Advances in Neuroimmune Biology 7 (2018) 89–99
DOI 10.3233/NIB-170135
IOS Press



Review

# Chronic Infections and the Hypothalamus-Pituitary-Adrenal Axis in the Context of Immune-Mediated Inflammation

Oscar Bottasso*
*Instituto de Inmunología Clínica y Experimental de Rosario, UNR-CONICET, Rosario, Argentina*



**Abstract**. The immune system plays an essential role in distinguishing between self and non-self and hence protecting the host from infections. Upon the pathogen encounter, the host seeks to ensure an adequate inflammatory reaction to combat infection but at the same time tries to prevent collateral damage due to excessive immune activation. As such, limiting inflammation during an infection is an essential goal, for which several counterregulatory mechanisms are put into play, like the production of adrenal steroid hormones. This will assure a successful defense and adaptation of the organism to injury, highlighting the relevance of the relationship between adrenal hormones and the immune response. Chronic infections with bacteria, or parasites were found to display several endocrine abnormalities, ranging from subtle disturbances to substantial alterations in the regulation of the HPA axis. Facts accounting for such disturbances encompass several non-mutually exclusive possibilities, inflammation in neuroendocrine tissues, partly due to the presence of pathogens and the ensuing structural and functional alterations; along with the exploitation of the host's hormonal microenvironment by the infectious agent. Alterations in the steroid hormone axis may be also viewed as one of the consequences resulting from the re-directioning of energy to the immune system during chronic infections. Collectively, these alterations further contribute to a deficient control of infection and immunopathology, together with metabolic changes, which promote an unsuitable scenario for disease prognosis.

Keywords: The HPA axis, cortisol, dehydroepiandrosterone, chronic infections

*Nothing in biology makes sense except in the light of evolution*[1]

## INTRODUCTION

A great variety of organisms including bacteria, viruses, parasites and fungi can cause infection in humans. In cases wherein, defensive mechanisms are not able to cope with the infectious insult, partly because pathogens escape from immune clearance, a state of chronic infection in the form of persistent or latent infections ensues.

Microorganisms are endowed with a recognizable pathogen-associated molecular pattern, which is recognized through pathogen recognition receptors present in many immune cells, i.e., macrophages, monocytes, and dendritic cells, among others. Phagocytic cells, quickly manage to deal with such a threat through the ability to phagocytose pathogens, and to secrete proinflammatory cytokines like tumor necrosis factor alpha (TNF-$\alpha$), interleukin 1 beta (IL-1$\beta$), and IL-6 [1, 2]. Beyond their immunological effects, these cytokines produced at the site of inflammation also signal the brain directly or by induction of second intermediate messengers as well as the signaling activation through afferents in the vagus nerve. This activation of the stress system within the central nervous system (CNS) in response to neural- or blood-borne signals leads to the activation of the hypothalamic-pituitary-adrenal (HPA)

[1] Dobzhansky T. Am Biol Teacher 1973;35:125-129.

*Correspondence to: Dr. Oscar Bottasso, Instituto de Inmunología Clínica y Experimental de Rosario, UNR-CONICET, Suipacha 590, Rosario 2000, Argentina. E-mail: bottasso@idicer-conicet.gob.ar.

ISSN 1878-948X/18/$35.00 

axis and sympathetic nervous system, as effectors arms [3–6]. As such, the immune response mounted against pathogens is paralleled by a significantly altered hormonal response, as documented in a large series of experimental and clinical studies [3–6].

Many studies point out to an influential role of the interaction between immune and endocrine systems in orchestrating an effective defense strategy against the infective insult [7, 8]. Endocrine and immune systems are strictly connected by multiple mutual regulatory pathways. As above stated, proinflammatory cytokines IL-1β, IL-6, TNF-α produced in response to an infectious challenge activate the HPA axis leading to the production of adrenal steroids [3–6]. In relation to the immunomodulatory influences of adrenal steroids, glucocorticoids (GCs) suppress the immune system at several levels, avoiding the possible adverse effects of an excessive immune response and helping to terminate it once the noxious stimulus was eliminated [9–12]. Under some circumstances, particularly at the beginning of the immune response, GCs can also exert proinflammatory effects [13]. But at high concentrations, GCs generally suppress immune and inflammatory responses arising during activation of innate and adaptive immune responses. These are critical for coping with intracellular pathogens like bacteria, fungi, and parasites (cellular immunity) as well as extracellular bacteria, soluble toxins, some viruses, and multicellular parasites (humoral mechanisms). In addition, the activation of HPA axis induces the production of dehydroepiandrosterone (DHEA) and DHEA-sulphate (DHEA-s), which are known to exert anti-GC functions [14–16]. There is evidence that GCs and DHEA display opposite effects on adaptive immune cells. While GCs can inhibit both Th1 and Th2 cytokine production by activated human T cells, they predominantly affect Th1 cytokine production, shifting T cell response towards a Th2 profile [17]. Unlike this, DHEA favors a shift towards Th1 responses by upregulating the production of IL-2 and interferon gamma (IFN-γ), in addition to downregulating Th2 cytokine synthesis [18]. Within this context, DHEA and its derivatives have been proved to enhance protective immune responses against pathogens with an intracellular habitat [19–22].

As an integrated physiological circuit, the HPA axis represents a well-conserved mechanism to control/support an intense immune-inflammatory reaction as well as for the early mobilization of immune cells and their redistribution to mount an adequate defensive response. Nevertheless, when dealing with infections, immune-endocrine interactions turn out to be more complex, since pathogens *per se* can modulate endocrine function either by releasing soluble factors or by directly colonizing endocrine tissue [7, 23, 24]. In the case of chronic infections, in which pathogens are not cleared and the immune response must be sustained in time, a chronic inflammatory state establishes which results in substantial changes in immune and endocrine responses [24, 25].

This review is addressed to describe the alterations at the level of HPA in a series of chronic infectious diseases of great impact in human health as well as their repercussion in disease pathology and clinical manifestations (summarized in Table 1). For a better clarification of the diseases under analysis, supplementary information about the main features of them is provided in Box 1.

## ALTERATIONS OF ADRENAL STEROIDS DURING CHRONIC INFECTIOUS DISEASES

### *Bacterial diseases*

A study carried out several years ago in adult men with syphilis revealed higher serum levels of cortisol in presence of reduced amounts of DHEA, rendering the DHEA/Cortisol ratio in syphilitic men less than 50% respect the one seen in matched controls. Men with progressive disease -secondary syphilis- showed an even worse profile [46]. Another study by the same group showed that 17 beta-estradiol and estriol levels were reduced during the third trimester of pregnancy of syphilitic women. Analysis in newborns with congenital syphilis showed subnormal umbilical cord serum levels of DHEAs compared with data from age- and weight-matched control infants born to women with uncomplicated pregnancies. Cortisol and estriol levels were respectively increased or decreased in neonates delivered by syphilitic women [47].

Leal and cols [48]. Also analyzed the functional status of adrenocortical hormones and their relationship to the pattern of inflammatory cytokines in a series of patients with lepromatous or tuberculoid leprosy. Both baseline and stimulated adrenocorticotropic hormone (ACTH) and cortisol plasma levels were not different between patients and control subjects. In contrast, DHEAs plasma levels were significantly lower in both groups of leprosy patients. Plasma levels of IL-1β, IL-6, TNF-α, and C-reactive protein (CRP) as well as erythrocyte sedimentation rates (ESR) were significantly augmented in

**Box 1 Main clinical and pathological features of diseases under analysis**

➢ Chagas disease is a parasite infection caused by the protozoan *Trypanosoma cruzi*, usually transmitted to humans through the bite of a triatomine bug. Nowadays it has a more worldwide distribution affecting at least 8–10 million people throughout South and Central America, USA and Europe. The major complications of this disease are mega syndromes from the gastrointestinal tract and particularly the heart involvement. About 30% of individuals infected with *T. cruzi* develop chronic chagasic myocarditis resulting in severe heart disorders, which cause approximately 50,000 deaths annually [26].

➢Human African trypanosomiasis (HAT) or sleeping sickness is a vector-borne parasitic disease endemic in sub-Saharan Africa resulting from the infection with an extracellular parasite called Trypanosoma (genus) brucei (species) transmitted by a tsetse fly bite. The disease in humans, which are mainly caused by *T. brucei gambiense* (98% of all reported HAT cases) and *T. brucei rhodesiense* threatens the health of about 70 million people and 50 million cattle. Other important species causing animal diseases alongside *Trypanosoma brucei* include *Trypanosoma vivax* and *Trypanosoma congolense* [27, 28].

➢As regards Leishmaniasis this disease presents in three major clinical forms: cutaneous, mucosal, or visceral involvement. In the Americas, the most frequent etiological agents are *Leishmania braziliensis*, *Leishmania mexicana*, *Leishmania panamensis*, *Leishmania amazonensis*, and *Leishmania guyanensis*, whereas in the Old World the responsible species are *Leishmania major*, *Leishmania ethiopica*, and *Leishmania tropica*. Cutaneous leishmaniasis can manifest as a single ulcer in the skin, or in rare cases the disseminated form presenting large numbers of lesions. There also exists the diffuse cutaneous leishmaniasis consisting of nodular composed of heavily infected macrophages. In some cases, parasites from cutaneous leishmaniasis metastasize to the nasal–pharyngeal mucosa, leading to a severe form named mucosal leishmaniasis. In visceral leishmaniasis or Kala Azar the parasite replicates in the spleen, liver, and bone marrow, and in the absence of drug treatment, this form is fatal [29, 30].

➢Leprosy, whose etiological agent is *Mycobacterium leprae*, affects mainly the skin and peripheral nerves. It is endemic in many regions of the world and presents a wide spectrum of clinical manifestations dependent on the interaction of *M. leprae* with host specific immunity. At one end there are patients with tuberculoid disease that possess suitable cell-mediated immune response and few lesions with no detectable mycobacteria. The other pole of the spectrum is composed by patients with lepromatous leprosy who are anergic towards *M. leprae* and present multiple lesions plenty of bacilli. Between both extremes lie borderline leprosy patients, with detectable but unstable cell-mediated immunity and numerous lesions [31].

➢Malaria caused by *Plasmodium vivax* is a serious threat to human health, attacking 100 to 400 million people each year among the 2.5 billion living at endemic risk. *Plasmodium falciparum* is another important cause of malaria, involving similar global burden estimates [32–34]. The three-remaining species responsible for human malaria -*Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi*- are less relevant [32–34]. The asexual blood stage of Plasmodium infects mature erythrocytes and is responsible for the most aggressive forms of human malaria, killing at least one million children per year. Severe malaria includes multiple additional pathologies like anemia and cerebral malaria [35].

➢Neurocysticercosis (NCC), constitutes a brain infection by *Taenia solium* larvae and represents one of the leading causes of epilepsy and neurological morbidity worldwide. The disease in humans results from the ingestion of the larval form of *Taenia solium* by faeco-oral contamination [36, 37]. These larval oncospheres have predilection to different sites like eyes, heart, skeletal muscles and the brain. NCC occurs in both adults and children consisting of single or multiple cysts that progress from viable vesicular to colloidal and granuloma states and final calcification [38]. Cysticerci localization in the CNS and the intensity of inflammation accounts for disease severity [39].

➢Schistosomiasis is another chronic disease affecting nearly 260 million people worldwide mainly in tropical and subtropical regions [40]. *Schistosoma mansoni* is a major causative agent of human intestinal schistosomiasis which may present with hepatomegaly, splenomegaly and portal hypertension [40]. The transmission cycle is initiated when the miracidium larval stage of the parasite infects a suitable molluscan host. In a compatible infection, the intramolluscan parasite undergoes asexual multiplication and the human infecting cercaria larval stage is released into water. Human infection occurs when the cercariae come in contact with human skin through contaminated freshwater [40, 41].

➢Syphilis, on its own, is a sexually transmitted disease caused by the spirochete *Treponema pallidum*. Syphilis is a multistage disease which is usually transmitted through sexual contact or mother-infant transmission route. The disease presents a series of highly variable clinical manifestations during the first 2-3 years of infection, followed by a typically prolonged latent stage. This can evolve into clinically apparent tertiary stage years or even decades after initial infection, with neurosyphilis constituting a typical late manifestation. Though the incidence of primary and secondary syphilis is still increasing, the incidence of tertiary syphilis has decreased due to widespread availability of effective treatment [42, 43].
➢*Toxoplasma gondii* is an obligate intracellular parasite able to infect about 30% of humans globally. Sources of infection for humans include food, the water supply, and organ transplants as well as direct contact with cat feces in the soil and domestic litter. Most people infected postnatally have no recognized symptoms, but toxoplasmosis can result in severe disease in immune-compromised individuals or when acquired congenitally with serious damage of the brain and eyes [44].
➢Tuberculosis (TB) is one of the most important infectious diseases and cause of death around the world. It is estimated that 2 billion persons are infected with *Mycobacterium tuberculosis*, and 8 to 12 million new cases of active tuberculosis occur each year, accounting for 2-3 million deaths annually [45]. Most people infected with *M. tuberculosis* have a clinically latent infection, which remains dormant constituting asymptomatic and non-contagious carriers. The development of clinical post-primary TB occurs in 5%–10% of latently infected persons. Pulmonary disease is the most common form of post-primary TB and comprises a great spectrum of manifestations, ranging from few foci in the upper lobes to bilateral involvement with strong tissue damage [25].

LL/BL (lepromatous/borderline lepromatous) leprosy patients. There was a significant inverse correlation between DHEAs and IL-6, TNF-α, and CRP concentrations, whereas levels of IL-6, TNF-α, CRP and ESR appeared positively correlated.

By evaluating hormonal and cytokine levels in patients with TB, we have shown imbalanced immune-endocrine responses. This was characterized by increased levels of pro-inflammatory cytokines, cortisol and estradiol, reduced amounts of testosterone and DHEA, together with an increased Cort/DHEA ratio, more pronounced in patients with progressive disease [49]. Studies in active TB patients from Turkey and South Africa also revealed decreased DHEA levels [50–52], whereas cortisol concentrations appeared unchanged [50, 51] or slightly increased [52].

*Parasitic diseases*

Galindo-Sevilla and cols [53] measured the serum concentrations of cortisol and DHEA in patients with diffuse (DL) or localized (LL) cutaneous leishmaniasis due to *L. mexicana mexicana*. Hormone levels were lower in DL compared with controls and LL. Also, a lower percentage of IFN-γ positive cells along with higher levels of IL-6 and anti-leishmania antibodies were found in DL patients. In the whole group of patients, IL-6 and DHEA were inversely correlated [53].

Another study carried out in Brazil in cases with LL evaluated plasma levels of cortisol, DHEAs, estradiol, prolactin and testosterone and their association with clinical disease parameters (lesion size, treatment schedule and time to reach clinical cure) together with the *in vitro* synthesis IFN-γ, IL-10 and TNF-α to antigen-specific stimulation. Patients displayed lower levels of prolactin and testosterone, with no changes in cortisol and estradiol concentrations. DHEAs concentrations were found decreased in male patients resulting in altered DHEA/cortisol ratio. Plasma levels of cortisol, estradiol or prolactin correlated positively with at least one clinical parameter; whereas cortisol and prolactin levels exhibited a negative correlation with *in vitro* levels of IFN-γ [54].

Some years ago, we have also studied the features of immunoneuroendocrine responses in patients with chronic Chagas disease with different degree of heart involvement (indeterminate, mild/moderate or severe) [55]. A systemic inflammatory scenario was evident in patients with severe myocarditis, exemplified in increased levels of TNF-α, IL-17, IL-6, IFN-γ and nitric oxide serum levels. Levels of ACTH and cortisol were similar among groups, whereas DHEAs levels appeared diminished as disease severity progressed, with an unbalanced cortisol/DHEA-s ratio, implying that severe cases are devoid of an adequate neuroendocrine anti-inflammatory milieu.

Libonati et al. [56] analyzed the levels of cortisol and DHEA in patients with uncomplicated

*Plasmodium falciparum* malaria, before treatment as well as 1 and 8 days after its initiation. The sample was composed of 24 patients ranging from 15 to 47 years, half of them primoinfected. Among the 12 multi-infected patients, two thirds of them had malaria for the second time. The levels of both hormones were significantly higher on Day 0 than on Day 7, in coincidence with a decreasing parasitemia [53]. Since the study did not include a control population sample the status of adrenal steroid production in relation to healthy people cannot be appraised. Another study in Vietnamese patients with malaria challenged with corticotrophin-releasing hormone - CRH- (CRH-test) revealed an impaired ACTH and adrenal response respect to healthy controls, partly related to increased IL-6 levels [57].

In a cross-sectional sample of 12–18-year-old schoolgirls from an area of intense transmission in Kenya, DHEAs levels were significantly associated with decreased *P. falciparum* parasitemia, even after adjustment for age. Individuals with low DHEAs levels had significantly higher parasite densities than those with higher DHEAs amounts [58].

In a sample of patients with NCC, Cardenas et al. reported lower concentrations of DHEA respect to healthy controls. Male patients also had lower concentrations of 17b-estradiol and higher concentrations of luteinizing hormone, whereas those with severe disease exhibited higher amounts of follicle-stimulating hormone and lower testosterone levels, as well. In the clinically severe group of women, progesterone and androstenedione appeared lowered. Within males, estradiol levels correlated with IL-10 concentrations in cerebrospinal fluid while in female cases DHEA and androstenedione levels correlated with the respective *in vitro* synthesis IL-1β and IL-17 [59].

Concerning schistosomiasis, a study carried out in 135 Ethiopian residents showed a significant negative correlation between serum levels of DHEAs and intensity of *S. mansoni* infection, regardless of age [60]. Further evidence in favor of a protective role of DHEA during this parasitosis comes from the demonstration of a more favorable evolution of schistosomiasis when DHEA levels appeared increased [61]. At the experimental level, baboons with primary *S. mansoni* infection had decreased CRH serum levels, whereas in animals undergoing a secondary infection CRH concentrations appeared increased [62].

De la Torre et al., carried out a study in individuals with evidence of *Toxoplasma gondii* infection distributed into the following groups: chronic and asymptomatic cases; chronic patients with retinal scars of retinochoroiditis; and acute symptomatic patients with active retinochoroiditis. Patients revealed no changes in DHEAs levels compared to seronegative controls, even when adjusting for sex and age [63]. In a parallel study, *Toxoplasma gondii*-infected men showed low levels of gonadotrophic hormones and gonadal insufficiency [64–66].

Moving to another relevant protozoan disease, African trypanosomiasis, infection in humans with *Trypanosoma brucei* is also accompanied by adrenal insufficiency in presence of increased levels of TNF-α and IL-6 [67, 68]. In line with this, challenge with CRH (CRH-test) in cattle infected with *Trypanosoma congolense* revealed an impaired ACTH and adrenal response [69].

## POTENTIAL MECHANISMS INVOLVED IN HPA DISRUPTION

The processes by which chronic infectious diseases result in dysregulated adrenal steroid production can be varied. The pathogen persistence along with the protracted immune-inflammatory response is much likely to interfere not only with the classical regulatory axis involved in hormonal synthesis but also at the local glandular level. For instance, there is ample evidence for the interactions occurring in the adrenal gland between resident cells, i.e., endothelial cells, chromaffin and adrenocortical cells with infiltrating immune cells [70]. Regardless of the type of interaction, direct cell-cell contact or paracrine influences, the hormonal production results modified.

There is evidence that *T. brucei* infection may cause adrenal inflammation unrelated to an antibody-driven inflammatory reaction [68]. Cattle infected with *T. congolense* also had alterations in the pituitary microvasculature along with a pituitary dysfunction related to the presence of the parasite *in situ* [69]. Other histopathological studies also evidence pituitary necrosis in concomitancy with inflammatory infiltrates and parasite nests during HAT [71]. Studies during *T. cruzi* infection revealed histological alterations of endocrine glands characterized by T cell and macrophage infiltration [reviewed in 7]. There is also evidence of an immunological destruction of *T. cruzi*-infected glial, astrocytic and Schwann cells which may indirectly affect neuroendocrine functions [72]. Other studies in acutely *T. cruzi*-infected mice showed the presence of amastigote nests in the

adrenal gland [73, 74], along with the identification of parasite-derived antigens at the adrenal and pituitary level [73]. Microscopic analysis of tissue specimens from patients with acute Chagas disease revealed the presence of amastigote nests in the ovary, testis, thyroid, as well as cells from the nervous system [72].

Our studies in human TB also provided evidence of an immune-endocrine cross talk leading to an altered hormonal production. In fact, culture supernatants (SN) from *M. tuberculosis* antigen-stimulated PBMC of TB patients inhibited DHEA secretion by the human adrenal cell line NCI-H295-R [49]. Moreover, treatment with anti-transforming growth factor beta (TGF-β) antibodies abrogated the inhibitory effects of these SN on DHEA release by cultured adrenal cells [75].

In discussing possibilities, changes in hormonal production may also have to do with some unidentified pathogen influences addressed to ultimately create a more favorable microenvironment for pathogen growth. For instance, larvae from *Toxocara canis* were found to express PR receptors, with PRL stimulation accelerating the larval growth [76]. Work from the same group also demonstrated that exposure of *Haemonchus contortus* larvae to progesterone inhibited the *in vitro* molting process of larvae from one to another larval stage increasing their motility during the time of hormonal exposure [77].

Turning to adrenal steroids, *in vitro* exposure to cortisol or DHEA results in a respective increase or decrease of malaria parasites growth [78, 79]. In the same sense, *in vitro* exposure of *Entamoeba histolytica* trophozoites to DHEA markedly inhibited parasite proliferation, adherence and motility, with some evidence of trophozoite lysis. In contrast, a recovered parasite proliferation was found when trophozoites were treated with cortisol. Yet, infected hamster recipients of DHEA treatment had exacerbated amebic liver abscesses [80].

Several pieces of evidence indicate that DHEA can be beneficial in many infectious processes. For instance, treatment with a synthetic DHEA derivative improved the course of experimental murine tuberculosis [20], whereas the administration of DHEA sulphate improved IgG and IFN-γ production in mice immunized with heat shock proteins from *M. tuberculosis* [81]. In dexamethasone-immunosuppressed mice undergoing an experimental infection by the coccidian parasite, *Cryptosporidium parvum*, treatment with DHEA significantly reduced both fecal oocyst shedding and parasite colonization of the ilea. Immunosuppressed mice given DHEA had more splenic total T cells, CD4+ T cells, and CD8+ T cells than the untreated counterparts [82]. Another mouse study of experimental infections with *Cryptosporidium parvum* or avirulent *Toxoplasma gondii* also showed that DHEA administration reduced mortality rates along with a significant reduction in the cryptosporidial oocyst count in stool and intestinal villi or toxoplasma cysts in the brains [83]. Moving to *T. cruzi*, infection in rodents with this protozoan parasite was also found ameliorated by DHEA administration, partly due to the beneficial effects of DHEA on the host immune response [84, 85]. Apart from these demonstrations, there is also evidence that gonadal steroids can also exert immunomodulatory effects or relevance in infectious pathology [86, 87].

Beyond the typical mechanistic explanation for biological phenomena, from a more teleological standpoint the question also arises as to the adaptive component shaped throughout evolution. In general, responses to environmental stimuli comprise physiological adaptations that can be working in seconds or minutes, sometimes days to weeks or lifetime due to the development of plasticity [88]. The major functions for which humans have been selected, and the ensuing trade-offs deal with preservation, growth, reproduction, and defensive mechanisms for combating infections. Infectious diseases of chronic nature may have started to appear later when life expectancy prolonged because of an improved standard of living. Although non-fatal in the short-term, such pathogen persistence results in a state of chronic inflammation characterized by a protracted, dysregulated and maladaptive response comprising active inflammation, tissue destruction and attempts at tissue repair [89]. Persistent inflammation is not an exclusive hallmark of infectious pathology but also many other chronic human conditions and diseases, like atherosclerosis, or autoimmune diseases, among others [90, 91]. Studies in patients with chronic disabling inflammatory diseases, i.e., rheumatoid arthritis, demonstrated that the state of prolonged immune aggression coexists with a deficient production of DHEA [90, 91]. In trying to cope with chronic inflammation the host attempts to preserve cortisol production a highly influential hormone in the response to several types of stress, including the immunologically mediated one. In this hierarchical conciliation, production of other steroid hormones may result more compromised. This would not only those produced by the adrenal gland but also at the gonad level. In this regard, we have recently demonstrated that male TB patients also display a disruption of the hypothalamic-pituitary-

Table 1
Alterations in cortisol and DHEA levels during major chronic infectious diseases

| Disease | Country | Cortisol | DHEA (DHEAs) | Ratio | Ref. # |
|---|---|---|---|---|---|
| African trypanosomiasis | Uganda | Decreased | Not assessed | NA | 64,65 |
| Chagas disease | Argentina | Not different | Decreased | Abnormal[a] | 52 |
| Leishmaniasis | Mexico | | | Non-estimated | 50 |
| DCL | | Decreased | Decreased | | |
| LCL | | Less decreased | Less decreased | | |
| LCL | Brasil | Not different | Lower | Abnormal | 51 |
| Leprosy | Brasil | Not different | Decreased in both | Non-estimated | 48 |
| Lepromatous | | | | | |
| Tuberculoid | | | | | |
| Malaria[b] | Brasil | Decreased by treatment | Decreased by treatment | Non-estimated | 53 |
| Malaria | Vietnam | Relatively decreased | Not assessed | NA | 54 |
| Malaria[c] | Kenya | Not assessed | Decreased | NA | 55 |
| Neurocysticercosis | Mexico | Not different | Decreased | Non-estimated | 56 |
| Schistosomiasis | Ethiopia and Kenya | Not assessed | Negatively correlated with the intensity of infection | NA | 57,58 |
| Syphilis[d] | USA | Increased | Decreased | Abnormal | 46,47 |
| Toxoplasmosis | Colombia | Not assessed | Not different | NA | 60 |
| Tuberculosis | Argentina | Increased | Decreased | Abnormal | 49 |
| Tuberculosis | Turkey | Increased | Not assessed | NA | 51 |
| Tuberculosis | Turkey | Not different | Decreased | Non-estimated | 52 |
| Tuberculosis | South Africa | Not different | Decreased | Non-estimated | 50 |

DCL, diffuse cutaneous leishmaniasis; LCL, localized cutaneous Leishmaniasis. NA: not applicable. [a]In severe patients. [b]The study lacked controls. [c]After adjustment for age, individuals with low DHEAs levels had significantly higher parasite densities than did individuals with higher DHEAs levels. [d]Progressive disease (secondary syphilis) showed a worse profile.

gonadal axis resulting in a decreased testosterone production [49, 92].

## CLINICAL AND PATHOLOGICAL IMPLICATIONS

In addition to the well-known implications of chronic infectious disease, in terms of tissue damage, long-lasting inflammation and the accompanying hormonal disturbances may be able, *per se*, to result in a series of alterations impairing the clinical status of patients and disease evolution. Alterations of steroid hormone axes may account for an impaired immune response leading to a deficient control of infection and immunopathology, because of the above commented effects of cortisol and DHEA on the immune responses [9–12, 14–18].

Without being necessarily evident in clinical terms, the thymic microenvironment may be an additional target of organ involvement during chronic infectious diseases. This will further contribute to a deficient immune competence not only because of direct affectation but also due to the adverse effects of the unbalanced production of GCs and DHEA on thymocyte differentiation [93].

From another standpoint, exposure to life-threatening infectious pathogens also impact in resource availability since developing an immune response is expensive in metabolic terms [94]. Studies in children demonstrated that each degree of temperature augment from fever leads to an 11.3% increase of the metabolic rate [95]. The establishment of a new metabolic set point during infections intends to attain an optimal functioning of the immunological needs [96, 97], without compromising the needs of some essential physiological functions. Nevertheless, energy is not an unlimited resource, for which situations wherein the infection cannot be controlled may result in a metabolic deficit further affecting the defensive reaction and disease outcome. This will help to explain the debilitating chronic weight loss seen in a wide range of diseases, including the infectious ones [98, 99]. This seems to be due to an unbalanced relation between metabolism and the immune response, in which immunologic and neuroendocrine factors, as well as products released by the adipose tissue play an essential role [100].

Within this context, TB is a clear example in which the disease can lead to a consumption state [101], formerly defined as phthisis (Greeek *phthisis* = consumption). While being from ancient times,

the impact of such negative metabolic balance on the specific immune response and disease outcome has received much less attention. We have shown that the impaired clinical state of TB patients, i.e. weight loss, is related to the immune-endocrine disturbances, supporting the view that immune and endocrine mediators play a role in energy expenditure and metabolism [102]. By using a multivariate analysis, it was shown that defective *in vitro* immune responses of TB patients to mycobacterial antigens (decreased lymphoproliferation and increased IL-10 and TGF-β production) loss statistical significance when adjusted to their reduced body mass index (BMI). Correlation studies indicated that the BMI was negatively associated with IL-6 circulating levels, whereas the levels of this cytokine correlated positively with cortisol concentrations. Stepwise regression analysis further demonstrated that 74% of the variability in IL-6 concentrations was related to the BMI, as well as cortisol and IFN-γ serum concentrations [102].

## CONCLUDING REMARKS

There seems to be a delicate balance between protective and harmful influences of adrenal steroid hormones. In fact, chronic hyper-activation of HPA axis may increase susceptibility or exacerbate the course of infectious diseases because of the immunosuppressive effects of GCs, whereas blunted HPA axis response may be related to an increased vulnerability to immune-based diseases. The experimental and clinical data discussed here strongly suggest a role of an inadequate HPA axis response in the physiopathology and outcome of chronic infectious diseases.

The long evolutionary history of the bi-directional communication between the neuroendocrine and immune systems implies the need of thinking in a wider perspective to eventually reveal the mechanisms and factors that are of major relevance for disease outcome to a pathogen. Indeed, an imbalance in the interplay between neuroendocrine and immune systems can result in substantial changes in the resistance/susceptibility state to infections. Improving our knowledge about these interactions is mandatory. Particularly, a more detailed analysis on the cross-talk between hormones and immune mediators, and the role of such interactions in the clinical setting will provide valuable insights into how disruption within one or more of these compartments may influence our ability to cope with pathogens, regulate inflammation, or tissue repairing. In parallel, a better understanding of these processes may help to delineate valuable new interventional approaches to improve disease control.

## ACKNOWLEDGMENTS

This work was partly supported by grants from FONCYT (PICT 2016-0279).

## CONFLICT OF INTEREST

The author has no conflict of interest to declare.

## REFERENCES

[1] Medzhitov R, Janeway Jr C. Innate immunity. N Engl J Med. 2000;343(5):338-44.
[2] Feghali CA, Wright TM. Cytokines in acute and chronic inflammation. Front Biosci. 1997;2:d12-26.
[3] Webster J, Tonelli J, Sternberg EM. Neuroendocrine regulation of immunity. Annu Rev Immunol. 2002;20:125-63.
[4] Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. New Eng J Med. 1995;332(20):1351-62.
[5] Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve-an integrative interface between two supersystems: The brain and the immune system. Pharmacol Rev. 2000;52(4):595-638.
[6] Besedovsky H, del Rey A. Immune-neuro-endocrine interactions: Facts and Hypothesis. Endocr Rev. 1996;17(1):64-95.
[7] Perez AR, Bottasso O, Savino W. The impact of infectious diseases upon neuroendocrine circuits. Neuroimmunomodulation. 2009;16(2):96-105.
[8] Roggero E, Perez AR, Tamae-Kakazu M, Piazzon I, Nepomnaschy I, Besedovsky HO, et al. Endogenous glucocorticoids cause thymus atrophy but are protective during acute *Trypanosoma cruzi* infection. J Endocrinol. 2006;190(2):495-503.
[9] Hu X, Wai-Ping Li, Meng C, Ivashkiv LB. Inhibition of IFN-γ signaling by glucocorticoids. J Immunol. 2003;170(9):4833-39.
[10] Wiegers GJ, Reul JM. Induction of cytokine receptors by glucocorticoids: Functional and pathological significance. Trends Pharmacol Sci. 1998;19(8):317-21.
[11] Auphan N, DiDonato JA, Rosette C, Helmberg A, Karin M. Immunosuppression by glucocorticoids: Inhibition of NFκB activity through induction of IκB synthesis. Science. 1995;270(5234):286-90.
[12] Scheinman RI, Cogswell PC, Lofquist AK, Baldwin Jr AS. Role of transcriptional activation of IκB in mediation of immunosuppression by glucocorticoids. Science. 1995;270(5234):283-86.
[13] Cruz-Topete D, Cidlowski JA. One hormone, two actions: Anti- and pro-inflammatory effects of glucocorticoids. Neuroimmunomodulation. 2015;22(1-2):20-32.
[14] Padgett DA, Loria RM. Endocrine regulation of murine macrophage function: Effects of dehydroepiandrosterone,

androstenediol, and androstenetriol. J Neuroimmunol. 1998;84(1):61-8.

[15] Kimura M, Tanaka S, Yamada Y, Kiuchi Y, Yamakawa T, Sekihara H. Dehydroepiandrosterone decreases serum tumor necrosis factor-alpha and restores insulin sensitivity: Independent effect from secondary weight reduction in genetically obese Zucker fatty rats. Endocrinology. 1998;139(7):3249-53.

[16] Blauer KL, Poth M, Rogers WM, Bernton EW. Dehydroepiandrosterone antagonizes the suppressive effects of dexamethasone on lymphocyte proliferation. Endocrinology. 1991;129(6):3174-79.

[17] Ashwell JD, Lu FWM, Vacchio MS. Glucocorticoids in T cell development and function. Ann Rev Immunol. 2000;18:309-45.

[18] Kasperska-Zajac A. Asthma and dehydroepiandrosterone (DHEA): Facts and hypotheses. Inflammation. 2010;33(5);320-4.

[19] Brazao V, Santello FH, Caetano LC, Del Vecchio Filipin M, Paula Alonso Toldo M, et al. Immunomodulatory effects of zinc and DHEA on the Th-1 immune response in rats infected with *Trypanosoma cruzi*. Immunobiology. 2010;215(5):427-34.

[20] Hernandez-Pando R, Aguilar-Leon D, Orozco H, Serrano A, Ahlem C, Trauger R, Schramm B, et al. 16α-Bromoepiandrosterone restores T helper cell type 1 activity and accelerates chemotherapy-induced bacterial clearance in a model of progressive pulmonary tuberculosis. J Infect Dis. 2005;191(2):299-306.

[21] Loria RM, Conrad DH, Huff T, Carter H, Ben-Nathan D. Androstenetriol and androstenediol. Protection against lethal radiation and restoration of immunity after radiation injury. Ann NY Acad Sci. 2000;917:860-7.

[22] Reading C, Dowding C, Schramm B, Garsd A, Onizuka-Handa N, Stickney D, et al. Improvement in immune parameters and human immunodeficiency virus-1 viral response in individuals treated with 16α-bromoepiandrosterone (HE2000). Clin Microbiol Infect. 2006;12(11):1082-8.

[23] Kelestimur F, Unlu Y, Ozesmi M, Tolu I. A hormonal and radiological evaluation of adrenal gland in patients with acute or chronic pulmonary tuberculosis. Clin Endocrinol. 1994;41(1):53-6.

[24] Chrousos GP, Zapanti ED. Hypothalamic-pituitary adrenal axis in HIV infection and disease. Endocrinol Metab Clin North Am. 2014;43(3):791-806.

[25] Bottasso O, Bay ML, Besedovsky H, del Rey A. Adverse neuro-immune-endocrine interactions in patients with active tuberculosis. Mol Cell Neurosci. 2013;53:77-85.

[26] Rassi Jr A, Rassi A, Marin-Neto JA. Chagas disease. Lancet. 2010;375(9723):1388-402.

[27] Büscher P, Cecchi G, Jamonneau V, Priotto G. Human African trypanosomiasis. Lancet. 2017. pii: S0140-6736(17)31510-6.

[28] Aksoy S, Buscher P, Lehane M, Solano P, Van Den Abbeele J. Human African trypanosomiasis control: Achievements and challenges. PLoS Negl Trop Dis. 2017;11(4):e0005454.

[29] Barral A, Costa JM, Bittencourt AL, Barral-Netto M, Carvalho EM. Polar and subpolar diffuse cutaneous leishmaniasis in Brazil: Clinical and immunopathologic aspects. Int J Dermatol. 1995;34(7):474-9.

[30] Carvalho LP, Passos S, Schriefer A, Carvalho EM. Protective and pathologic immune responses in human tegumentary leishmaniasis. Front Immunol. 2012;3:301.

[31] Rodrigues LC, Lockwood DNJ. Leprosy now: Epidemiology, progress, challenges, and research gaps. Lancet Infect Dis. 2011;11(6):464-70.

[32] Mendis K, Sina BJ, Marchesini P, Carter R. 2001. The neglected burden of *Plasmodium vivax* malaria. Am J Trop Med Hyg. 2001;64(1-2 Suppl):97-106.

[33] Guerra CA, Howes RE, Patil AP, Gething PW, Van Boeckel TP, Temperley WH, et al. The international limits and population at risk of *Plasmodium vivax* transmission in 2009. PLoS Negl Trop Dis. 2010;4(8):e774.

[34] Guerra CA, Snow RW, Hay SI. Mapping the global extent of malaria in 2005. Trends Parasitol. 2006;22(8):353-8.

[35] Haldar K, Murphy SC, Milner DA, Taylor TE. Malaria: Mechanisms of erythrocytic infection and pathological correlates of severe disease. Annu Rev Pathol. 2007;2: 217-49.

[36] Nash TE, Mahanty S, Garcia HH. Neurocysticercosis-more than a neglected disease. PLoS Negl Trop Dis. 2013;7(4):e1964.

[37] Sciutto E, Fragoso G, Fleury A, Laclette JP, Sotelo J, Aluja A, Vargas L, et al. *Taenia solium* disease in humans and pigs: An ancient parasitosis disease rooted in developing countries and emerging as a major health problem of global dimensions. Microbes Infect. 2000;2(15):1875-90.

[38] Garcia HH, Del Brutto OH, Cysticercosis Working Group in Peru. Neurocysticercosis: Updated concepts about an old disease. Lancet Neurol. 2005;4(10):653-61.

[39] Fleury A, Dessein A, Preux PM, Dumas M, Tapia G, Larralde C, et al. Symptomatic neurocysticercosis: Host and exposure factors relating with disease heterogeneity. J Neurol. 2004;251(7):830-7.

[40] WHO. Schistosomiasis and soil-transmitted helminthiases: Number of people treated worldwide in 2015. Weekly Epidemiol Rec. 2016;49/50, 91:589-600.

[41] Morales-Montor J, Hall CA. The host–parasite neuroimmunoendocrine network in schistosomiasis: Consequences to the host and the parasite. Parasite Immunol. 2007;29(12):599-608.

[42] Hook EW III, Marra CM. Acquired syphilis in adults. N Engl J Med. 1992;326(16):1060-9.

[43] Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. PLoS One. 2015;10(12):e0143304.

[44] Remington JS, McLeod R, Thulliez P, Desmonts G. Toxoplasmosis. In: Remington JS, Klein G, Wilson C, Baker C, editors. Infectious disease of the fetus and newborn infant. Philadelphia: W.B. Saunders; 2010. 6th ed. p. 947-1091.

[45] WHO. Global tuberculosis report 2016, http://apps.who.int/iris/bitstream/10665/250441/1/9789241565394-eng.pdf (accessed Nov 6, 2017).

[46] Parker Jr CR, Schuster MW. Effects of syphilis infection on adrenocortical function in men. Proc Soc Exp Biol Med. 1991;197(2):165-7.

[47] Parker Jr CR, Wendel GD. The effects of syphilis on endocrine function of the fetoplacental unit. Am J Obstet Gynecol. 1988;159(6):1327-31.

[48] Leal AMO, Magalhaes PKR, Souza CS, Foss NT. Adrenocortical hormones and interleukin patterns in leprosy. Parasite Immunol. 2003;25(8-9):457-61.

[49] del Rey A, Mahuad CV, Bozza V, Bogue C, Farroni MA, Bay ML, et al. Endocrine and cytokine responses in humans with pulmonary tuberculosis. Brain Behav Immun. 2007;21(2):171-9.

[50] Keven K, Uysal AR, Erdogan G. Adrenal function during tuberculous infection and effects of antituberculosis treatment on endogenous and exogenous steroids. Int J Tuberc Lung Dis. 1998;2(5):419-24.
[51] Ellis E, Tayoub F. Adrenal function in tuberculosis. Br J Dis Chest. 1986;80 :(1)7-12.
[52] Kelestimur F, Goktas Z, Gulmez I, Unluhizarci K, Bayram F, Ozesmi M, et al. Low dose (1 microg) adrenocorticotropin stimulation test in the evaluation of hypothalamo-pituitary-adrenal axis in patients with active pulmonary tuberculosis. J Endocrinol Invest. 2000;23(4):235-9.
[53] Galindo-Sevilla N, Soto N, Mancilla J, Cerbulo A, Zambrano E, Chavira R, et al. Low serum levels of dehydroepiandrosterone and cortisol in human diffuse cutaneous Leishmaniasis by Leishmania mexicana. Am J Trop Med Hyg. 2007;76(3):566-72.
[54] Baccan GC, Oliveira F, Duranes Sousa A, Cerqueira NA, Lopes Costa JM, Barral-Netto M, et al. Hormone levels are associated with clinical markers and cytokine levels in human localized cutaneous Leishmaniasis. Brain Behav Immun. 2011;25(3):548-54.
[55] Pérez AR, Silva-Barbosa SD, Berbert LR, Revelli S, Beloscar J, Savino W, et al. Immunoneuroendocrine alterations in patients with progressive forms of chronic Chagas disease. J Neuroimmunol. 2011;235(1-2):84-90.
[56] Libonati RM, de Mendonca BB, Maués JA, Quaresma JA, de Souza JM. Some aspects of the behavior of the hypothalamus–pituitary–adrenal axis in patients with uncomplicated *Plasmodium falciparum* malaria: Cortisol and dehydroepiandrosterone levels. Acta Tropica. 2006;98(3):270-6.
[57] Davis TM, Li TA, Tran QB, Robertson K, Dyer JR, Phan TD, et al. The hypothalamic-pituitary-adrenocortical axis in severe falciparum malaria: Effects of cytokines. J Clin Endocrinol Metab. 1997;82(9):3029-33.
[58] Leenstra T, ter Kuile FO, Kariuki SK, Nixon CP, Oloo AJ, Kager PA, et al. Dehydroepiandrosterone sulfate levels associated with decreased malaria parasite density and increased hemoglobin concentration in pubertal girls from western kenya. J Infect Dis. 2003;188(2): 297-304.
[59] Cárdenas G, Valdez R, Sáenz B, Bottasso O, Fragoso G, Sciutto E, et al. Impact of Taenia solium neurocysticercosis upon endocrine status and its relation with immunoinflammatory parameters. Int J Parasitol. 2012;42(2): 171-6.
[60] Abebe F, Birkeland KI, Gaarder PI, Petros B, Gundersen SG. The relationships between dehydroepiandrosterone sulphate (DHEAS), the intensity of *Schistosoma mansoni* infection and parasite-specific antibody responses. A cross-sectional study in residents of endemic communities in north-east Ethiopia. APMIS. 2003;111(2):319-28.
[61] Fulford AJ, Webster M, Ouma JH, Kimani G, Dunne DW. Puberty and age-related changes in susceptibility to schistosome infection. Parasitol Today. 1998;14(1):23-26.
[62] Morales-Montor J, Newhouse E, Mohamed F, Baghdadi A, Damian RT. Altered levels of hypothalamic-pituitary-adrenocortical axis hormones in baboons and mice during the course of infection with *Schistosoma mansoni*. J Infect Dis. 2001;183(2):313-20.
[63] De la Torre A, Ríos-Cadavid AC, Cardozo-García CM, Padilla L, Gómez-Marín JE. Serum levels of dehydroepiandrosterone sulfate (DHEAS) in ocular toxoplasmosis. J Microbiol Immunol Infection. 2012;45(1):65-8.
[64] Oktenli C, Doganci L, Ozgurtas T, Araz RE, Tanyuksel M, Musabak U, et al. Transient hypogonadotrophic hypogonadism in males with acute toxoplasmosis: Suppressive effect of interleukin-1 beta on the secretion of GnRH. Hum Reprod. 2004;19(4):859-66.
[65] Setian N, Andrade RS, Kuperman H, Manna TD, Dichtchekenian V, Damiani D. Precocious puberty: An endocrine manifestation in congenital toxoplasmosis. J Pediatr Endocrinol Metab. 2002;15(9):1487-90.
[66] Massa G, Vanderschueren-Lodeweyckx M, Van Vliet G, Craen M, de Zegher F, Eggermont E. Hypothalamo-pituitary dysfunction in congenital toxoplasmosis. Eur J Pediatr. 1989;148(8):742-4.
[67] Reincke M, Heppner C, Petzke F, Allolio B, Arlt W, Mbulamberi D, et al. Impairment of adrenocortical function associated with increased plasma tumor necrosis factor-alpha and interleukin-6 concentrations in African trypanosomiasis. Neuroimmunomodulation. 1994;1(1): 14-22.
[68] Reincke M, Arlt W, Heppner C, Petzke F, Chrousos GP, Allolio B. Neuroendocrine dysfunction in African trypanosomiasis. The role of cytokines. Ann NY Acad Sci. 1998;840:809-21.
[69] Abebe G, Eley RM, Ole-MoiYoi OK. Reduced responsiveness of the hypothalamic-pituitary-adrenal axis in Boran *(Bos inducus)* cattle infected with *Trypanosoma congolense*. Acta Endocrinol (Copenh). 1993;129(1): 75-80.
[70] Kanczkowski W, Sue M, Bornstein SR. Adrenal gland microenvironment and its involvement in the regulation of stress-induced hormone secretion during sepsis. Front Endocrinol. 2016;7:156.
[71] Murray M. The pathology of African trypanosomiasis. In: Brent L, Holborow J editors. Progress of Immunology II. Amsterdam: North-Holland Publishing Co.;1974. Vol 4: pp. 182-92.
[72] Teixeira AR, Nascimento RJ, Sturm NR. Evolution and pathology in Chagas disease: A review. Mem Inst Oswaldo Cruz. 2006;101(5):463-91.
[73] Correa-de-Santana E, Paez-Pereda M, Theodoropoulou M, Kenji Nihei O, Gruebler Y, Bozza M, Arzt E, et al. Hypothalamus pituitary-adrenal axis during *Trypanosoma cruzi* acute infection in mice. J Neuroimmunol. 2006;173(1-2):12-22.
[74] Teixeira Vde P, Hial V, Gomes RA, Castro EC, Reis M das G, Rodrigues ML, et al. Correlation between adrenal central vein parasitism and heart fibrosis in chronic chagasic myocarditis. Am J Trop Med Hyg. 1997;56(2): 177-80.
[75] D'Attilio L, Bozza VV, Santucci N, Bongiovanni B, Dídoli G, Radcliffe S, et al. Inhibition of DHEA production by factors released from *M. tuberculosis*-stimulated peripheral blood mononuclear cells is abrogated by transforming growth factor-β neutralization. Ann NY Acad Sci. 2012;1262:1-9.
[76] Chávez-Güitrón LE, Morales-Montor J, Muñoz-Guzmán MA, Nava-Castro KE, Ramírez-Álvarez H, Moreno-Mendoza NA, et al. The *in vitro* effect of prolactin on the growth, motility and expression of prolactin receptors in larvae of *Toxocara canis*. Vet Parasitol. 2016;224:33-8.
[77] Gutiérrez-Amézquita RA, Morales-Montor J, Muñoz-Guzmán MA, Nava-Castro KE, Ramírez-Álvarez H, Cuenca-Verde C, et al. Progesterone inhibits the *in vitro* L3/L4 molting process in *Haemonchus contortus*. Vet Parasitol. 2017;248:48-53.

[78] Maswoswe SM, Peters W, Warhurst DC. Corticosteroid stimulation of the growth of *Plasmodium falciparum* gametocytes *in vitro*. Ann Trop Med Parasitol. 1985;79(6): 607-16.

[79] Freilich D, Ferris S, Wallace M, Leach L, Kallen A, Frincke J, et al. 16alpha-bromoepiandrosterone, a dehydroepiandrosterone (DHEA) analogue, inhibits *Plasmodium falciparum* and *Plasmodium berghei* growth. Am J Trop Med Hyg. 2000;63(5-6):280-3.

[80] Carrero JC, Cervantes C, Moreno-Mendoza N, Saavedra E, Morales-Montor J, Laclette JP. Dehydroepiandrosterone decreases while cortisol increases *in vitro* growth and viability of *Entamoeba histolytica*. Microbes Infect. 2006;8(2)323-31.

[81] Ribeiro F, Lopes RP, Nunes CP, Maito F, Bonorino C, Bauer ME. Dehydroepiandrosterone sulphate enhances IgG and interferon-gamma production during immunization to tuberculosis in young but not aged mice. Biogerontology. 2007;8(2):209-20.

[82] Rasmussen KR, Healey MC, Cheng L, Yang S. Effects of dehydroepiandrosterone in immunosuppressed adult mice infected with *Cryptosporidium parvum*. J Parasitol. 1995;81(3):429-33.

[83] Khalifa AM, Ibrahim IR, el-Kerdany ED. Coccidial infection in immunosuppressed mice: Prophylaxis and treatment with dehydroepiandrosterone. East Mediterr Health J. 2000;6(5-6):908-18.

[84] Santos CD, Toldo MP, Santello FH, Filipin MD, Brazão V, do Prado Júnior JC. Dehydroepiandrosterone increases resistance to experimental infection by *Trypanosoma cruzi*. Vet Parasitol. 2008;153(3-4):238-43.

[85] Santos CD, Toldo MP, Levy AM, Kawasse LM, Zucoloto S, do Prado Jr JC. Dehydroepiandrosterone affects *Trypanosoma cruzi* tissue parasite burdens in rats. Acta Trop. 2007;102(3):143-50.

[86] Bini E, Bottasso O, Hernandez Pando R. Immunity, sex hormones and infection. Adv Neuroimmune Biol. 2011;1(2):163-77.

[87] Legorreta-Herrera M, Mosqueda-Romo NA, Nava-Castro KE, Morales-Rodríguez AL, Buendía-González FO, Morales-Montor J. Sex hormones modulate the immune response to *Plasmodium berghei* ANKA in CBA/Ca mice. Parasitol Res. 2015;114(7):2659-69.

[88] Wells JC, Stock JT. The biology of the colonizing ape. Am J Phys Anthropol. 2007;134(suppl 45):191-222.

[89] Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454(7203):428-35.

[90] Straub RH, Besedovsky HO. Integrated evolutionary, immunological, and neuroendocrine framework for the pathogenesis of chronic disabling inflammatory diseases. FASEB J. 2003;17(15):2176-83.

[91] Straub RH, Bijlsma JW, Masi A, Cutolo M. Role of neuroendocrine and neuroimmune mechanisms in chronic inflammatory rheumatic diseases-The 10-year update. Semin Arthritis Rheum. 2013;43(3):392-404.

[92] Bini EI, D´Attilio L, Marquina-Castillo B, Mata-Espinosa D, Díaz A, Marquez-Velasco R, et al. The implication of pro-inflammatory cytokines in the impaired production of gonadal androgens by patients with pulmonary tuberculosis. Tuberculosis. 2015;95(6):701-6.

[93] Savino W, Mendes-da-Cruz DA, Lepletier A, Dardenne M. Hormonal control of T–cell development in health and disease. Nat Rev Endocrinol. 2016;12(2):77-89.

[94] Lochmiller RL, Deerenberg C. Trade-offs in evolutionary immunology: Just what is the cost of immunity? Oikos. 2000;88(1):87-98.

[95] Benhariz M, Goulet O, Salas J, Colomb V, Ricour C. Energy cost of fever in children on total parenteral nutrition. Clin Nutr. 1997;16(5):251-5.

[96] Bonneaud C, Mazuc J, Gonzalez G, Haussy C, Chastel O, Faivre B, et al. Assessing the cost of mounting an immune response. Am Nat. 203;161(3):367-9.

[97] Hotamisligil G, Erbay E. Nutrient sensing and inflammation in metabolic diseases. Nature Rev Immunol. 2008;8(12):923-34.

[98] Plata-Salaman CR. Cytokines and feeding. Int J Obes Relat Metab Disord. 2001;25(Suppl 5):S48-S52.

[99] Langhans W. Anorexia of infection: Current prospects. Nutrition. 2000;16(10):996-1005.

[100] Straub RH, Cutolo M, Buttgereit F, Pongratz G. Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases. J Intern Med. 2010;267(6):543-60.

[101] Schwenk A, Macallan DC. Tuberculosis, malnutrition and wasting. Curr Opin Clin Nutr Metab Care. 2000;3(4): 285-91.

[102] Mahuad C, Bozza V, Pezzotto SM, Bay ML, Besedovsky H, del Rey A, et al. Impaired Immune Responses in tuberculosis patients are related to weight loss that coexists with an immunoendocrine imbalance. Neuroimmunomodulation. 2007;14(3-4):193-9.