

Neuroimmunoendocrine System During Infection by *Trypanosoma cruzi*: Mechanisms of Immunoregulation

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Abstract

Alterations induced by stress activate communication pathways controlled by the brain, such as the hypothalamic pituitary adrenal axis and the autonomic nervous system. There is a balance between neuropeptides, catecholamines, glucocorticoids and pro-inflammatory cytokines, which under conditions that change the state of containment or homeostasis in the body can modulate the host immune response and determine the severity of an infection or disease. Some pathogens, in particular *Trypanosoma cruzi*; promote an imbalance that could influence lymphocyte dynamics with consequences in local and systemic immune response. This review aims to show some of the pathways that drive bi-directional communication between the immune and neuroendocrine systems with emphasis on pro-inflammatory cytokines and various immunomodulatory hormones such as glucocorticoids and how this dynamic interaction can be altered during infection with this protozoan.

Keywords: Hypothalamic Pituitary Adrenal Axis; Autonomic Nervous System; Immune System; Cytokines; Glucocorticoids; *Trypanosoma cruzi*

Abbreviations

ACTH: Adrenocorticotrophic Hormone; ADH: Antidiuretic Hormone; ANS: Autonomic Nervous System; AVP: Arginine Vasopressin; cAMP: Adenosine Monophosphate Cyclic; CD4+: Cluster of Differentiation 4 of Helper T Lymphocyte; CD8+: Cluster of Differentiation 8 of Cytolytic T Lymphocyte; CNS: Central Nervous System; CRH: Corticotropin Releasing Hormone; DHEA: Dehydroepiandrosterone; DHEAs: Dehydroepiandrosterone Sulfate; FSH: Follicle Stimulating Hormone; GC: Glucocorticoid; GH: Growth Hormone; GR: Glucocorticoid Receptor; GRES: Glucocorticoid Response Element; HAMP: Gene Coding for Hepcidin; HPA: Hypothalamic Pituitary Adrenal Axis; IGF-1: Insulin like Growth Factor 1; IgM: Immunoglobulin M; IgG2a: Immunoglobulin G Subtype 2a; IFN- α : Interferon Alfa; IFN- γ : Interferon Gamma; IL-1: Interleukin-1; IL-2: Interleukin-2; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-18: Interleukin-18; MR: Mineralocorticoid Receptor; MC2R: Melanocortin 2 Receptor; NO: Nitric Oxide; nGRES: Negative Glucocorticoid Response Element; PIAS-3: Protein Inhibitor of Activated STAT 3; PRL: Prolactin; PRLR: Prolactin Receptor; RH: Releasing Hormone; RIH: Hormone Inhibitor of the Liberation; SCN: Suprachiasmatic Nucleus; SNS: Sympathetic Nervous System; SNPS: Parasympathetic Nervous System; SOCS-3: Suppressor of Cytokine Signaling 3; StAR: Steroidogenic Acute Regulatory Protein; STAT-3: Signal Transducer and Activator of Transcription 3; STAT-5: Signal Transducer and Activator of Transcription 5; Th1: T Helper Cells; TNF- α : Tumor Necrosis Factor Alpha; TGF- β : Transforming Growth Factor Beta; TSH: Thyroid Stimulating Hormone; VIP: Vasoactive Intestinal Peptide

Introduction

When individuals are exposed to any situation that causes an alteration of homeostasis (infections, inflammatory/autoimmune diseases or trauma), numerous neurophysiological and neurochemical changes occur that in turn alter the mechanisms involved in the immune response [1,2]. The communication between the immune and neuroendocrine systems is carried out through messenger molecules that are produced by the cells of the systems and released into the bloodstream [3]. Once these messengers reach their target tissue they bind to specific receptors triggering intracellular signaling cascades whose gene products activate or suppress the immune response (both innate and adaptive), as well as the nervous and endocrine system [4,5]. The catecholamines synthesized and released by the autonomic nervous system are also involved in this communication [2] (Figure 1).

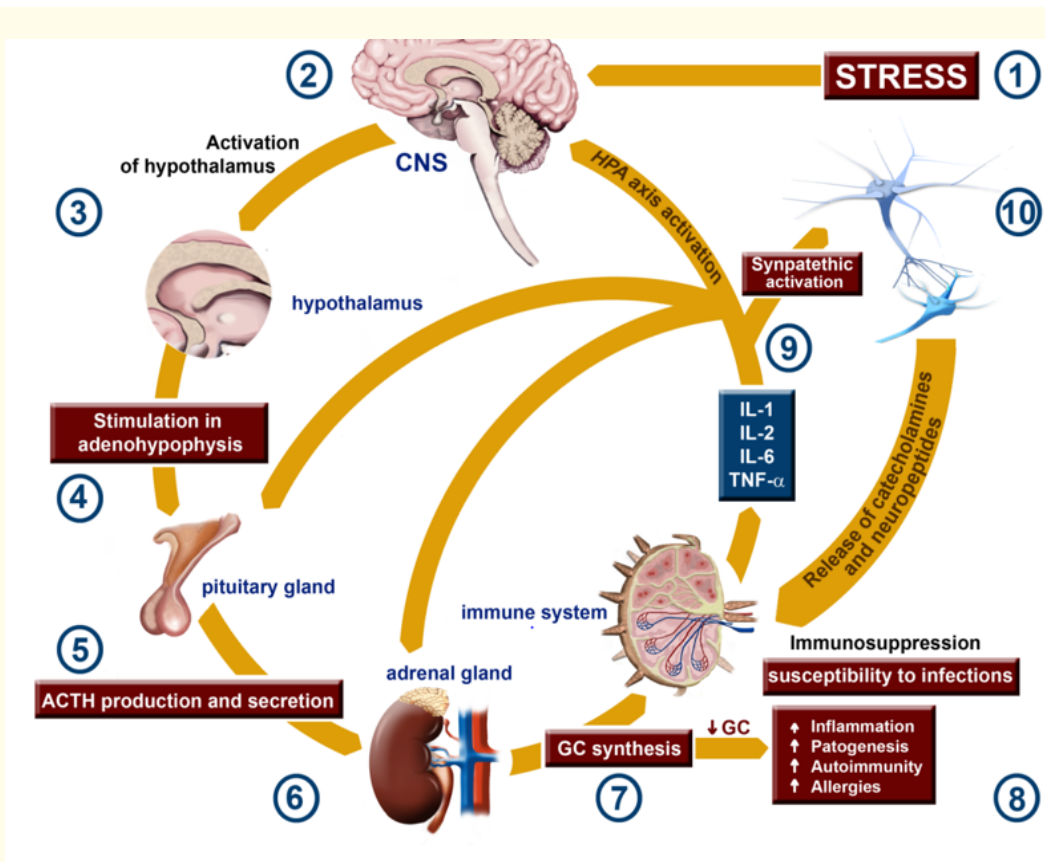


Figure 1: Bidirectional communication between HPA axis and immune system. Stress or any other signal that causes alteration of homeostasis activate to the central nervous system at level of hypothalamus inducing the synthesis and release of ACTH in the anterior pituitary, ACTH circulates in the blood and binds with high affinity to receptors expressed in the cortex of the adrenal gland to stimulate the synthesis and secretion of GC. GC in high concentrations induce immunosuppression which generates susceptibility to infections and a deficient production of these hormones causes increase in pathogenesis of autoimmune, inflammatory and allergic diseases. Additionally, the IL1, IL-2, IL-6 and TNF- α cytokines produced in response to stress can activate the HPA axis and sympathetic nervous system and stimulate release of catecholamines and neuropeptides.

The messengers are synthesized and released in cycles of 24 hours of action called circadian rhythms, which are controlled by the hypothalamus (central nervous system) [6]. A wide range of immunological parameters, such as the number of red blood cells, peripheral blood mononuclear cells, as well as the level of critical mediators such as cytokines, undergo daily fluctuations [7]. Current experimental data indicate that circadian information reaches the lymphoid organs mainly through diurnal patterns of autonomous and endocrine rhythms. In addition, cytokines can provide an information flow between the neuroendocrine and immune systems. This is how this network of neuroimmunoendocrine interactions provides an integrated molecular feedback that works in synchrony with the aim of optimizing the immune response [8].

An important aspect of cellular communication that has arisen as a result of the study of neuroimmunoendocrine interactions is the redundancy in the use of a large number of chemical messengers. In this way, “the loss of exclusivity” by specific systems can be a rule rather than an exception [9]. However, although a large amount of experimental evidence suggests that neuronal, endocrine and immunological cells produce neurotransmitters, catecholamines, peptide, hormones and steroids, as well as cytokines and although the same cells synthesize and express the receptors for these molecules, it remains to be clarified role of these interactions in health and various diseases [10].

Physiology of the hypothalamic pituitary adrenal axis (HPA)

The cell bodies of neuroendocrine cells are located within the Central Nervous System (CNS), but their axons extend out of it. The neurohormones synthesized in the cell bodies travel through the axons and are released in the axonal terminals, which are located within a specialized neurohemal organ consisting of one or more groups of axon terminals with a bed of blood capillaries [11].

The hypophysis (pituitary gland) lies beneath the hypothalamus and is made up of two parts: the adenohypophysis (anterior hypophysis) and the neurohypophysis (posterior hypophysis). The posterior hypophysis emerges from the lower portion of the brain and is formed by three segments: middle eminence, which comprises part of the base of hypothalamus, the pars nervosa also called posterior lobe, and a segment that connects them, the infundibular stalk. In most mammals, there are two hormones that are released from the pars nervosa towards the blood: vasopressin and oxytocin [12,13]. Vasopressin, also called antidiuretic hormone (ADH), limits the production of urine and stimulates arteriolar vasoconstriction [14]. Oxytocin, on the other hand, causes uterine contraction during childbirth and ejection of milk by the mammary glands during lactation. In mammals, two groups of cell bodies in the hypothalamus (paraventricular and supraoptic nucleus) are the main production sites of these two peptides [15].

The anterior hypophysis (adenohypophysis) is subdivided into: pars distalis, pars intermedia and pars tuberalis. All hormones secreted by this region of the hypophysis are polypeptides, proteins or glycoproteins (proteins covalently linked to hydrocarbon chains). The capillaries of the middle eminence form portal vessels that cross a short distance through the infundibular stalk until they reach the anterior hypophysis where they form capillary beds that surround the endocrine cells of the adenohypophysis. This network of blood vessels is called the hypothalamus pituitary portal system [16].

The middle eminence is a structure in which axons of neurosecretory cells are found. These cells produce neurohormones that control the secretion of specific groups of cells of the adenohypophysis. Some hypothalamic neurohormones stimulate the secretion of hormones and are called releasing hormones (RH), while those that inhibit the secretion of hormones from the anterior hypophysis are called hormones inhibiting the release (RIH) [2].

When secretions of one endocrine gland act on another in a sequential manner, endocrinologists give system the name of axis. In this section we will describe the Hypothalamus-Pituitary-Adrenal axis (HPA), to illustrate how the rates of endocrine secretion are regulated or modified by means of hormonal and neural influences.

Among the hormones secreted by the adrenal gland are glucocorticoids, which are a type of steroid hormones that are released in response to stress and whose release is controlled by the circadian clock that is located in the suprachiasmatic nucleus (SCN) [17]. Glucocorticoids are referred to by the fact that they promote an increase in blood glucose concentrations ("gluco") and are secreted by the adrenal cortex ("cortico") [18].

The hypothalamic pituitary adrenal axis (HPA) it is constituted by three organs: the hypothalamus, pituitary and adrenal gland; and its activation after the arrival of a stimulus induces paraventricular nucleus neurons to release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which when arriving at the adenohypophysis induce production and secretion of adrenocorticotrophic hormone (ACTH) [2]. At the same time, ACTH induces synthesis and secretion of glucocorticoids was as: cortisol y corticosterone, the mineralocorticoid aldosterone and androgens that are released from the suprarenal gland cortex into the bloodstream. The increase in cortisol levels suppresses the release of CRH and ACTH through a negative feedback mechanism that allows the HPA axis to return to its basal condition after an activation state [19,20].

CRH regulates the secretion of ACTH in two ways: it stimulates the release ACTH already stored within the pituitary venous effluent and then through the inferior petrosal sinuses in the internal jugular vein. ACTH acts on the adrenal gland to stimulate the release of cortisol through the melanocyte type two receptor (MC2R) expressed in the fascicular and reticular zone [21,22]. This mechanism is mediated by the activity of a G protein which leads to the increase of the intracellular levels of cyclic AMP (cAMP), thus promoting the release of the acute steroidogenic regulatory protein (StAR). The limiting step of the speed of adrenal steroidogenesis is the entry of cholesterol through the mitochondrial membranes external and internal; this requires the participation of several proteins, particularly StAR. The StAR protein has a very short half-life and its synthesis it is rapidly induced by trophic factors (corticotropin); therefore, it is the main regulator of steroid hormone biosynthesis in the short term (from minutes to hours) [23].

The adrenal gland also possesses circadian clock genes expressed in the glomerular and the fascicular zone regulated by the splanchnic nerve (sympathetic nerve originating from the paravertebral thoracic ganglia), which establishes specific time intervals during which the adrenal cells are more sensitive to stimulation by ACTH [24].

Mechanisms of signaling glucocorticoids

Among the functions of glucocorticoids are the stimulation of mobilization amino acid in muscle and hepatic gluconeogenesis to increase blood glucose levels, they also increase the transfer of fatty acids from adipose tissue to the liver and have anti-inflammatory action [13].

Biological actions of glucocorticoids are mediated by the glucocorticoids receptors (GR), which act as ligand-dependent transcription factors. Similar to the other members of steroid receptors, GR has a modular structure constituted by the following domains: domain of transactivation (amino-terminal), domain DNA binding (central) and a domain ligand binding (carboxy-terminal) [17]. Between DNA binding domain and the ligand-binding domain is a hinge region that confers structural flexibility for genomic interactions and that possesses a signal sequence for targeting to the nucleus [17].

In absence endogenous ligand or synthetic glucocorticoids (dexamethasone, betamethasone, hydrocortisone, prednisone), GR resides predominantly in cytoplasm as part of a great multiprotein complex that includes chaperone proteins (heat shock protein hsp 90, hsp70 and hsp23) and immunophilins of the FK506 family (FK506 binding protein (FKBP) 51 and FKBP52) [25,26]. The binding of the GR to its ligand causes a conformational change in it that leads to its dissociation from the multiprotein complex, exposing the nuclear localization signals and rapidly translocating it to the nucleus where it binds to specific DNA sequences called response elements to GR (GRES) [27], which present the following consensus sequence (AGAACA_nnnTGTTCT). The consensus sequences are imperfect palindromes, hexameric and inverted where the letter n refers to a position that does not require a specific nucleotide for the union to occur. The GR bound to DNA promotes changes in the degree of chromatin compaction and induces the recruitment of co-receptor proteins that initiate the transcription process.

The binding of GR to DNA does not necessarily imply an increase in gene transcription. On the one hand there are reports about the occupation of GREs can lead to gene repression, which suggests that the sense of transcription would be influenced more by the factors, epigenetic regulators and modulators of the chromatin than by the sequence itself. On the other hand, there are negative GRE sequences (nGRE) in which case the union of the GR mediates the repression of transcription and whose consensus sequence is (CTCC (n)₀₋₂ GGAGA) differs from GRE in that the spacer goes from 0 to 2 nucleotides, which prevents homodimerization of the GR, then joining each palindrome as monomers. Thus, the binding of GR to nGREs leads the recruitment of co-repressors and transcriptional repression [28,29].

Both glucocorticoids and mineralocorticoids bind to the mineralocorticoid receptor (MR) [30]. MR is expressed in several tissues, such as the kidney, colon, heart, central nervous system (hippocampus), adipose tissue and sweat glands. In epithelial tissues, the activation of the mineralocorticoid receptor causes expression of proteins that regulate the transport of water and ions, especially the epithelial sodium channel, sodium and potassium pump, etc., which increases the reabsorption of sodium and water and, as a consequence, the extracellular volume is increased, blood pressure increases and potassium is secreted outside the body to maintain the normal concentration of salts in the body [31]. However, signaling through MR is necessary for the cognitive response to stress.

Ethyl alcohol or ethanol is an organic chemical compound formed by a two carbon chain in which hydrogen has been replaced by a hydroxyl group. Although it is used in medicine and widely consumed, the understanding of its effects on the human body remain limited [32]. Several studies have shown that alcohol increases the concentration of GC in plasma a physiological level [33,34] and activates GR signaling through conventional GC-GR interaction. Mandrekar, *et al.* [35] found that acute alcohol increases translocation to the GR nucleus without being bound ligand. However, in this study the biological significance of free GR was not defined.

Pong, *et al.* [32] carried out a genomic analysis of the influence of alcohol on genic expression, which showed that acute alcohol positively regulates a group of genes sensitive to GC, among which are GILZ [36], ALOX15B [37], SYNPO2 [38] and PTEN [39]. GILZ acts as an endogenous bearer with therapeutic anti-inflammatory and immunosuppressive actions [36] and its expression is reduced or even absent in several inflammatory disorders, such as chronic rhinosinusitis, Crohn's disease and atherosclerosis [40-42]. These results indicate that the suppression of GILZ expression predisposes the host to suffer inflammatory type disease. In contrast, the expression of GILZ in transgenic mice protects animals from colitis [43].

In the afore mentioned study; it was demonstrated that the depletion of GILZ in MM6 cells (cell line GR -/- obtained by the genomic editing method CRISPR/Cas9) abolished the suppressive effect of alcohol in production of inflammatory cytokines caused by LPS. Based on the results obtained, authors propose a model in which alcohol interferes with stability of GR complex. Because alcohol is a versatile solvent, miscible in water and with organic solvents, this amphiphilic property gives this molecule the ability to disturb protein-protein interactions that depend on weak bonds, as in the GR complex. Upon disassembly of the GR complex, free receptor migrates to the nucleus and interacts with GRE and activates target genes such as GILZ, suggesting that the "free" form of GR possesses biological activity [32].

In summary, GR intracellular signaling can be activated by classical via the ligand binding or alcohol induction (non- canonical pathways). It is unknown how the two GR activation pathways mutually influence each other, which may collectively define the ultimate outcome of the HPA-GR signal transduction under the condition of alcohol exposure. This finding represents an exception to the current paradigm that GR must be coupled to its ligands to undergo a conformational change and translocate to nucleus.

Immune and neuroendocrine systems: ways of communication

The term stress has been applied to different situations and although it has always been attributed negative connotations, it is necessary to study this adaptive phenomenon as a series of events triggered by a stimulus that activates the central nervous system leading to the generation of a systemic physiological response that affects almost all body structures. Within this systemic physiological response, the secretion of glucocorticoids is one of the main and most studied. An excessive production of glucocorticoids alters the metabolism and

behavior and induces immunosuppression, which in turn can generate a greater susceptibility to infections and cancer. However, a deficient production of these hormones makes the individual more vulnerable to increases the pathogenesis of autoimmune, inflammatory and allergic diseases ([44], Figure 1). Additionally, it prevents the increase in cardiac output and tissue perfusion as a coping response to a stressful challenge, suggesting that corticosteroids mediate the cardiovascular stress response in a permissive manner.

Arthrocytes and microglia have the ability to secrete cytokines. Among these mediators of cellular communication are mainly IL-1, IL-2, IL-6, TNF- α , IFN- α and IFN- γ , while hypothalamus and pituitary gland secreted IL-1, IL-6, TGF- β , IL-10 and IL-18 [45-47]. In adenohypophysis the secretion of ACTH is stimulated by IL-2, a cytokine produced by T helper cells of Th1 pattern involved in numerous cellular processes that allow the implementation of defense mechanisms and immune tolerance [22]. It has been observed that in rats cytokine IL-1 produced by multiple cell lines, increases plasma concentrations of ACTH and stimulates the release of GH, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [48], while IL-6 induces hepcidin synthesis during inflammatory process through the activation cascade of signal transducers and activators STAT3 [49].

Many hormones and their receptors have been detected and identifies in cells and tissues of the immune system participate in processes of development, differentiation and regulation of the immune response during lymphocyte activation once his encounter with the antigen [50,51]. Additionally, lymphocytes produce hormones such as GH, PRL, ACTH, TSH, IGF-1, leptin and gonadotropins [52]. In lymphocytes of fish and humans the expression of HAMP in neutrophils and macrophages has also reported *in vivo* [53] and *in vitro* studies [54].

In addition to the HPA axis, the autonomic nervous system (ANS) can also regulate the immune system. Sympathetic innervation and neuropeptides have been shown to be released at sites inflammation by peripheral nerves, which plays a paracrine role in the regulation of inflammatory processes [55,56]. The ANS this constituted by two branches: sympathetic (SNS) and parasympathetic (SNPS). Preganglionic fibers of the SNS and the SNPS use acetylcholine as neurotransmitter. Adrenaline is the main product of the adrenal medulla, although small amounts of noradrenaline (20%) are released into the circulation. Hormones as well as nerve stimulation are involved in the normal synthesis catecholamines by the adrenal medulla. Functions of said catecholamines in their target tissues are carried out by means specific adrenergic receptors, of which 5 types have been identified (α 1, α 2, β 1, β 2 and β 3) [57].

The most specialized tissues in the immune system are bone marrow, thymus (primary lymphoid organs), spleen, lymph nodes (secondary lymphoid organs) and lymphoid tissues associated mucous including the tonsils and Peyer's patches. However, other tissues and glands also contribute to diverse immunological activities, including the lacrimal glands (secretion of immunoglobulins), submandibular glands (integrity of the intestinal tract) and liver (synthesis of acute phase proteins). These tissues have afferent (sensory) and efferent (autonomic) nerve fibers that allow homeostatic neural regulation of the adaptive immune response. There is evidence that the parenchymal compartments lymphoid tissues are innervated, suggesting that the ANS regulates the immune response directly through cellular contacts with cells immune system, stromal cells, and accessory cells [58].

Between cytokines that can activate both the HPA axis and the ANS, the most studied are IL-1, IL-2, IL-6 and TNF- α (Figure 1). These cytokines are produced by nonspecific stress, due to pathological effects caused by infections or inflammation (pain, hypotension, hypoglycemia, lactic acid), or through primary nociceptive and sensory afferents that activate reflexively to the hypothalamus, which is the main white site of activity of said cytokines [59-61].

Expression of cytokine receptors in the brain has been demonstrated, particularly in hypothalamus, hippocampus, middle eminence, third ventricle and pituitary [61-63]. Although there is evidence that the cytokines released into the circulation in an immune response have effects on the brain, it must be considered that these proteins, which have molecular weights in the range of 17 to 26 kDa, are not able to cross the barrier hematoencephalic and there is no evidence of any transport mechanism. However, there are certain important

areas located outside the blood-brain barrier, such as the median eminence and vascular organ middle lamina of third ventricle, which are white sites for the action of cytokines released in circulation [59]. In addition, any stimulus that induces local inflammation could non-specifically increase the permeability of cerebral vasculature.

Another mechanism by which cytokines may have some impact on the brain, involves actions of prostanoids. Cytokines secreted in the circulation can act at the level of the endothelium and could stimulate production of cytokines by CNS activating the functions of prostanoids. The hypothalamic production of prostaglandins, for example; it increases after the administration of IL-1 β , IL-6 and TNF- α or endotoxin [64,65]. Prostaglandins can transfer peripheral inflammatory signals to hypothalamic neurons, which can induce not only the release of cytokines in the brain, but also the activation HPA pathway and sympathetic system [66-68].

Thus, the cellular communication messengers among which stand out neurotransmitters, neuropeptides, catecholamines, cytokines and hormones interact with receptors located in the cells of three systems, allowing the CNS to detect changes or alterations in the immune activity through a sensory system; after which a modulation is generated in the immune response in presence of certain stimuli [10].

Immune and neuroendocrine system against infection with *Trypanosoma cruzi*

Interactions between immune and neuroendocrine systems are critical for maintenance of a homeostatic balance within the organism and alterations in them in response to metabolic disturbances, stress, injury or disease, can cause significant changes in immune response and in susceptibility to infections. Multicellular animals have cells or tissues that exclusively face the threat of infections. Some of these responses are immediate, in such a way that an infectious agent can be contained quickly; others are slower, but also more specific for the infectious agent. Collectively, this protection is known as the immune system. The human immune system is essential for our survival in a world full of potentially dangerous microbes, and serious deterioration, even from one branch of this system, can make us susceptible to serious, life-threatening infections. During the course of an infection, defense mechanisms are activated in the host that include the secretion of cytokines that generate not only an innate and adaptive immune response, but also significant endocrine effects that in turn lead to important changes in immunological activity, metabolic and neuronal [69]. Immunity to intracellular pathogens such as protozoa and is mediated by the cytokines IL-1, TNF- α and IFN- γ , which enhance the microbicidal capacity of macrophages. Such cytokines stimulate the HPA axis by increasing the serum levels of GC and DHEA [70].

Due to previously mentioned findings, many lines of research have focused their interest in evaluating the way in which the complex interactions of the neuroimmunoendocrine system modulate or regulate certain infectious process, particularly those generated by parasites. In *Schistosoma mansoni* it has been observed that hormones of the HPA axis exert a direct effect inhibiting the proliferation of the trematode as well as an indirect effect modulating the host immune response [71].

Secretion of CRH, ACTH and GC in stress response, modulation of pro-inflammatory cytokines and regulation of the peripheral immune response mediate control of neuroimmunoendocrine interactions [3]. Therefore, mechanisms involved in activation and function of the HPA can be considered as a main point in human and experimental Chagas disease.

Chagas disease is a zoonosis caused by the protozoan *Trypanosoma cruzi* that affects 10 million people in the world, mainly in Latin America; although in recent decades it has been observed more frequently in the United States of America, Canada, many European countries and some in the Western Pacific. This is mainly due to the mobility of the population between Latin America and the rest of the world [72,73]. Despite this, there is a passive attitude caused by the ignorance of the magnitude of the disease and only the cases in which the patient has developed a specific pathology are reported. This situation diminishes the perception of its true impact, reinforces the idea that it is a silenced and forgotten disease that leads to an underestimation of design and development of rational drugs, taking into account that currently available drugs generate side effects in the host.

Whatever the route of infection with *T. cruzi*, the disease develops through two phases: acute and chronic. The most characteristic signs of the acute phase are the Romaña sign consisting of a unilateral bipalpebral edema with the preauricular ganglion increased in volume, which occurs when the parasite penetrates through the ocular conjunctiva [74,75] and the inoculation chagoma as a nodule or ulcer, when the parasite penetrates through the skin; Some of the clinical manifestations observed during this stage of the infection are: fever, cardiac, digestive, neurological alterations, hepatomegaly and splenomegaly; which disappear at the end of this phase together with the disappearance of circulating parasites, which are controlled by the immune response [76].

In chronic phase, infected individuals develop clinical symptoms characterized by cardiovascular manifestations, damage to cardiac muscle tissue and disturbances in the conduction of the electrical signal of the heart, leading the patient to an insufficiency cardiac, which facilitates the production of thromboembolic processes. Neurological and digestive manifestations with enlargement of some viscera produce megaesophagus and megacolon [77].

Despite the time elapsed since its discovery, effective chemotherapy is not yet available for all clinical phases of Chagas disease. *T. cruzi* has challenged attempts to eliminate it because currently used drugs are relatively effective and there are no vaccines to prevent the disease. In addition, the production of drugs for relatively small or low-income populations is discarded or postponed, which has led them to consider as “orphan drugs” those destined for the treatment of the disease.

So far, the only drugs available for the etiological treatment of Chagas disease are nitrofurans and nitroimidazoles [78,79]. Although these compounds exhibit trypanocidal effects, are ineffective in chronic cases, patients require long periods of treatment under medical supervision, are expensive and have low accessibility, produce side effects and some strains of *T. cruzi* are resistant to them [80]. In this sense, the development and identification of drugs that can be considered as chemotherapeutic targets in the parasite and that do not generate side effects in the host is required.

The compounds available for the treatment of this parasitosis are Nifurtimox and Benznidazole [78,79]. Numerous clinical studies have shown that both drugs are effective in the treatment of congenital infection and acute phase of the disease, however; the main limitation of these drugs is their low antiparasitic activity in the chronic phase [81]. The reasons for the marked difference in the antiparasitic efficacy of nitroheterocyclic compounds in the acute and chronic phase of the disease are related to unfavorable pharmacokinetic properties such as short half-life and limited tissue penetration [82]. Additionally, the side effects generated by both drugs can lead to the suspension of treatment, in the case of Nifurtimox these include anorexia, nausea, vomiting, weight loss, insomnia, irritability and less frequently peripheral polyneuropathy, while that for Benznidazole the most common adverse effects are: allergic dermatopathy, gastrointestinal syndromes and, less frequently, bone marrow depression, thrombocytopenic purpura, agranulocytosis, polyneuropathy, paraesthesia and polyneuritis of the peripheral nerves. The incidence of these side effects is variable depending on the age of the patient, the geographic region, and the quality of the clinical supervision of the treatment [83].

Combined therapies have several objectives, including reducing the dose and duration of treatment with the consequent reduction of side effects and costs, exploiting the synergistic effect of concomitant treatments and preventing the development of drug resistance by the etiologic agent [84]. This strategy has been incorporated into the evaluation of specific chemotherapeutic agents for Chagas disease, due to limitations in terms of available drugs and the duration of treatment.

Parasites found in tissues of individuals in acute phase of Chagas' disease induce changes neuroimmunoendocrines that could be relevant to pathogenic mechanisms and/or pathophysiological during progression of the disease. In particular, parasites and parasitic antigens have been detected in HPA axis accompanied by presence of inflammatory infiltrate with macrophages and T lymphocytes and an increase in deposition of components of the extracellular matrix. Researchers have reported an increase in serum GC in the acute and chronic phases of the infection; which could be associated with the increase in the levels of IL-1, IL-6 and TNF- α . However, a decrease in CRH levels was observed at the level of the hypothalamus, while those of circulating ACTH did not change significantly, indicating an interruption in the hormonal control of the HPA axis [85].

One study evaluated the possible over-regulation of cellular immune response caused by prolactin (PRL), one of several hormones involved in immunoregulation in rats infected with *T. cruzi*. Results obtained showed that PRL induces proliferation T cells coupled with an activation macrophages and production nitric oxide (NO), which leads reduction in number of blood trypomastigotes during the peak of parasitaemia. These results suggest that PRL may be an alternative hormone able to exert a positive regulation on the immune response of the host and consequently reduce pathological effects of *T. cruzi* infection. Interestingly, chagasic patients have not shown any alteration in PRL levels [86].

Increase in serum levels GC and decrease in intrathymic content corticosterone in acute phase mice of *T. cruzi* infection indicating that control intrathymic production GC is independent of systemic levels GC. Lepleteir, *et al.* [86], found a decrease in amount of PRL blood of and detected changes in serum levels of PRL and GCs. Evaluating intrathymic production of corticosterone and PRL, found that the GC content decreased in thymus, whereas PRL increased (Figure 2).

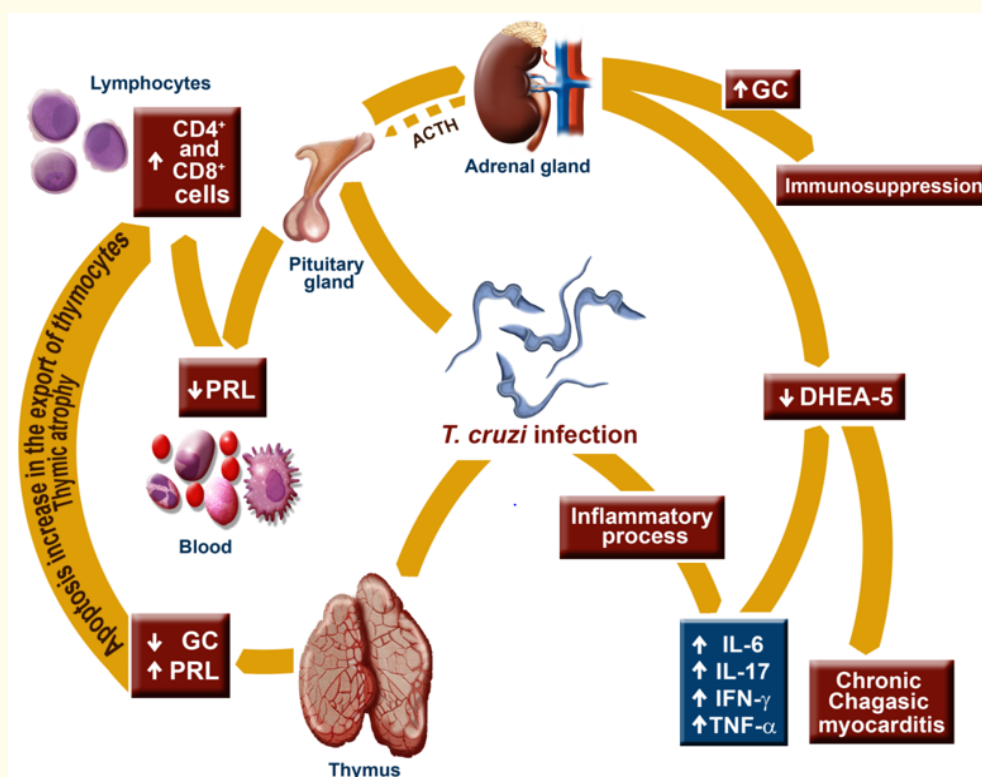


Figure 2: Immunity to intracellular pathogens such as protozoa is mediated by IFN- γ , TNF- α and IL-1 that activate the microbicidal capacity of macrophages. Such cytokines stimulate the HPA axis by increasing the serum levels of glucocorticoids (GC). In acute phase infection with *T. cruzi* found that GC content decreased transiently in thymus, whereas PRL increased progressively. A systemic inflammatory scenario in patients with severe myocarditis is characterized by high levels of TNF- α , IL-6, IL-17 and IFN- γ in serum when compared with healthy individuals. This is accompanied by a decrease in concentration of dehydroperasesterone sulfate (DHEA-s) and an imbalance in the cortisol/DHEA-s relationship.

In infected mice it has been observed that CD4+ and CD8+ thymocytes showed a reduction of the GCR- α transcript in parallel to an increase in PRL receptor gene expression (PRLR), indicating that PRL counteracts effects of GC through a cross-action that affects directly signaling of GR in CD4+ and CD8+ cells. These results agree with the data that show that transcriptional activity of phosphorylated STAT5 caused by signaling generated after the PRLR/PRL binding significantly annuls apoptosis in T cells induced by GC [87]. In this sense, the restoration of systemic levels of PRL by treatment with metyrapone (stimulates the secretion of PRL by the pituitary gland) prevented thymic atrophy by decreasing the apoptosis of CD4+ and CD8+ cells, thus demonstrating thymus protection PRL-mediated also influences the abnormal export of potentially immature autoreactive T cells.

Doing research signaling molecules that could be involved in the production of ACTH in mice with acute *T. cruzi* infection, Corrêa-de-Santana, *et al.* [88], observed parasites in adrenal gland, while amplification DNAk the parasite's was found in pituitary and adrenal gland. However, an increase in corticosterone content and decrease in serum CRH and at the hypothalamus level were detected, no changes in ACTH levels. When evaluated effects of *T. cruzi* on atT-20 (ACTH-producing cell line), found that cultures that contained the parasite had low levels of ACTH when they were compared with the control. In these cells was observed an increase in the synthesis of IL-6, phosphorylation of STAT-3 and increase levels of SOCS-3 and PIAS-3, which could explain the block in production of ACTH. These findings indicate that during acute infection with *T. cruzi*, there could be an indirect influence or direct of the parasite on endocrine homeostasis, which generates an unbalance in the HPA axis.

Studies in mice with acute phase of infection revealed progressive thymic atrophy. When systemic levels of GC and leptin were measured, it was evident that as the levels of GC increased, serum content of leptin decreased [89,90]. However, exogenous replenishment of leptin in these animals did not normalize thymic atrophy or altered metabolic parameters in infected animals, such as glycemia, for example. This shows that other parameters may be involved in hormonal control of thymus abnormalities induced by infection with the parasite.

Pérez, *et al.* [85] evaluated characteristics of neuroimmunoendocrine response in patients with different degrees of chronic chagasic myocarditis. The researchers found that in patients with severe myocarditis there are high levels of the cytokines TNF- α , IL6, IL-17, CCL-2, IFN- γ and NO in serum, as well as a decrease in the concentration of DHEA-s and an imbalance in the ratio cortisol/DHEA-s (Figure 2). Given that DHEA-s is an androgen with immunomodulatory functions, a lack in the control of the inflammatory response could contribute to the evolution of the pathology of the disease.

Given that HPA axis operates in concert with sympathetic nervous system (SNS), Roggero, *et al.* [91] evaluated whether the noradrenergic nerves can affect the course of *T. cruzi* infection and sexual dimorphism observed in the disease. Finding a decrease in concentration of splenic noradrenaline together with a reduction of noradrenergic nerve fibers in spleen of infected C57BL/6 mice and an increase in activity of HPA axis, these alterations being more marked in males than in females. When spontaneous loss of noradrenergic nerve fibers was advanced by chemical sympathectomy prior to infection, males died earlier and mortality increased significantly in females. Chemical denervation did not significantly affect the concentration of IgM and IgG2a antibodies specific for *T. cruzi* and did not worsen myocarditis but resulted in an increase in parasitemia and serum levels of IL-6 and IFN- γ . The results obtained in this model parasitic disease provide additional evidence of relevance interactions between immune system and Sympathetic Nervous System in the defense of host.

Participation of neuropeptides in digestive tract has been investigated in experimental infection with *T. cruzi* and in patients in chronic phase of the infection. Digestive Chagas Disease is characterized by megacolon with motility disturbances. The distribution of substance P and intestinal vasoactive peptide (VIP), were investigated in myenteric plexus of mice infected with *T. cruzi* [92]. The observed decrease in levels of both neuropeptides in infected animals could be result of denervation myenteric plexus and be related to intestinal motility disorders observed in chronic phase Chagas disease [93].

Conclusions

Communication between immune and neuroendocrine systems uses a biochemical language through glucocorticoids, catecholamines, neuropeptides and cytokines that can act as immunomodulators and metabolic regulators through a common pathway of receptors. The immune system receives information (infections, or malignant cells) and responds to them, communicating said information (through cytokines) to the neuroendocrine system, which in response to these messengers synthesizes and releases neurotransmitters and hormones that travel through the torrent circulatory and bind to receptors expressed in the cells of the immune system. In recent years, information has been gathered that has generated knowledge about the molecular signals that are involved in the development of an integrated immune response and has allowed us to focus on the investigation of systemic mediators that control an effective protective response, as well as alterations in signaling pathways that may be involved in susceptibility and/or persistence to an infection.

Throughout evolution, hosts have evolved a series of physiological responses that result in restraining potentially damaging pathogen attack, broadly designed as the immunoneuroendocrine response. The strong interconnection between the neuroendocrine and immune systems, not only optimizes the defensive response, but also sets basis for an altered immunoendocrine regulation and detrimental tissue damage when pathogen cannot be cleared. Infection induces in host a global response that may result in a wide range of physiological and biochemical changes. Additionally, protracted chronic inflammation associated to chronic infections may impair endocrine response, with severe consequences for the host.

During human Chagas disease there are disturbances in hormonal circuits, mainly in HPA axis, which may contribute to myocardial pathophysiological events, namely a deficient control of the inflammatory component and tissue damage encompassing this reaction. Establishment of a dysregulated immunoendocrine circuitry during Chagas disease may be linked to the lack of responsiveness observed in HPA axis, judging by the normal ACTH and cortisol levels observed. This scenario could be caused and sustained by elevated amounts of proinflammatory cytokines, which may restraint HPA axis function by blocking stimulatory properties of CRH and ACTH on pituitary and adrenal glands, respectively. SNS can favor survival to infection with *T. cruzi* by mechanisms that most likely involve the control of excessive production of certain pro-inflammatory cytokines, although other processes related to immune cell mobilization and restriction of parasite spreading and homing may contribute to this effect. Decreased sympathetic activity that naturally occurs during infection with the parasite may interfere with these potentially protective effects. These evidences emphasize the relevance of interactions between the immune system and SNS for immunoregulation and host defense. Furthermore, they provide a clear example that the outcome of complex pathologies, such as those caused by parasites depend on fine balanced response of different bodily systems.

The field of neuroimmunoendocrine interactions is an example of interdisciplinary research that includes immunology, neurobiology, neuroendocrinology and behavioral sciences. A more precise understanding of effects of alterations in these systems that condition the organism to be more susceptible to diseases, could clarify how the disturbances in a system, such as stress-induced neuroendocrine stimulation, affect immune system in development of infectious, autoimmune, inflammatory diseases and cancer. The molecular and anatomical definition of multiple levels of interaction immune and neuroendocrine systems would allow a more rational design of drugs to treat infectious diseases such as the case of trypanosomiasis and strategies for controlling the immune response associated with protection.

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