceps*	(Carrero *et al.*, 2010)
	Entamoeba histolytica	(Carrero *et al.*, 2010)
	AIDS	(Reading *et al.*, 2006)
	Feline immunodeficiency virus	(Pedersen *et al.*, 2003)
	Plasmodium falciparum *Plasmodium berghei*	(Freilich *et al.*, 2000)

Table 2. Therapeutic use of DHEA or an analogue (EpiBr) during several parasitic infections.

2. Concluding remarks

The evidence presented above illustrates the complexity and importance of neuroimmunoendocrine interactions during CC 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 this parasitic disease in porcine and humans. In practical importance, the complexity of the cysticerci-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 cysticerci to sex steroids may also be involved in their ability to grow faster in the murine female or feminized male host. Host and parasite sex-associated biases may be combined to favor their evolution towards a mutually acceptable relationship. Moreover, the changes in behavior observed during CC, should not be regarded as simple biological curiosities but more as strong evidence of the plasticity of the host phenotype in response to infection by parasitic helminthes. Furthermore, by changing the reproductive, aggressive and dominant capacity of the host, parasites generate novel questions regarding to the evolution of host-parasite relationships in addition to only the prey/predator interaction.

Finally, we have documented here that a complex interactive network involving the immune, endocrine and nervous systems of the mouse, as well as the reproductive system of the cysticerci, is in control of the parasite load of each infected individual mouse. If such complex a management of the parasite loads, as that we shown here between mice and cysticerci, extends to other parasite diseases of mammals, as current research seems to indicate in a number of infections, their means of exploration, fuller understandings and

forms of control must be reviewed and approached with designs matching in complexity and plasticity that of the infections.

Author details

Karen Nava-Castro
Facultad de Química, Departamento de Biología, Universidad Nacional Autónoma de México, México DF, México

Romel Hernández-Bello
Departamento de Microbiología, Facultad de Medicina, Universidad Autónoma de Nuevo León, Monterrey, NL, México, México

Lorena López-Griego, Jhonatan A. Hernández-Valdés,
Valeria López-Salazar, Nelly Tiempos-Guzmán and Jorge Morales-Montor
Departamento de Inmunología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, México DF, México

Saé Muñiz-Hernández
Subdirección de Investigación Médica, Instituto Nacional de Cancerología, Secretaria de Salud, México

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