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REVIEW

The neuroimmunoendocrine network during worm helminth infections

K Nava-Castro[1], S Muñiz-Hernández[2], R Hernández-Bello[3], J Morales-Montor[3]

[1]Departamento de Inmunología e Infectología Perinatal, Instituto Nacional de Perinatología, Secretaría de Salud, México, D.F. CP 11000. México
[2]Subdirección de Investigación Básica, Instituto Nacional de Cancerología, Secretaría de Salud, México, D.F. CP 14080. México
[3]Departamento de Inmunología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, AP 70228, México, D.F. 04510, México

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Abstract

The physiological interactions during the course of the immune response to helminthes are complex. As our understanding of the neuroendocrine system grows, it has become increasingly clear that this complex network of neurotransmitters, hormones, and cytokines plays an important role in mediating immunity, in general, but in the case of helminthes this interaction among different systems is crucial. Helminthes present a complex relationship in the host's physiological systems, with neuro and hormonally dependent host factors such as sex, age, and the host physiological status correlated with parasite success. On top of the effect that this particular type of parasites may have on the invaded host, recent experimental evidence suggest that helminth parasites not only actively evade immune response, but are also able to exploit the hormonal microenvironment within their host to favor their establishment, growth and reproduction. The close interaction of the worm with the host's homeostatic systems, the molecules produced by them, and the activation of immune mediated mechanisms to eliminate it, activate a complex neuroendocrine network, that produces strong behavioral changes in the infected host. Understanding how the host's neuroendocrine system can under certain circumstances favor the establishment of a parasitic infection opens interesting perspectives into the host parasite relationship field. This review focuses on the host-parasite neuroendocrine network activated by parasite worm infections.

Key Words: neuroendocrine network; helminthes; worm; immunity; endocrine host-parasite relationship

Introduction

The interaction of the nervous, endocrine and immune systems is crucial in the maintenance of homeostasis in vertebrates, and is absolutely vital in mammals. The capacity of the immune system to discriminate between self and non-self is based on a wide spectrum of specificity expressed by the immune system cells. This feature of the immune system implies that it can perceive an internal image of the organism's components and react to the distortions of this image (such as transformed cells of the self). The immune response, as a homeostatic response under physiological control, contributes to maintain the integrity of the body cells and tissues. Hormones and neurotransmitters present in the immune cell microenvironment can restrict its autonomy, probably by acting on the receptors of these neuroendocrine factors. Efficient communication among these three systems implies the existence of afferent and efferent pathways, constituting a complex feedback system. The alterations of this network trigger pathologies that involve its components (Bottasso and Morales-Montor, 2009; Perez *et al.*, 2009).

In recent years, information on the multiple functions of the immune system has expanded remarkably. One of these functions has been biological adaptation through pathogens, such as helminthes, and its elimination from the organism. Immune functions, in turn, require delicate control of the involved cells, which allow adaptation of the organism to the different physiological and

Corresponding author:
Jorge Morales-Montor
Departamento de Inmunología
Instituto de Investigaciones Biomédicas
U.N.A.M., AP 70228, México D.F. 04510
E-mail: jmontor66@biomedicas.unam.mx

pathological situations that it will face along life. To meet this end, interaction with the nervous and endocrine systems of the organism is necessary. This interaction is constant and makes the merged functioning of the three systems possible. This communication involves common messengers and receptors, simultaneously participating in a complex feedback system. Alterations in communication among the three systems, lead to different pathologies. This is the case with the neuropsychiatric disorders that cause immunosuppression, such as depression (Blume *et al.*, 2011), and immune disorders that cause endocrinological problems such as Hashimoto's thyroiditis (Tomer and Huber, 2009) and diabetes mellitus type I (Lehuen *et al.*, 2010), both examples of the functional interaction between the immune and the neuroendocrine systems (Wilder, 1995).

Numerous experimental data show that, as with other body cells, the cells of the immune system are influenced by the neuroendocrine system, which displays various control levels, from metabolism to cell division, regulated by hormones and neurotransmitters (Jacobs *et al.*, 2010; Muñoz-Cruz *et al.*, 2011). The immune response is possibly the only physiological phenomenon in which the amplification of the response is based on cell proliferation and the specific transformation of its components. This process requires metabolic changes and growth factors, which make the immune response dependent on neuroendocrine control (Fig. 1).

It is well known that $CD4^+$ T cells play an important role on the adaptive immunity against pathogens as well as on autoimmune diseases. Also they are a crucial key for immunological memory. The activation phase of non-differentiated $CD4^+$ T lymphocytes is determined by the specific recognition of antigenic determinants, which appear in the context of major histocompatibility complex class II molecules (MHC-II) and are expressed on professional antigen-presenting cells, such as macrophages, B or dendritic cells (Zhu *et al*., 2010). The specificity of the immune response determined by $CD4^+$ T lymphocytes is modulated by selective expansion of the clones capable of recognizing these antigenic determinants and, thus, of differentiating into helper cells (Th1, Th2, Th17 and Tregs) which contribute to the protection of the organism against infectious diseases (Zhu *et al*., 2010). The classification of Th1 and Th2 was based on the specific pattern of cytokines they produce: Th1 lymphocytes produce cytokines such as interleukin 2 (IL-2), gamma interferon (IFN-γ) and the tumor necrosis factor alpha (TNF-α) are mainly involved in protection against intracellular pathogens through cell-mediated immunity, macrophage activation, and also in delayed hypersensitivity (Cox *et al*., 2011). On the other hand, Th2 lymphocytes produce interleukins IL-4, IL-5, IL-6, IL-10 and IL-13, and regulate the humoral immune response through the proliferation of B lymphocytes and the change of the specific antibody isotype, beside promoting eosinophil and mastocyte differentiation (reviewed in Wan and Bramson (2001)). Th17 lymphocytes, the third effector population of CD4 T cell, are characterized by producing IL-17, IL-21 and IL-22 principally (Nurieva *et al*., 2007). The T regulatory cells (Tregs) are implicated on the control and regulation of particular subsets of CD4 T cells (Zhu *et al*., 2010). However, both hormones and neurotransmitters have influence on immune cells, since they affect the production of several cytokines, and various products of the immune response, both Th1 and Th2, have a regulatory effect on the neuroendocrine system (Fig. 1).

The host-parasite neuroimmunoendocrine network

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 (Derijk and Berkenbosch, 1991; Grossman *et al.*, 1991). Hormones regulate a variety of cellular and physiological functions of organisms such as growth, reproduction and differentiation. 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 (Escobedo *et al.*, 2005). Host's adrenal hormones are well known as immune modulators (Loria *et al.*, 1996), whilst sex steroids (estradiol, progesterone and testosterone) are recognized to also significantly affect the immune system's functions (Hughes and Randolph, 2001; Roberts *et al.*, 2001). More recently, the ability of hormones to affect the immunological response directed against pathogenic agents, particularly helminthes, has gained attention (Bottasso and Morales-Montor, 2009). This is clearly evident during various parasitic diseases including malaria (Cernetich *et al.*, 2006), schistosomiasis (Morales-Montor *et al.*, 2008), toxoplasmosis (Henriquez *et al.*, 2009), cysticercosis (Larralde *et al.*, 1995), trypanosomiasis (Brazão *et al.*, 2009), leishmaniasis (Snider *et al.*, 2009), where strong hormonal regulation of the immune response has been described. However, other factors than the immunoendocrine response affect the course of a parasitic infection.

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 (Damian, 1997).

The case of helminthes

Helminthes are estimated to include 18,000 to 24,000 species, and are divided into two subclasses

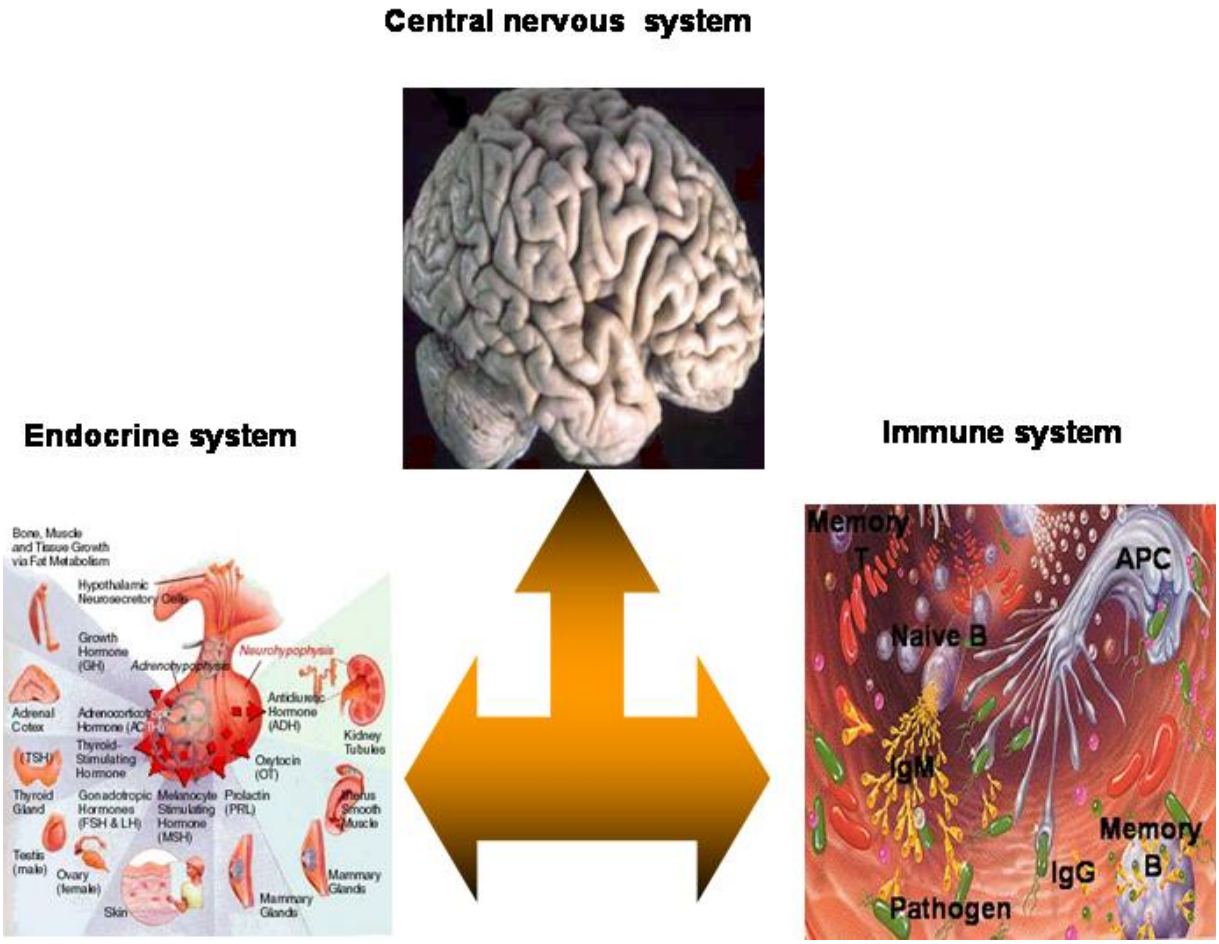

Fig. 1 Proposed neuroimmunological interactions that occur in higher vertebrates. In physiological conditions there is a crosstalk between neurological and immune systems of the host. External stimuli, such as infections, results in a Th1/Th2 systemic cytokine production of the immune response. In addition to, central nervous system (CNS) is able to actively induce cytokines expression, which may affect the CNS function.

(Touassem *et al.*, 1992). Nearly all trematodes are parasites of molluscs and vertebrates. The smaller Aspidogastrea, comprising about 100 species, are obligated parasites of molluscs and may also infect turtles and fishes, including cartilaginous fishes (Rosas-Valdez and Leon, 2011). The Digenea, which constitute the majority of trematode diversity, are obligate parasites of both molluscs and vertebrates, but rarely occur in cartilaginous fishes. One-quarter of a billion people are infected with parasitic trematode worms worldwide (Razo-Mendivil and Perez-Ponce de Leon, 2011). Disease-associated symptoms occur in 120 million people, and 20 million people suffer from severe morbidity (Cribb *et al.*, 2002).

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 (Olson and Caira, 1999). 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 (Hoberg, *et al.*, 1999). Two important tapeworms are the pork tapeworm *Taenia solium*, and the beef tapeworm *T. saginata* (Levron *et al.*, 2010).

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 within the host that facilitate their establishment (Hoberg, 2006). These mechanisms can be roughly grouped into two types. The first is evasion of the immune response by molecular mimicry or by inactivating effector immune processes (*i.e.*, complement inhibition) (Ludin *et al.*, 2011). In the second mechanism, the parasite exploits the host system to its benefit in its establishment, growth or reproduction (Long and Boots, 2011). 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 (Long *et al.*, 2011).

Effect of steroid hormones on helminth infections

In last years, research has proved the influence of sex hormones in the immune system regulation (Arteaga *et al.*, 2002), and the idea of a neuroimmunoendocrine network was released. Since then, investigations focused in the role of these hormones and their possible mechanism to intervene in the host susceptibility or resistance have grown (Klein, 2000). It is well-known that males of vertebrate species tend to exhibit higher rates of parasites than females, and sex-associated hormones may influence immunocompetence. Thus, sex hormones are hypothezised to lead to this bias (Hoby *et al.*, 2006). In this point, females have also been shown to have higher susceptibility to many parasitic infections, a finding particularly striking in helminth infections such as those produced by *Taenia solium* (Morales-Montor *et al.*, 2004) and *Trichinella spiralis* (Hernandez-Bello *et al.*, 2011). There are enough evidence about corticoids and their influence in the regulation of the immune response involved in parasitic infections (Aly *et al.*, 2010). However, there is recent data about their direct influence on the growth of the parasite, without an immune regulation. For instance, in a moderately resistant strain of mice, cysts of *E. multilocularis* developed into hydatid cysts in cortisone-treated mice (Barnard *et al.*, 1998). Cortisone treatment significantly increased the average number of cysts, the average area of each cyst, and the total surface area occupied by cysts when compared with the untreated mice. Collectively, the cysts in the treated mice occupied more of the surface area of the liver but less of the same area in the untreated mice (Barnard *et al.*, 1998). Treatment of a *E. multilocularis* resistant mouse strain with cortisone drastically increased both the number of cysts and the average size of each cyst if the treatment occurred early in the infection. Consequently, this treatment increases the susceptibility of mice to primary infections with *E. multilocularis*. Based on these results, it could not be determined whether the increased susceptibility results from physiological or immunological effects caused by the cortisone treatment (Hildreth *et al.*, 2003).

These results are in agreement with studies of the nematode *Heligmosomoides polygyrus*. In this infection, peripheral immune responsiveness in male laboratory mice was reduced by infection with the parasite. Responsiveness was also lower among high-rankers or aggressive males regardless of infection status. Reduced responsiveness on infected animals and high rankers was associated with elevated serum corticosterone concentration among high-ranking males (Perkins *et al.*, 2008). Although glucocorticoids have a stimulatory effect on the initial cell proliferation phase of T lymphocytes, and thus some elevation might have been expected on this account, the change in corticosterone concentration during the infection phase was the best hormone-measure predictor of eventual worm burden. The negative relationship between the immune status and high corticosteroids levels is more in keeping with the later impact of glucocorticoids on the secretion of Th2 cytokines and thus depression of the Th2 arm of the immune response. This is consistent with effects of glucocorticoids in prolonging intestinal nematode infections, increasing the susceptibility of rodent hosts to *H. polygyrus* and depressing the expression of acquired resistance to *H. polygyrus*. There was no testosterone-dependent increase in parasite burden among high rankers in this experiment, perhaps because resistance to the parasite relies on a different emphasis on the Th1 and Th2 arms of the acquired immune response (Barnard *et al.*, 1998).

Schistosomiasis is another example in which steroids play an important role in the host susceptibility (Kurtis *et al.*, 2006). The disproportionately high intensity and prevalence of schistosome infection in children, compared with adults, has been documented for decades, so understanding the mechanisms of this naturally occurring protection may guide efforts to develop a vaccine for schistosomiasis (Kurtis *et al.*, 2006). Then, the importance of the hormonal changes during pubertal development, including increases in the levels of the adrenal hormones DHEA-S (dehydroepiandrosterone sulfate) and DHEA (dehydroepiandrosterone) may have part of responsibility for the dramatic reduction in age susceptibility to schistosome infection.

Another evidences that points out to the relationship between increasing pubertal development, DHEA-S levels, and resistance to schistosome infection are: (1) in mice, exogenous administration of DHEA-S leads to decreased schistosome worm burdens after challenge infection, thus dehydroepiandrosterone sulfate treatment of mice modulates infection with *Schistosoma mansoni*; (2) DHEA-S kills larval and adult parasites in culture at physiologic concentrations; (3) in another 2 cross-sectional studies increased DHEA-S levels are associated with decreased intensity of infection in humans; and (4) increased DHEA-S levels are associated with decreased intensity of re-infection after treatment with praziquantel (PZQ) (Kurtis *et al.*, 2006).

DHEA-S is known to have potent immunomodulatory activities, including up-regulation of Th2-driven antibody isotypes and down-regulation of pro-inflammatory cytokines. Finally DHEA-S could mediate resistance through a direct anti-parasite effect. But also via innate immune mechanisms, such as host skin thickness or fat deposition, then capitalizing on these mechanisms for vaccine development will be difficult. However, if DHEA-S mediates resistance via enhancement of acquired protective immune responses, then vaccine strategies designed to induce and augment these protective acquired immune responses, including hormonal adjuvants, may be promising (Kurtis *et al.*, 2006) (Fig. 2).

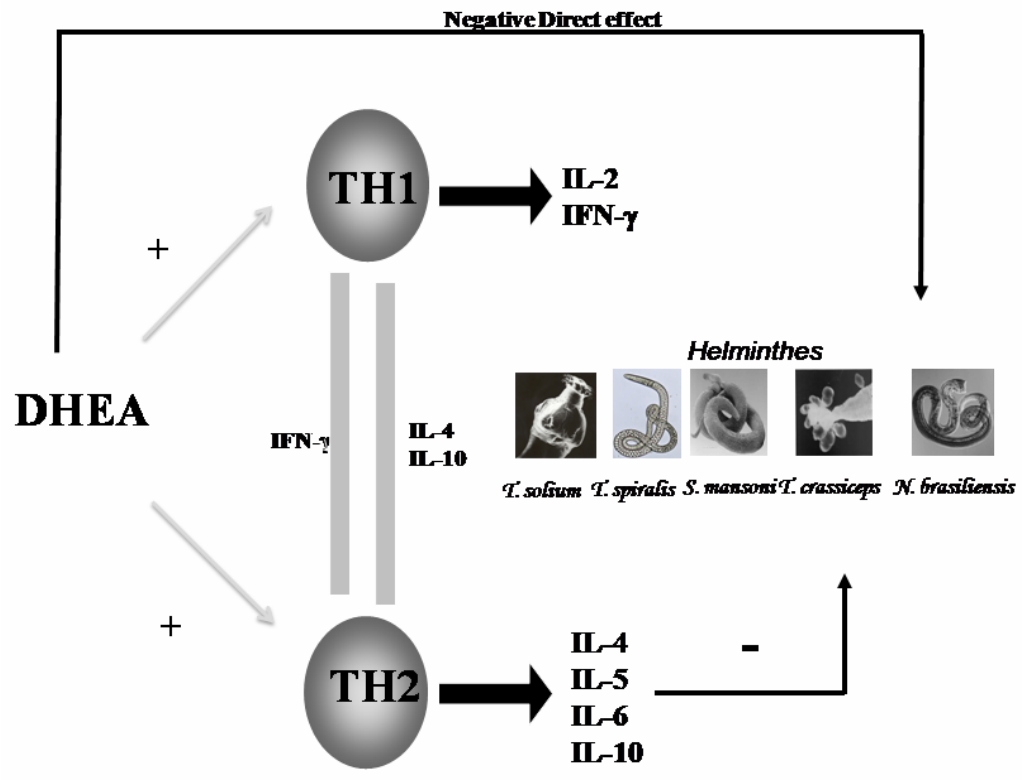

Fig. 2 Regulation of cytokine production in Th1 and Th2 lymphocytes by DHEA. The differentiation from Th0 towards Th1 or Th2 is simetric, each one controls a unique type of immune response and increases the development of cells of the same subclass while suppress the expansion and effector functions of the other subtype. DHEA can control Th1/Th2 balance by inducing the development of one subtype and inhibit the other subtype. DHEA effects could depend on concentration, having a dual effect. Also, DHEA has been demonstrated to have direct helminticidal effects on different parasites, without mediation of immune response.

Finally, the prediction of male biased parasitism was tested in free ranging chamois (*Rupicapra rupicapra*), which are infested intensely by gastrointestinal and lung helminthes. Male chamois had a higher output of gastrointestinal eggs and lungworm larvae when compared to females. Male biased parasitism originating in sex related hormone levels was confirmed for the elevated output of lungworm larvae, but not for the gastrointestinal nematodes. The faecal output of lungworm larvae was significantly correlated with androgen and cortisol metabolite levels. The immunosuppressant effects of these hormones may explain the greater susceptibility of males to infection by parasites and developing disease. The stress of the rutting season with elevated glucocorticoid levels is hypothesized to reduce humoral antibodies, and to enhance larval output of nematodes in males. However, it should be considered that the subset samples were collected predominantly around the period when androgen levels between sexes differ most significantly. In contrast to the output of lungworm larvae, the male bias in quantitative gastrointestinal nematode output was not significantly correlated with sex differences in steroid levels (Hoby *et al.*, 2006). For instance, a strong negative correlation was found between sex and adrenal steroid hormone circulating levels and some pro-inflammatory cytokines in microfilaremic women. Plasma samples from amicrofilaremic women contained higher concentrations of testosterone and estradiol than those from microfilaremic ones. Testosterone was also negatively correlated with IL-6 and estradiol with IFN-γ. The fact that cortisol concentrations were not elevated in women with filariasis may be related to the chronic nature of the disease (Mavoungou*, et al.*, 2005).

Another research that focused on the immune-endocrine system relationship in an helminth infection, is a study designed in rodents infected with *Strongiloides ratti*, in which a sex-related differences in host susceptibility was previously known. In this infection, male mice were more susceptible to *S. ratti* and the difference was seen in migrating larvae. It has been shown that natural immunity against migrating larvae of *Strongyloides ratti* is regulated by macrophages. In the small intestine, host mast cells were related to adult worm expulsion (Watanabe *et al.*, 1999). According to this study, the sex-related difference are clearly mediated by testosterone during the migration of larvae, suggesting that testosterone renders mice

susceptible to migrating larvae by modulating their natural defense mechanisms (Watanabe *et al.*, 1999).

So, steroid hormones produced by the adrenal cortex, such as DHEA-S and cortisol, influence the intensity of the immune response during *S. mansoni* infections and have been implicated among the most important host factors controlling the onset, establishment, and pathogenesis of schistosomiasis. These hormones inhibit oviposition by *S. mansoni* both *in vitro* and *in vivo*. *In vivo*, the increased numbers of worms, larger number of eggs and more vigorous hepatic granulomas can be related to the lack of circulating glucocorticoids, whose presence in some way ameliorates the inflammatory immune response in the liver. The effect of adrenalectomy produced high levels of infection and more severe pathology, a fact that can be related to the well-known glucocorticoid anti-inflammatory effect. Low levels of cortisol could promote vigorous granuloma formation and the production of cytokines necessary for schistosome reproduction, such as TNF-α. The immunosuppresive effects of hydrocortisone and dexamethasone are counteracted by DHEA, suggesting a tightly controlled balance in the secretion of these hormones to regulate the inflammatory response. An intriguing question is how the lack of adrenal hormones affects the infection in the parasitized host. Host derived candidates that could possibly be affected by adrenalectomy are the interleukins (IL's), which are known to be altered during schistosomiasis. Potential endocrinological-immunological mediators of this process are IL-1, IL-6, TNF-α and macrophage migratory inhibitory factor, all known regulated by adrenal steroids. The changes produced in the infected adrenalectomized host could thus be cytokine mediated. Further work could elucidate the mechanism by which adrenalectomy induces changes in the immune function during disease progression and could establish causal links, if indeed they exist (Morales-Montor *et al.*, 2004).

Trichuris muris infection is an ideal model for defining T-cell-driven immunity, and also provides essential insights that may impact on potential helminth therapies currently in development. The female-associated hormone 17-β estradiol (E2) significantly enhanced the generation of a Th2 response *in vitro* (Hepworth *et al.*, 2010); however, this stimulatory effect was found to be dispensable for the generation of immunity to *Trichuris* in the gender-biased IL-4 KO mouse model (Hepworth*, et al.*, 2010). These mice are compromised in their ability to generate an efficient Th2 response, necessary for parasite expulsion, as they lack IL-4 a key Th2 polarizing cytokine. In addition, female IL-4 KO BALB/c mice mount an unusually delayed Th2 response, associated with T-cell and accessory NK cell-derived IL-13 and an associated decrease in the levels of the pro-inflammatory cytokines TNF-α and IL-6, which combine to mediate worm expulsion (Hepworth *et al.*, 2010). Conversely, male littermates are unable to expel the parasite and retain high adult worm burdens, a phenotype found to be dependent on IL-18. In contrast, the male-associated hormone dihydrotestosterone (DHT), significantly inhibited the T-cell stimulatory capacity of DC and directly suppressed the immune response of male IL-4 KO mice, with worm expulsion restored following castration (Hepworth *et al.*, 2010). This finding was associated to a dramatically reduced IL-18 mRNA expression, suggesting that androgens may act via this cytokine to suppress Th2 immunity to *Trichuris* muris infection (Hepworth *et al.*, 2010).

Behavioral changes in the infected host

Several behavioral changes that are induced by infections with parasites have been described. For instance, there are sexual changes in body morphology as well as sex-related behavioral changes in crabs when parasitized with a rhizocefalan, through mechanisms that are still obscure but could involve changes in the hormonal pattern of the host (cited in Larralde *et al.*, 1995). *Taenia taeniformis* is also known to alter reproduction in rats by interfering with sex-steroids (Lin *et al.*, 1990). Perhaps the most studied helminth that induces strong hormonal, and behavioral changes is the helminth parasite *Taenia crassiceps*.

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 alterations in sexual behavior were due to the change in the normal production of sex-steroids by the mouse, since the testosterone or dihydrotestosterone restitution of infected male mice, showed a complete restoration of their sexual behavior (Morales-Montor *et al.*, 2002). Since *c-fos* and progesterone receptor (PR), both are key estradiol-regulated genes involved in the regulation of sexual behavior, we studied possible changes of *c-fos* and PR expression in the central nervous system (CNS) of infected male mice. Indeed, *c-fos* and PR 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.*, 1999, 2004).

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.*, 2002).

Significant CNS changes in *c-fos,* and progesterone receptor (PR) expression during infection signifies the brain senses the infection

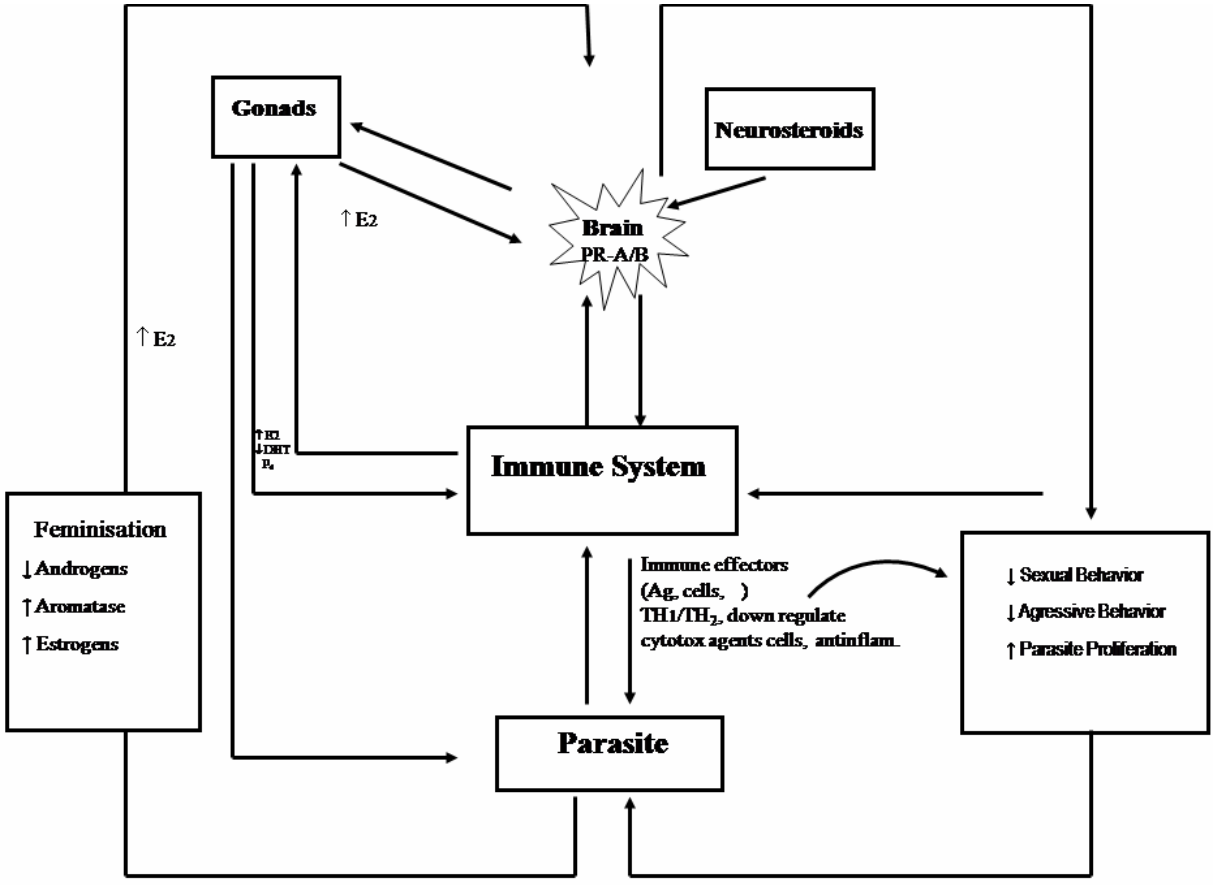

Fig. 3 Chart of the proposed host-parasite neuroimmunoendocrine network. Sex steroids may act directly upon the parasite whereby progesterone (P_4), and oestradiol (E_2) favor its reproduction. Also, sex steroids act upon parasite via the immune system, E_2 favoring a permissive Th2 response that inhibits the restrictive Th1. The brain of the host shows changes in PR, that could be the result of the high oestrogens levels that reveal that it senses and may react to the infection. Also, the outcome of the feminization process is shown, that directly affects the sexual behavior of the infected male mice, through out the binding of sex steroids and/or neurosteroids to PR. The arrows show the interconnection among all system components. (+) Positive stimulation; (-) negative stimulation.

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 (Morales-Montor *et al.*, 1999, 2004). One could argue that feminization of male hosts favors the parasite by allowing its reproduction, however it is equally arguable to consider feminization of the male host as deleterious to the parasite's completion of its cycle since there is a reduction of 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 (Fig. 3).

Not only male mice are behaviorally affected by cysticercosis, female mice also suffer perturbations in their sexual behavior, *i.e.*, receptivity to the male, as well as disruption of the estrous cycle (Arteaga *et al*., 2010).

Concluding Remarks

Until some years ago, the immune system was perceived as a system isolated from other body systems. The present review makes evident that the immune and neuroendocrine systems share numerous ligands and receptors, which results in a constant bidirectional communication. In fact, it has been postulated that an important function of the immune system is to serve as a sensory organ for cognitive stimuli that pass unnoticed to the nervous system, as could be infectious agents, such as parasites. Our present proposal is to reintegrate an important system to the physiological context of the whole organism. This will doubtlessly lead to an improved understanding of physiology, and generate changes in modern medical practice. For further understanding of the bidirectional communication process between the immune and neuroendocrine systems, it will be necessary to continue the search for ligands and receptors common to both systems, and to examine in depth

the similarities and differences in their functional regulation. In addition, it will also constitute a challenge for physiologists to integrate this information to the context of the whole organism during helminth infections. On the other hand, new information about immunoneuroendocrine interactions in infected hosts will help us to design novel therapies for the treatment and diagnosis of human diseases of apparently immune or endocrine origin. We have documented here that a complex interactive network involving the immune, endocrine and nervous systems, is in control of the parasite growth, reproduction and establishment. If such complex a management of the parasite loads, as that we shown here between different hosts and worms, extends to other parasite diseases of mammals, as current research seems to indicate in a number of helminthes 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. The evidence presented above illustrates the complexity and importance of neuroimmunoendocrine interactions during cysticercosis 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 porcines 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.

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