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Review

Immune-neuroendocrine and metabolic disorders in human and experimental *T. cruzi* infection: New clues for understanding Chagas disease pathology

Florencia B. González, Silvina R. Villar, M. Florencia Pacini, Oscar A. Bottasso, Ana R. Pérez*

Institute of Clinical and Experimental Immunology of Rosario (IDICER-CONICET-UNR), Rosario, Argentine

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ABSTRACT

Studies in mice undergoing acute *Trypanosoma cruzi* infection and patients with Chagas disease, led to identify several immune-neuroendocrine disturbances and metabolic disorders. Here, we review relevant findings concerning such abnormalities and discuss their possible influence on disease physiopathology.

1. Introduction

The interactions between the immune and neuroendocrine systems, as well as metabolic pathways, play central roles during acute or chronic infectious diseases. Upon exposure to infectious stress, these major systems act in an integrated fashion to promote both pathogen control and host protection, as well as avoiding tissue damage and hence contributing to homeostasis recovery. Such physiologic and appropriate anti-stress response is sustained for a reasonable period being turned off once homeostasis is achieved [1].

In contrast, prolonged stress leads to a chronic and not always beneficial situation [2], in which the immune, neuroendocrine and metabolic communication becomes abnormal or disrupted. As such, in a wide range of acute and chronic infectious diseases, the anti-infectious immune response coexists with endocrine and metabolic alterations [3,4].

Particularly, in the context of experimental and human Chagas disease, diverse alterations from the immune-neuroendocrine systems and metabolic disorders have become evident in the last years. Here, we review relevant findings concerning such abnormalities during *T. cruzi* infection and discuss their possible influence on disease physiopathology.

The clinical course of Chagas disease comprises both an acute and a chronic phase. Depending on the route through which the infection is established (vectorial, congenital, transfusional, oral, transplant, or laboratory accidents), the acute phase may range from an asymptomatic form (mainly in vectorial cases) to severe disease manifestations, including acute myocarditis, meningoencephalitis, and sudden death. In general, the acute stage self-resolves 2–3 months later, and individuals remain chronically infected. Once the chronic stage is established, nearly 30% of infected people progress to the symptomatic chronic disease (myocardial or gastrointestinal compromise), with the remaining ones persisting in a symptomless chronic stage, formerly called indeterminate form [5,6].

Reasons accounting for such a diverse spectrum of clinical outcomes are still debatable. As to the chronic form, the current view points out to inflammation as the main determinant of progression, in coexistence with other well-known potential contributory factors like parasite persistence, strain virulence, autoimmune reactions and tissue tropism [2,7–9]. There is a reason to believe, however, that the disturbed neuroendocrine and metabolic responses are also likely to exert a detrimental influence on disease course [10].

In a broad sense, the integrated response from the host against infectious agents involves not only the generation of an inflammatory response addressed to pathogen elimination but also the redirection of energy supply, promotion of tissue repair and finally homeostasis recovery. When this integrated response fails to do so, it acquires a new status and may become detrimental. In this way, the same components taking part in the establishment and regulation of the inflammatory response (cytokines, counteracting elements like regulatory T cells, glucocorticoids, and neurotransmitters) may also mediate harmful effects. Many disturbances identified during *T. cruzi* infection in both

* Corresponding author at: Instituto de Inmunología Clínica y Experimental de Rosario, Suipacha 590, 2000 Rosario, Argentina.
E-mail address: perez@idicer-conicet.gob.ar (A.R. Pérez).

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humans and experimental models, fit well with this conceptual framework [10,11].

A crucial factor in the signaling networks involving the immune and neuroendocrine systems as well as energy metabolism is the fact that cytokines, hormones, neuropeptides, neurotransmitters, and even metabolic factors are common elements from lymphoid, endocrine, neural or specialized metabolic tissues, allowing permanent sensing of intrinsic and extrinsic signals [12,13]. A classic example of this interaction is well represented by the stress response, which is mainly driven by neural inputs, although proinflammatory cytokines are particularly involved in its activation. As a result, cortisol (in humans) or corticosterone (in rodents) are released by the adrenal glands, well known for inducing metabolic effects like glucose availability, promotion of antibody production and downregulating immune influences, among others [12]. In the same way, gonadal cells express receptors for cytokines and neural factors, whereas immune cells can be influenced by sex hormones. In turn, lymphoid organs and endocrine glands are innervated and exhibit receptors for neural factors, rendering them responsive to neurotransmitters and neuropeptides [12].Within this regulatory loop, the adipose tissue, can release not only hormones but also cytokines and adipocytokines [14].While being extensively innervated by sympathetic fibers, locally secreted factors from the adipose tissue may reciprocally affect the functioning of sensory nerve fibers [15].

2. Changes in the physiology of the hypothalamus-pituitary-adrenal (HPA) axis during *T. cruzi* infection

Before addressing this issue, it is worth discussing the main physiological and molecular basis of the HPA axis. Usually, proinflammatory cytokines released by activated immune cells, not only initiate immune reactions but also gain access to the central nervous system through the systemic route. Cytokines like IL-1β, TNF-α, IL-6, and IFN-γ act at the paraventricular nucleus of the hypothalamus to release corticotropin-releasing hormone (CRH). Via the hypophyseal-portal circulation, CRH reaches the anterior pituitary to stimulate the release of adrenocorticotropic hormone (ACTH) into the circulatory system resulting in the secretion of glucocorticoids (GC) from the adrenal gland cortex [16].In addition to acting on central structures, proinflammatory cytokines were recently found to directly modulate GC synthesis at the adrenal level [17].

Endogenously synthesized GC displays a plethora of beneficial effects, especially, as a regulator of inflammatory responses [18]. When cytokines are synthesized in excessive amounts, GC suppresses their production as well as the leukocyte chemotaxis and peripheral cellular traffic [19,20]. GC also promotes a Th1 → Th2 bias to prevent excessive cellular responses and hence avoiding the in situ deleterious effects of activated macrophages and Th1 lymphocytes [21].The relevance of the anti-inflammatory effects of GC during an infectious process is substantial, given that the deprivation of steroid activity through adrenalectomy increases fever and mortality [22]. In essence, HPA activation during the inflammatory response constitutes a very important protective mechanism to limit the immune-mediated damage [18].

In parallel to the production of GC, HPA axis activation also leads to the release of DHEA, another adrenal steroid with important immunoregulatory effects. DHEA seems to act in synergy with the anti-inflammatory effect of GC given the well-known anti-phlogotic effects of this androgen [23]. Al the same time, DHEA stimulates cellular responses for which it counteracts the inhibitory effect of GC on IL-2 synthesis [24]. Disrupted activation of the HPA axis in humans but not in rodents [25], is also characterized by decreased concentrations of DHEA or their metabolite DHEA-sulfate (DHEAs) leading to an unbalanced cortisol/DHEA or cortisol/DHEAs ratio [26–28].

Studies analyzing neuroendocrine and metabolic responses during the acute phase of human Chagas disease are scarce. Vectorial and congenital infections, mainly occurring in children, are usually difficult to identify, rendering the study of immune, neuroendocrine and metabolic parameters in them quite challenging. Additionally, the expected results of these studies may be influenced by diverse variables like age, nutritional factors, environmental conditions, etc. However, the symptomatic cases of oral Chagas disease represent an attractive field for future studies addressed to synchronically evaluate the activity of this complex immune-neuroendocrine network and how the integrative response may influence disease course. Currently, our knowledge about this type of interactions during the acute stage comes from animal models of *T. cruzi* infection, suitable for evaluating and manipulate multiple factors at the same time. On the other hand, data about immune-neuroendocrine and metabolic changes during the chronic phase mostly came from studies in human Chagas disease. Therefore, here we will concentrate on evidence obtained from animal models of acute infection, and individuals with chronic Chagas disease.

2.1. HPA axis in murine models of acute *T. cruzi* infection

During the last two decades, our laboratory has provided convincing evidence that cytokines released by the immune system after the infection with the Tulahuén strain of *T. cruzi* have profound effects on the HPA axis, and hence affecting disease course. Acute *T. cruzi* infection induces the release of IL-1β, IL-6, TNF-α, and IFN-γ, able to elicit a 10-fold increase in corticosterone blood levels [29–31]. Comparative studies between susceptible C57BL/6 (Th1-biased) and resistant BALB/c (Th2-biased) male mice also indicated that disease susceptibility depends on the appropriate timing and extent to which the HPA axis is activated, rather than a difference in parasitemias. In this sense, the higher basal levels of corticosterone followed by a further early increase in corticosterone levels in infected BALB/c mice, is likely to account for the increased proportion of surviving BALB/c mice from acute infection [30,32]. In addition, infected BALB/c mice developed an earlier response of *T. cruzi*-specific IgG antibodies compared to C57BL/6 [33]. Since IL-1β is the most potent cytokine in terms of HPA axis activation [34], the earlier and higher circulating levels of IL-1β seen in BALB/c infected mice may be indicative of a more effective activity of this neuroendocrine axis [29]. Our studies revealed that appropriate HPA axis activation is clearly influential in terms of disease course and susceptibility [30,31] since GC depletion leads to a dramatical increase of circulating proinflammatory cytokines accompanied by an accelerated death of *T. cruzi*-infected mice, rendering the BALB/c group 100% susceptible. Furthermore, in accordance with an expected GC-driven Th2 response, infected BALB/c mice exhibited early increased levels of *T. cruzi* specific-IgG antibodies compared to C57BL/6 counterparts [33]. The essential features of HPA axis activation in both resistant and susceptible models of acute *T. cruzi* infection in male mice are summarized in Fig. 1A and B. Interestingly, C57BL/6 mice showed a clear sexual dimorphism in terms of susceptibility to infection. While 30–50% of females survived from the acute phase of infection, 100% of infected males succumbed. Although sexual hormones appear to have a protective role against the parasite, it was clear that females have a two-fold increase of baseline GC levels respect to males [35].

TNF-α is essential to protect against *T. cruzi* by enhancing the trypanocidal activity of IFN-γ-activated macrophages. However, a dysregulated production of TNF-α can be at the same time detrimental, because this cytokine also participates in tissue injury. Coincidentally, C57BL/6 susceptibility to *T. cruzi* infection was linked to an exacerbated TNF-α production, causing tissue damage and diverse toxic effects [33,36,37]. As shown schematically in Fig. 1B and C, the abolition of TNF signaling, by using C57BL/6 mice genetically deficient for both TNF-α receptors ($TNFR_{1/2}$ KO), increased blood parasites and myocardial parasite nests. Infected $TNFR_{1/2}$ KO mice had even higher concentrations of IL-1β than C57BL/6 wild type, as did IL-6, and IFN-γ, which may explain the pronounced stimulation of the HPA axis showed by this group in terms of GC production. Nevertheless, GC seems to be ineffective in cope with excessive inflammation, since $TNFR_{1/2}$ KO infected mice developed a marked disease severity, i.e., cachexia, and

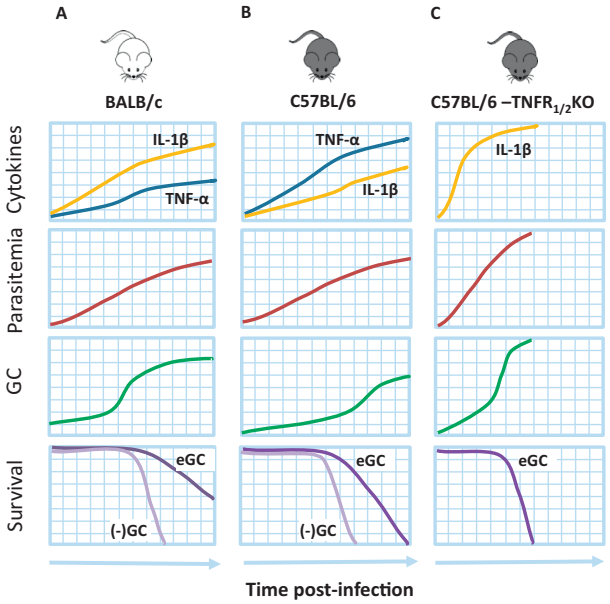

Fig. 1. Comparative representation of cytokine and corticosterone production, parasitemia and survival between different strain of mice acutely infected with *T. cruzi*.

Illustrative representation of variations in different parameters during *T. cruzi* infection in: A) resistant BALB/c, B) susceptible C57BL/6, and C) C57BL/6 mice deficient in both tumor necrosis factor receptors (C57BL/6-TNFR$_{1/2}$KO). Resistance to *T. cruzi* infection in BALB/c mice is associated to a more rapid increase in endogenous corticosterone levels and an early interleukin (IL)-1β production. Increased mortality in C57BL/6 mice is related to an excessive production of tumor necrosis factor-alfa (TNF-α). Blocking TNF-α signaling in C57BL/6 mice accelerates lethality and increases parasitemia, corticosterone and IL-β production. Corticosterone depletion by adrenalectomy prior to infection, renders BALB/c mice susceptible and shortens the survival time of C57BL/6 mice. eGC: survival in mice with endogenous corticosterone production. GC(−): survival in adrenalectomized mice.

early death [30]. Similar but less significant changes were also observed in C57BL/6 mice genetically deficient for each TNF receptor, being more pronounced in TNFR1 KO mice than TNF-R2 KO, highlighting the importance of TNF-R1 in the control of *T. cruzi* infection [30].

One study showed that HPA axis activation during *T. cruzi* infection in mice lacking adaptative immunity turns out to by excessive. In fact, experiments by using C57BL/6 RAG-1-defective mice revealed an earlier and robust increased of GC amounts upon *T. cruzi*-infection when compared to wild type counterparts. Such overreaction may be the result of an innate exacerbated production of IL-1β and IL-6; likely linked to MyD88/TRIF-dependent mechanisms, activated through Toll-like-2, TLR-4 and TLR-9 because of an excessive *T. cruzi*-derived PAMPs, given the 20-fold further increased parasitemia seen in RAG-1 infected mice [38].

More recent studies additionally indicated a hormonal signal disconnection between pituitary and adrenal glands towards the end of acute infection, since corticosterone continued to increase, whereas ACTH returned to basal levels [39,40]. Interestingly, studies by infecting a murine ACTH-producing cell line (atT-20) with *T. cruzi*, led to a profound reduction of ACTH release and the expression of its hormone precursor proopiomelanocortin (POMC) if compared to uninfected cells. These atT-20 infected cells also released high IL-6 amounts, although its stimulating effect on POMC synthesis seemed to be inhibited by an increase in SOCS3 -a suppressor of cytokine signaling molecule- [39]. In an additional study carried out in the same cells, an increase in the inhibitor of STAT-3 (called PIAS3) was observed. PIAS3 can bind STAT3 and blocks ACTH-transcriptionally activity, suggesting a possible direct role for PIAS3 in the ACTH decay [39].

Data from human sepsis or endotoxemia models indicate that GC increase decoupled from ACTH may be related to the presence of proinflammatory mediators released at the adrenal level. Resident immune cells or even adrenocortical cells can be a potential source of cytokines [41].Within this setting, *T. cruzi* infected mice, not only showed increased levels of TNF-α, IL-1β, and IL-6 in circulation but also intra-adrenally, implying that a local inflammatory microenvironment may account for the maintenance of the high GC output [40,42,43]. In parallel, GC synthesis can also be modulated locally by prostaglandin E2 and nitric oxide [44]. Some studies showed that pathogen antigens can trigger intra-adrenally the GC synthesis through the engagement of TLR-2 and TLR-4, as well. In this sense, TLR-2-deficient mice, have impaired adrenal corticosterone even in the presence of augmented ACTH levels [45]. The presence of parasite-derived antigens may promote this local inflammatory response and trigger the synthesis and secretion of GC. Even, during *T. cruzi* infection, the intra-adrenal synthesis of inflammatory cytokines may be triggered through TLR-2 since trypomastigote-derived glycosylphosphatidylinositol anchors are potent TRL-2 agonists [46].

2.2. HPA axis in human chronic Chagas disease

Our studies in patients with chronic Chagas disease demonstrated that a broad range of pro-inflammatory cytokines is produced during this stage, preferably in symptomatic cases. This inflammatory *milieu* may affect endocrine mechanisms, further implied in the disease course [47]. HPA axis abnormalities have been also recognized in human chronic Chagas disease. For instance, patients with heart affectation, the commonest dysfunction, display a high cortisol/DHEAs ratio, due to a profound diminution of DHEAs in presence of nearly preserved amounts of GC [47,48].Usually, DHEA fall with aging, but in chagasic patients, the diminution of this hormone is not related to their age status. Such imbalance, also observed in other forms of acute or chronic illnesses, is probably related to the rise of circulating cytokines [27]. Interestingly, chronic chagasic patients without apparent pathology showed lower levels of pro-inflammatory cytokines and a more balanced GC/DHEAs relationship [47].The mechanisms likely to explain such differences are not completely known, although variations in the circulating levels of diverse immune-endocrine mediators seem to be involved. Whatever the case, disturbances in cortisol/DHEA ratio seem to be detrimental to the host due to a deficient control of inflammation and the ensuing development of tissue injury [49]. Interestingly, malaria or human schistosomiasis, which showed a less torpid evolution than Chagas disease, are associated with increased levels of DHEA [50–52], suggesting a protective role for this hormone in such parasitosis. At the experimental level, treatment with DHEA improved the immune response during *T. cruzi* infection [53,54]; although the study did not analyze whether DHEA levels correlated with cytokines activating the HPA axis.

Focusing again on the chronic human disease scenario, the adverse endocrine context (i.e., the increased GC/DHEA ratio), along with the large number of antigenic constituents displayed by *T. cruzi* may favor the activation of a polyclonal immune response and the consequent risk of autoreactivity [55]. While the autoimmune basis of Chagas disease is still debatable, there is a reason to believe that suppression or an adverse adrenal counter-regulatory mechanism may act as a permissive factor for the development of autoimmune phenomena; for which studies concerning immune-endocrine imbalance and *T. cruzi*-driven autoreactivity are clearly needed.

3. Other hormones produced by the anterior pituitary are also altered in both experimental and human Chagas disease

Anterior pituitary hormones, including ACTH, growth hormone (GH), prolactin (PRL), thyroid-stimulating hormone (TSH), and the gonadotropins luteinizing (LH) and follicle-stimulating (FSH) hormones

can also modulate the immune response, whereas cytokines can equally influence their production [12]. GH and PRL which are regarded as stress hormones, appear increased during stressful conditions, as does GC, because of the direct pituitary action of pro-inflammatory cytokines. Interestingly, PRL and GH increase exert enhancing effects on the immune response, counterbalancing the downregulating influences of GC [56].

Data from experimental and human studies showed that PRL- and GH-physiological responses are altered during *T. cruzi* infection; possibly related to the demonstration that *T. cruzi* can infect the pituitary [39,57].In fact, in vitro *T. cruzi* infection of GH-/PRL-secreting GH3 cells, leads to a diminution of both GH and PRL secretion [58]. Moving to the in vivo scenario, acutely *T. cruzi* infected mice showed a reduction in circulating PRL levels [59], whereas PRL supplementation in rats undergoing this protozoan infection led to a better parasite control coupled to macrophage activation, nitric oxide production and T cell proliferation [60]. Thus, the decrease in PRL production evidenced in mice after *T. cruzi* infection could synergize the immunosuppressive role of GC.

PRL has a protective effect on the cardiovascular system, and its physiological raise (as seen during lactation), may stimulate the JAK-STAT pathway involved in cardiomyocyte hypertrophy [61]. When achieving levels above the physiological ones PRL may alter cardiac metabolism and microvasculature [62], for which increased PRL levels may favor physiopathological events involved in the development of cardiac damage being in line with the fact that patients with CCM tended to display increased PRL amounts [47].

GH exerts both immune-stimulant and metabolic effects. GH direct metabolic effects include up-regulation of insulin secretion, lipolysis, and gluconeogenesis. In turn, effects on glucose energy and protein metabolism are indirectly exerted via the Insulin-like Growth Factor 1 (IGF-I), constituting the GH/IGF-1 axis [63].Theoretically, GH levels may be increased during a *T. cruzi*-driven stress response, but evidence in this regard is lacking. Studies in acutely *T. cruzi*-infected rats showed that GH administration improves parasite control by enhancing TNF-α, nitric oxide and IFN-γ synthesis [64], implying a protective role of GH during the acute stage of infection. In the context of human Chagas disease, data from chronically infected individuals indicate a remarkable systemic increase of GH levels in patients with CCM along with an increased GH/IGF-1 ratio, compatible with an imbalance in the somatotropic axis [47]. Despite that, individuals with CCM also display a poor release of GH in response to glucose or insulin challenge compared to healthy subjects, suggesting some deficiency in GH reserve [65]. GH may act directly or indirectly as a modulator of myocardial structure through myocyte receptors for both GH and IGF-1. Therefore, increased GH levels seen in the CCM group may imply a facilitating role of this hormone on the immune mechanisms involved in myocardial damage, particularly the inflammatory component which is a major determinant for disease progression.

Studies carried out many years ago, showed that acutely *T. cruzi*-infected mice had thyroid hyperplasia, even more in females, along with an enhanced thyroid uptake of radioactive iodine. Such findings were interpreted as being due to thyroid parasite infection, an indirect consequence of stress response, or both [66]. Turning to the human counterpart, the seminal work of Carlos Chagas, who described most disease aspects in the first decade of 1900; classified chronic CD into cardiac, thyroid, and nervous clinical forms (this one different from the current neuro-autonomic form). The inclusion of the thyroid form of the disease was based on clinical features, the association of goiter with myxedema, and the presence of parasites and inflammatory infiltrates in thyroids removed from necropsies [67]. Currently, it is no longer accepted that Chagas disease causes goiter [68], mainly because hypothyroidism is instead due to iodine deficiency which prevails in zones also endemic for *T. cruzi* infection [69]. Studies conducted in a group of patients from endemic areas of Argentina (Santa Fe, Santiago del Estero, and Chaco), indicated that the pituitary-thyroid axis activity remains virtually unchanged during chronic Chagas disease. In both asymptomatic and CCM patients, TSH and T4 concentrations fell within values seen in healthy controls, whereas T3 levels were slightly diminished in patients with severe CCM [47].

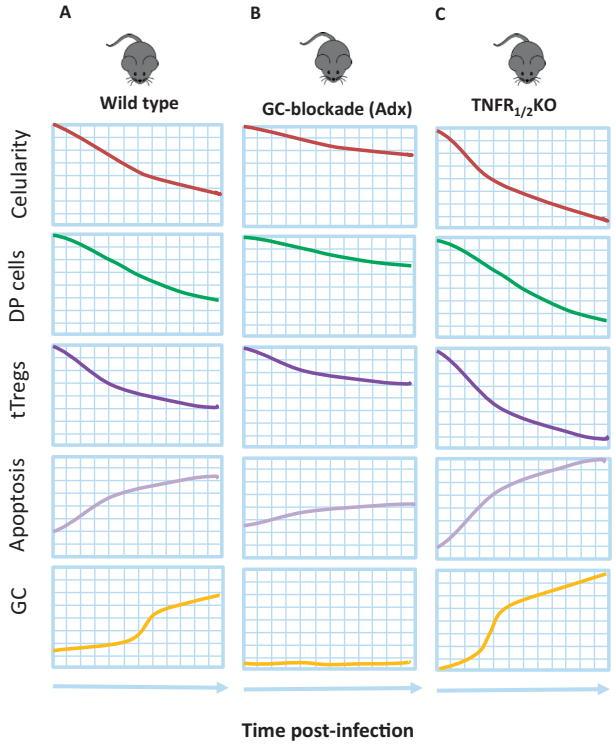

Fig. 2. Comparative representation of thymic parameters in C57BL/6 mice acutely infected with *T. cruzi*.
Schematic representation of changes in thymic parameters recorded in: A) Infected C57BL/6 wild type mice, B–C) or infected C57BL/6 mice lacking corticosterone (adrenalectomy) or tumor necrosis factor (TNF)-α signaling (TNF-$R_{1/2}$ deficiency). In the wild type mice, the thymic atrophy is characterized by the loss of $CD4^+CD8^+$ double positive (DP) cells and thymic regulatory T cells (tTregs) along with an increased cellular apoptosis, linked to raised corticosterone blood levels. Adrenalectomy (Adx) protects from thymic atrophy, avoiding DP and tTregs loss. The lack of TNF-α signaling in $TNFR_{1/2}$KO mice results in a more severe thymic atrophy compared to wild type mice, together with a pronounced increase in corticosterone levels.

4. Antagonist effects of GC and PRL on the murine thymic T cell compartment during *T. cruzi* infection

Several thymic functions, including T cell development, are physiologically controlled by a variety of hormonal influences [70]. Besides classical thymic hormones such as thymulin, thymosins, and thymopoietin; GH, PRL, and GC are also produced by microenvironmental thymic cells and thymocytes, exerting local paracrine/autocrine regulatory actions [70]. This complex neuroendocrine network operating at the thymic level has been particularly and systematically examined in the context of the experimental *T. cruzi* infection.

In general terms, increases in systemic GC levels due to acute or chronic stress, or their therapeutic administration cause thymus involution since immature thymocytes are particularly sensitive to GC-induced apoptosis [12]. As showed in Fig. 2, a consistent feature of *T. cruzi* infection in mice is the occurrence of thymus atrophy, closely related to HPA axis activation since GC blockade employing adrenalectomy or the administration of the steroid receptor antagonist RU486 prevented from such phenomenon [30,31].The shrinkage of the thymic gland is the result of massive GC-driven apoptosis of $CD4^+CD8^+$ double-positive (DP) cells, leading to the progressive loss of $CD4^+$ and

$CD8^+$ simple positive thymocytes and $CD4^+FoxP3^+$ regulatory T cells [30,31,71]. Such GC-induced apoptosis of DP cells is exerted through the activation of caspase-8 and caspase-9, but not caspase-3 [72]. Strikingly, serum increased levels of adrenal-derived GC were paralleled by a decrease in their intrathymic contents, implying that the control of intrathymic GC production during acute *T. cruzi* infection, is driven by mechanisms other than those operating at the adrenal level [59].

PRL has opposing actions to GC on the viability and proliferation of thymic cells [73]. In thymuses from infected mice, the presence of locally PRL is heightened, in contrast to their diminished levels seen in circulation [59]. Moreover, studies during *T. cruzi* infection showed that PRL-mediated STAT5 signaling in thymocytes interferes with GC signaling to inhibit the steroid-induced pro-apoptotic effects, probably as a compensatory phenomenon [59].

Testosterone is also known to exert a modulatory role on the thymus. Healthy individuals, recipients of testosterone supplementation have an increased death of cortical thymocytes, while the ablation of male gonads increases the thymus size [70]. In the context of experimental *T. cruzi* infection, testosterone administration diminishes thymocyte proliferation, whereas castration significantly increases the thymus size [74]. Interestingly [75], the role of testosterone seems to be linked to Trans-sialidase (TS), a virulence factor from *T. cruzi* involved in immune evasion [76]. In male mice, the apoptosis of DP cells after TS administration seems to be partly induced by testosterone [77]. Testosterone induces thymocyte apoptosis through a caspase-3-dependent pathway, dissimilar to the one elicited by GC, which activates caspase-8 and caspase-9 pathways [72,77].

In the mouse, TS and TNF-α bind extracellular matrix proteins and modulates the migratory properties of thymocytes, possibly contributing to the abnormal release of DP thymocytes to the periphery [78,79]. The detection of IFN-γ^+HLA-DR^+ activated DP cells in the blood from patients with CCM, and the IFN-γ^+GranzimeB^+-DP counterpart seen in infected mice, suggest the existence of thymic alterations in the selection processes. This raises new questions about the relevance of such potentially autoreactive cells in the pathogenesis of Chagas disease, possibly linked to intra-thymic immune-endocrine disturbances [80,81].

Leptin-deficient signaling in mice was shown to result in chronic thymic atrophy, pointing out to its role in thymic homeostasis [82]. Coincidently, acutely infected mice developed hypoleptinemia and a significant decrease in the intrathymic leptin contents when thymus atrophy became evident. Thymic leptin mRNA remained within the levels shown by non-infected mice, suggesting post-transcriptional regulation of its expression. By opposite, mRNA leptin receptor (ObR) expression was increased in the infected whole thymus, provably explained by a relative enrichment of the $CD4^+$ and $CD8^+$ simple positive subpopulations. Since leptin supplementation during an inflammatory setting restored thymic involution [83,84], it was also evaluated the effects of recombinant leptin administration on the *T. cruzi*-induced thymic atrophy. As expected, in non-infected C57BL/6 mice, leptin induced a slight thymic hypertrophy. When studying infected mice, leptin administration resulted in even greater thymic atrophy compared to non-treated and infected counterparts, suggesting that the over-increased GC response seen in *T. cruzi*-infected mice are likely to override the beneficial effects of leptin at the thymic level [85].

The series of thymic alterations seen during *T. cruzi* infection are summarized in Fig. 3.

5. Adipose tissue and metabolic disturbances during *T. cruzi* infection

5.1. Data from murine models of acute T. cruzi infection

Adipose tissue (AT) is a central organ for the regulation of energy metabolism capable of influencing the immune response, as well [86]. Adipocytes synthesize adipokines such as adiponectin and leptin which are influential not only on insulin sensitivity but also on the inflammatory response [86,87]. During an infectious process, the high energy expenditure required to cope with pathogens can cause a remarkable reduction in the mass of AT, further resulting in metabolic abnormalities which may worsen disease outcome [88]. The possible link between the energetic status and the course of *T. cruzi* infection was raised by the pioneering work of Tanowitz and collaborators, documenting that an unfavorable metabolic environment, i.e., diabetes, aggravated *T. cruzi* infection [89]. Metabolic alterations during acute experimental *T. cruzi* infection have been described by many research groups. The development of severe hypoglycemia, hypertriglyceridemia, the severe loss of AT and body weight are among the most salient disorders [85,90–93]. In turn, AT is a clear target of *T. cruzi* infection, constituting a parasite reservoir during the chronic phase from mice and humans [91,94]. The mouse acute infection courses with a profound AT loss, diminution in adipocyte size and increased expression of proinflammatory cytokines such as IL-6, TNF-α, IL-1β, and IFN-γ, clearly compatible with an inflammatory environment [90,91]. Proinflammatory cytokines frequently remain elevated within AT even during chronic infection. This phenomenon is paralleled by a loss of adipocyte features. In this sense, we and others found a decrease in the expression of the transcription factor peroxisome proliferator-activated receptor-gamma (PPAR-γ) during acute severe *T. cruzi* infection together with a diminution in the expression of the main enzymes involved in lipolysis and lipogenesis [90,92]. As seen in Fig. 4, PPAR-γ is a dominant regulator of adipogenesis and highly needed for the maintenance of the mature phenotype [95] of adipocytes. PPAR-γ depletion in mature adipocytes compromises their viability and fat storage because of the expression loss of the main metabolic enzymes [96,97]. Decreased expression in PPAR-γ in our mouse model is probably due to the concomitant rise of proinflammatory cytokines like TNF-α. Accompanying these findings, there was also a reduction in the expression of leptin and adiponectin, either in AT or in circulation [85,90,91]. The impaired adipocyte function together with changes in the adipocytokine profile may favor metabolic alterations and inflammatory reactions seen during acute experimental *T. cruzi* infection, collectively contributing to aggravated disease. In general terms, the lower the adiponectin amounts, the higher glycemic levels, illustrating the insulin-sensitizing activity of this adipocytokine [98–100] Our demonstration of a decreased adiposity and severe hypoglycemia during acute infection, in the presence of a decreased adiponectin expression in AT, adds another study-stimulating element to the complex network underlying disease pathogenesis. Given that adiponectin deficient mice are prone to develop myocardial inflammation [101], the relationship between decreased adiponectin production by AT and the concomitant proinflammatory status from acutely *T. cruzi*-infected host may favor the establishment of myocardial damage.

Also, whereas leptin-deficient mice exhibit hyperphagia, reduced energy expenditure, diabetes, and obesity [102,103]; the leptin decrease from acutely *T. cruzi* infected mice is paralleled by decreased food intake, body weight reduction and augmented energy expenditure. This may be taken to imply a dysregulation of leptin/hypothalamic ObR circuitry, dissociated from body weight and food intake control during acute infection [85]. Leptin administration to these mice even worsened inflammation and failed to normalize metabolic parameters [85].

Within the complex series accompanying acute experimental *T. cruzi* infection, severe hypoglycemia is usually present and may constitute a major factor for the fatal course. Hypoglycemia may be the consequence of a multifactorial process comprising the high energy demand from activated immune cells, the exacerbated increase of proinflammatory cytokines, and the reduced food intake seen in the late phase from acute infection. Deficiencies in the gluconeogenic pathway may be also envisaged given the liver damage seen during this trypanosomiasis [93]. Strikingly, infected animals did not lose their ability to handle glucose. Whereas base-line glucose levels from infected mice

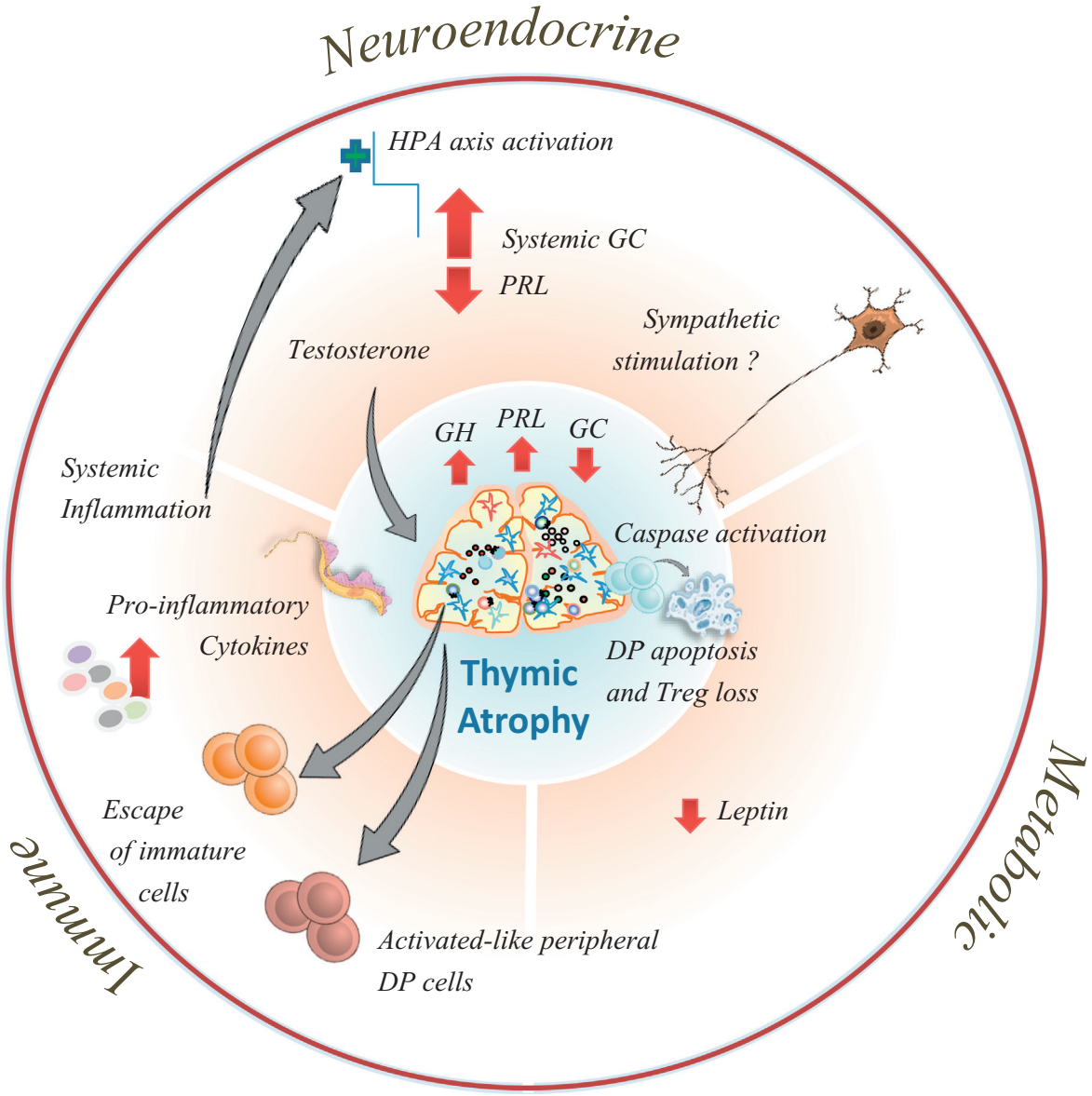

Fig. 3. Immune, neuroendocrine and metabolic changes associated to thymic atrophy during acute *T. cruzi* infection.
Preserved thymus may be essential for the development of an effective immune response against *T. cruzi*, but this organ is severely affected by a dysregulated loop of cytokine, hormonal and metabolic interactions. The exacerbated systemic production of pro-inflammatory cytokines, mainly interleukin (IL)-1β, tumor necrosis factor-alfa (TNF-α), IL-6, and interferon-gamma (IFN-γ), mediates the activation of hypothalamus-pituitary-adrenal (HPA) axis. The resulting systemic increase in glucocorticoids (GC) and the diminution in prolactin (PRL) favors the apoptosis of double positive (DP) cells and the loss of regulatory T cell (Treg). The intrathymic hormone circuitry shows an inverse modulation that seems to counteract the GC-related systemic deleterious effects. In males, testosterone influences DP cell loss by caspase activation, while leptin diminution may act as a permissive factor for GC-induced thymic atrophy. An anomalous exit of potentially autoimmune DP cells would contribute to the thymic atrophy and might have potential implications for the autoimmune component of Chagas disease. The *T. cruzi* infection-associated stress might also mediate a sympathetic response on the thymus affecting cellularity, worth exploring.

were always below normal values, oral glucose tolerance tests showed a relatively normal ability to clear ingested glucose [90,91].

In a diet-induced obesity model undergoing *T. cruzi* infection, most metabolic alterations appeared improved, although plasmatic apoB100 levels remained significantly increased, suggesting the presence of pro-atherogenic small and dense LDL particles [104]. Studies in obese mice subjected to an acute infection showed an insulin resistance state followed by chronic hyperglycemia and hypoinsulinemia, compatible with an infection-related diabetes progression. Collectively, in the obesity context, *T. cruzi* infection may be a risk factor for the development of metabolic disorders like atherosclerosis and diabetes [104].

5.2. Metabolic disturbances in human Chagas disease

In humans, the role that metabolic alterations may have in the pathogenesis and aggravation of CD has not been evaluated in depth. In a study carried out in Brazil, a higher prevalence of diabetes was observed in women presenting CCM compared to those from the general population [105]. Infected individuals living in endemic areas show low body weight (body mass index - BMI - less than 20 [106]), while infected people that have migrated to urbanized areas presents overweight and in some cases obesity [48,107–109]. Such increased BMI is related to radical changes in their eating habits upon migration, the city-associated sedentary lifestyle and the educational and socio-economic characteristics of these individuals [48,107–109]. In a study carried out by our group, we observed that urbanized chagasic patients

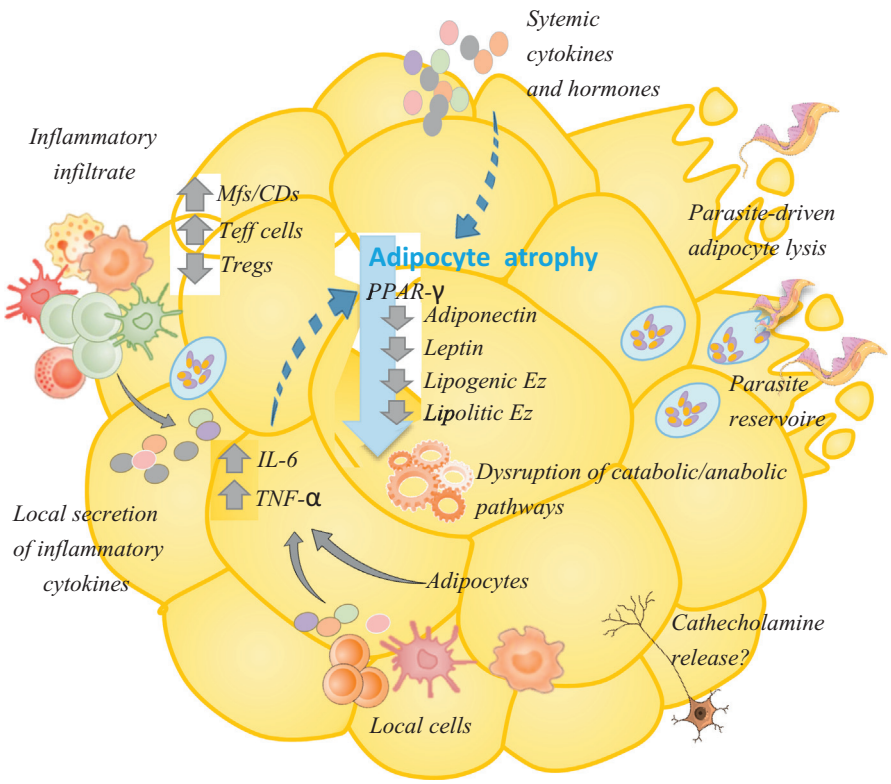

Fig. 4. Acute *T. cruzi* infection severely affects the homeostasis of adipose tissue.
Male mice acutely infected with *T. cruzi* showed a progressive and severe reduction in the adipose depots, mostly in the epididymal adipose tissue. This loss may be likely linked to immune-endocrine disturbances, enhanced energy expenditure and parasite-direct effects. Adipose tissue is infected by the parasite and amastigote nests are usually observed during the acute phase, constituting a potential parasite reservoir during chronic Chagas disease. Atrophy of adipose tissue results from adipocyte size diminution and parasite-driven cell destruction. The presence of *T. cruzi* or their antigens in the adipose tissue, induce an influx of inflammatory cells (mostly macrophages, dendritic cells and T lymphocytes) and reduced regulatory T cells. The local secretion of pro-inflammatory cytokines like tumor necrosis factor-alfa (TNF-α) and interleukin (IL)-6 seems to be promoted not only by local and infiltrating immune cells, but also by adipocytes. Moreover, infection disrupts both adipocyte catabolic and anabolic pathways (by down regulating adipogenic and lipogenic enzymes and adipocytokines) secondary to peroxisome proliferator-activated receptor gamma (PPAR-γ) robust downregulation.

had increased insulin and triglycerides levels in circulation, an augmented HOMA-IR index in presence of lower levels of HDL, resembling a prediabetic situation, which in turn may increase the risk for cardiovascular disease. Overweight and obesity have a strong impact on the immune response since they are regarded as indicative of chronic low-grade inflammation states [110,111]. In patients with CCM, we also found higher levels of IL-6 and changes in TNF-α [48]. Accordingly, an enhanced inflammatory background resulting from the overweight present in chagasic patients is likely to add risk factors favoring an early development of cardiac lesions. Regarding adipokines, results are inconclusive. One study reported decreased leptin levels in chagasic patients with congestive heart failure [112], whereas another report showed no differences between patients with CCM and controls. Unlike this, our study in chronically chagasic patients revealed a slight hyperleptinemia, particularly in CCM patients [48]. Since patient classification was different in the three studies, this issue may account for such reported differences. In line with our findings, leptin levels were found increased in non-chagasic individuals with chronic heart failure; this finding being possibly related to the hypertrophic effects of leptin on cardiomyocytes [113,114]. Since heart enlargement is a common feature of CCM, a detrimental role of increased leptin levels in this regard cannot be ruled out [115]. In parallel, augmented leptin levels may reflect increased inflammation, given its role as an inflammatory cytokine, particularly in CCM patients. At variance with a study in a dissimilar subgroup of patients with advanced heart failure showing an autonomic dysfunction related hyper-adiponectinemia [48,112], adiponectin levels in our series of chagasic patients remained unchanged. Although not much data is available about metabolic implications of CD in humans, we can conclude that overweight/obesity and its immune-metabolic consequences must be addressed when evaluating chagasic patients, largely because of the increasing presence of this comorbidity among them.

6. Immunomodulatory role of the autonomic nervous system during acute *T. cruzi* infection

There is now convincing evidence that both sympathetic and vagal parasympathetic branches of the ANS can modulate the immune response, mainly by skewing the Th1-response towards a Th2-biased profile [116–120]. In this sense, neurotransmitters released by sympathetic and parasympathetic nerve endings can bind to their specific receptors located on the surface of immunocompetent cells initiating regulatory mechanisms that help to shape the immune response.

It is widely documented that ANS dysfunctions occur in chronic chagasic patients with cardiac or gastrointestinal involvement, but whether these derangements are cause or consequence of the pathology [121,122], it is still a matter of debate, far beyond the scope of this review.

However, studies carried out after the initial parasite exposure, in which the development of cardiac or gastrointestinal pathology is quite unlikely to be established, indicate that the ANS response shapes the profile of the immune response conditioning disease susceptibility/outcome from infected mice.

Evidence about the parasympathetic modulation of the anti-*T. cruzi* immune response came from studies taking advantage from the vesicular acetylcholine transporter (VAChT). This transporter mediates the ACh storage inside the synaptic vesicles, allowing the subsequent release of Ach in the synaptic terminal. C57BL/6 VAChT knockdown mice infected with the Y strain exhibited a decreased ability to release endogenous ACh linked to a more flourished inflammatory response, diminished parasite load and an exacerbated mortality compared to infected wild type mice [123]. The enzyme acetylcholinesterase, which is involved in the extinction of impulse transmission by rapid hydrolysis of ACh and their inactivation, leads to ACh accumulation causing hyperstimulation of cholinergic pathways. As expected, the administration of the anti-acetylcholinesterase agent pyridostigmine bromide to *T. cruzi*-infected mice favored the parasite growth likely by the restrained inflammatory response, and hence, tending to increase the mortality [123].These findings evidenced a clear immunosuppressive role of

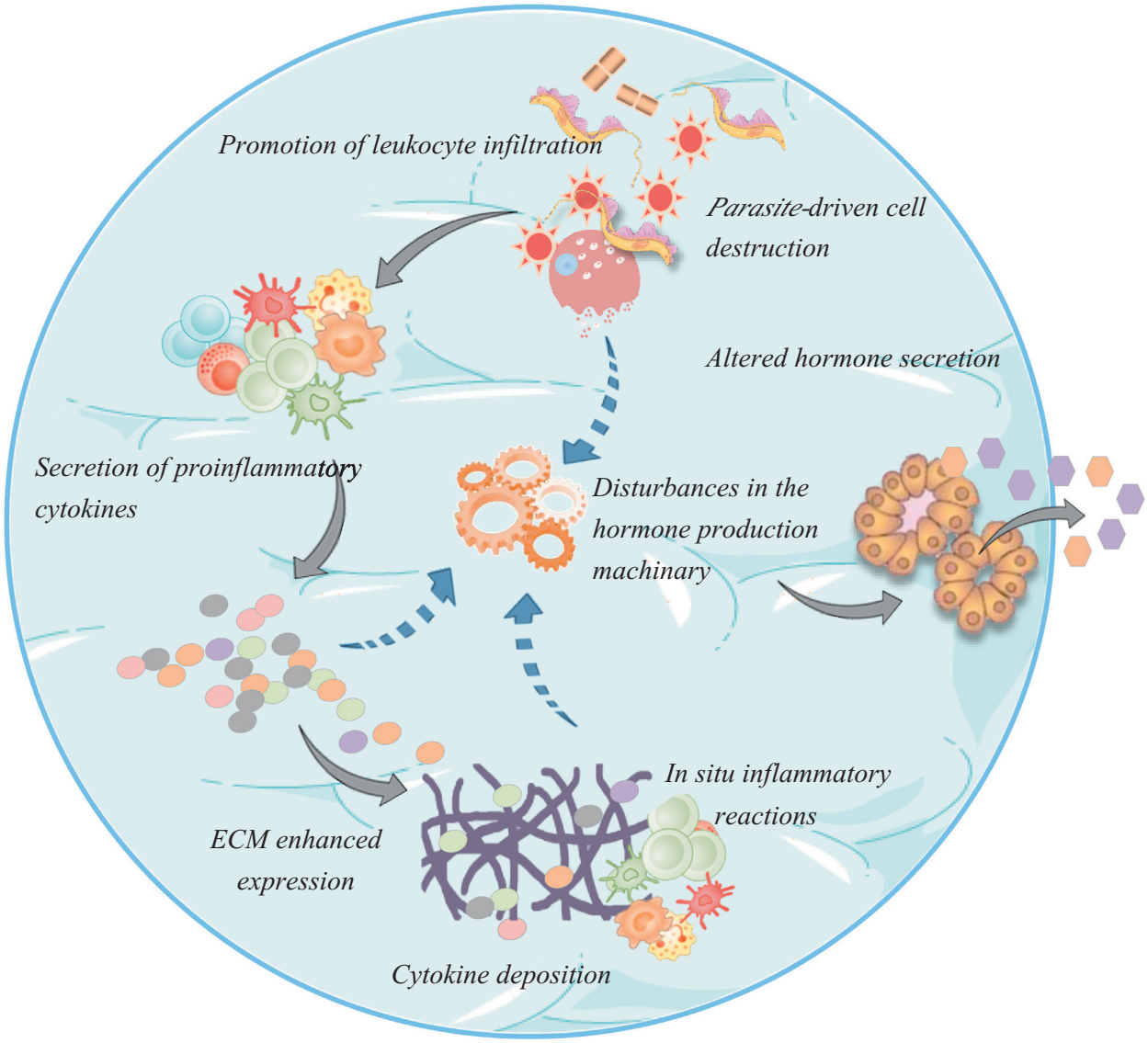

Fig. 5. Potential mechanisms underlying neuroendocrine and metabolic disturbances in Chagas disease.
Causes for the *T. cruzi* infection-associated neuroendocrine and metabolic disturbances include several and not mutually exclusive possibilities. Systemic or local cytokine abnormalities can enhance or suppress the activation of hormonal axes, by acting at the brain units and/or on peripheral glands. In situ inflammatory reactions or structural changes like vascular alterations or an enhanced deposition of extracellular matrix (ECM) molecules in the endocrine microenvironment may also lead to endocrine or metabolic dysfunctions.

cholinergic pathways during the earlier stages of *T. cruzi* infection.

Concerning to the immunomodulatory role of the sympathetic nervous system, a study carried out in β2-adrenergic receptor-deficient FVB mice infected with the Romildo strain of *T. cruzi*, showed increased parasitemias, less pronounced cardiac lesions and improved survival compared to wild type FVB mice [123]. In a more recent study, *T. cruzi*-infected mice whose sympathetic nerve fibers were destroyed previously by neonatal administration of the neurotoxin 6-hydroxy-dopamin, revealed increased parasitemia, raised circulating IL-6 and IFN-γ levels, dying earlier than non-denervated counterparts. Interestingly, circulating levels of TNF-α, IL-1β or anti-*T. cruzi* IgM or IgG2a antibodies from infected mice were unaffected by neonatal denervation [35]. Strikingly, the acute infection in C57BL/6 male mice induced a spontaneous fall in the total and relative splenic contents of noradrenaline, paralleled by a loss of noradrenergic nerve fibers. Additionally, the splenic reduction of noradrenaline was linked to a marked accumulation of tyrosine (noradrenaline precursor) and lack of tyrosine hydroxylase immunostaining. While the significance of these findings is not yet clear, the reduction in the splenic vascular sympathetic tone, may be an attempt to favor splenocyte mobilization to the blood to cope with the infection [35].

7. Potential mechanisms underlying immune-neuro endocrine disturbances during *T. cruzi* infection

Changes in the neuroendocrine activity observed both in experimental models and human Chagas disease can be induced by the anti-parasite immune response as a part of an immunoregulatory circuit (i.e., HPA axis activation), in addition to some influence arising from the functional alterations caused by the disease. Some possible explanations regarding neuroendocrine and metabolic changes include several and not mutually excluding possibilities (summarized in Fig. 5):

1) A direct effect of parasites on endocrine glands and the autonomic innervation. The parasites can destroy the cells they have invaded, generating a loss in the activity of glands or nervous terminals.

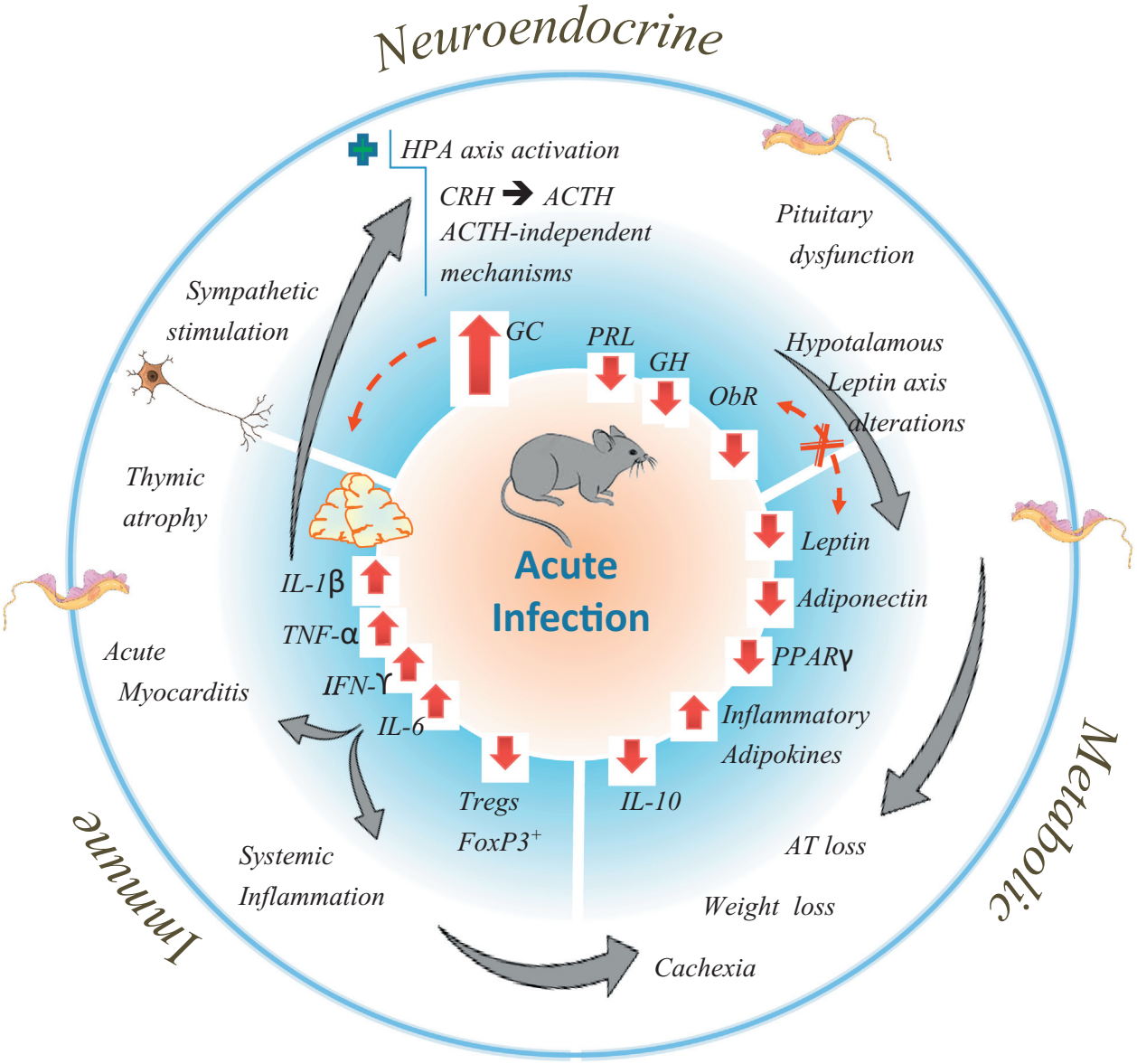

Fig. 6. Immune, neuroendocrine and metabolic changes associated to experimental acute *T. cruzi* infection.
Schematic illustration showing the main immune-neuroendocrine disturbances and metabolic disorders seen during acute *T. cruzi* infection in mice. Note that parasites or their antigens have been detected in different organs and tissues from the three systems. The center of the graph (with blue background) points to the main alterations from different immune-neuroendocrine and metabolic mediators during this stage, while systemic and clinical repercussions are mostly indicated in the periphery (border, edge) of the representation (in white background). ACTH: adrenocorticotropic hormone; CRH: corticotropin releasing hormone; GC: glucocorticoids; GH: growth hormone; INF-γ: interferon gamma; IL-1: interleukin 1 beta; IL-6: interleukin 6; IL-10: interleukin 10; ObR: leptin receptor. PPAR-γ: peroxisome proliferator-activated receptor gamma; PRL: prolactin; TNF-α: tumor necrosis factor alfa; Tregs Foxp3^{+}: regulatory T cells expressing the transcription factor FoxP3. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2) Variations in the systemic or local levels of cytokines, which can act on endocrine glands to enhance or suppress their specific hormonal function. The presence of parasite or their antigens in glands favors the influx of inflammatory cells and hence, the local production of inflammatory cytokines.
3) In situ inflammatory reactions, structural changes, vascular alterations or a greater deposition of the extracellular matrix in the microenvironment of endocrine glands perpetuates inflammation by promoting cytokine deposition, modulating leukocyte influx, chemotaxis, and the activation and survival of infiltrating immune cells. These changes able to induce a transient dysfunction.

Concerning the presence of *T. cruzi* at the neuroendocrine tissues, adrenal amastigote nests were observed in acutely infected mice, while *T. cruzi* kDNA and parasite antigens were detected in both the adrenal and pituitary glands [124–127]. Furthermore, in patients with acute infection, nests of amastigotes were found in the ovary, testis, thyroid, and cells from the nervous system [128]. Moreover, *T. cruzi* infection causes structural and inflammatory changes in neuroendocrine organs, like an increase in the deposition of the extracellular matrix, vascular stasis, and infiltration of macrophages and T cells [129].The extracellular matrix proteins participate in cellular traffic, and their deposition is enhanced by cytokines, for which an influx of inflammatory cells into the endocrine glands may be promoted. Furthermore, extracellular matrix molecules may bind diverse *T. cruzi*-derived antigens and pro-inflammatory cytokines, thus contributing to a protracted inflammation [79,130].

Additionally, cell adhesion is a key step in parasite invasiveness, and

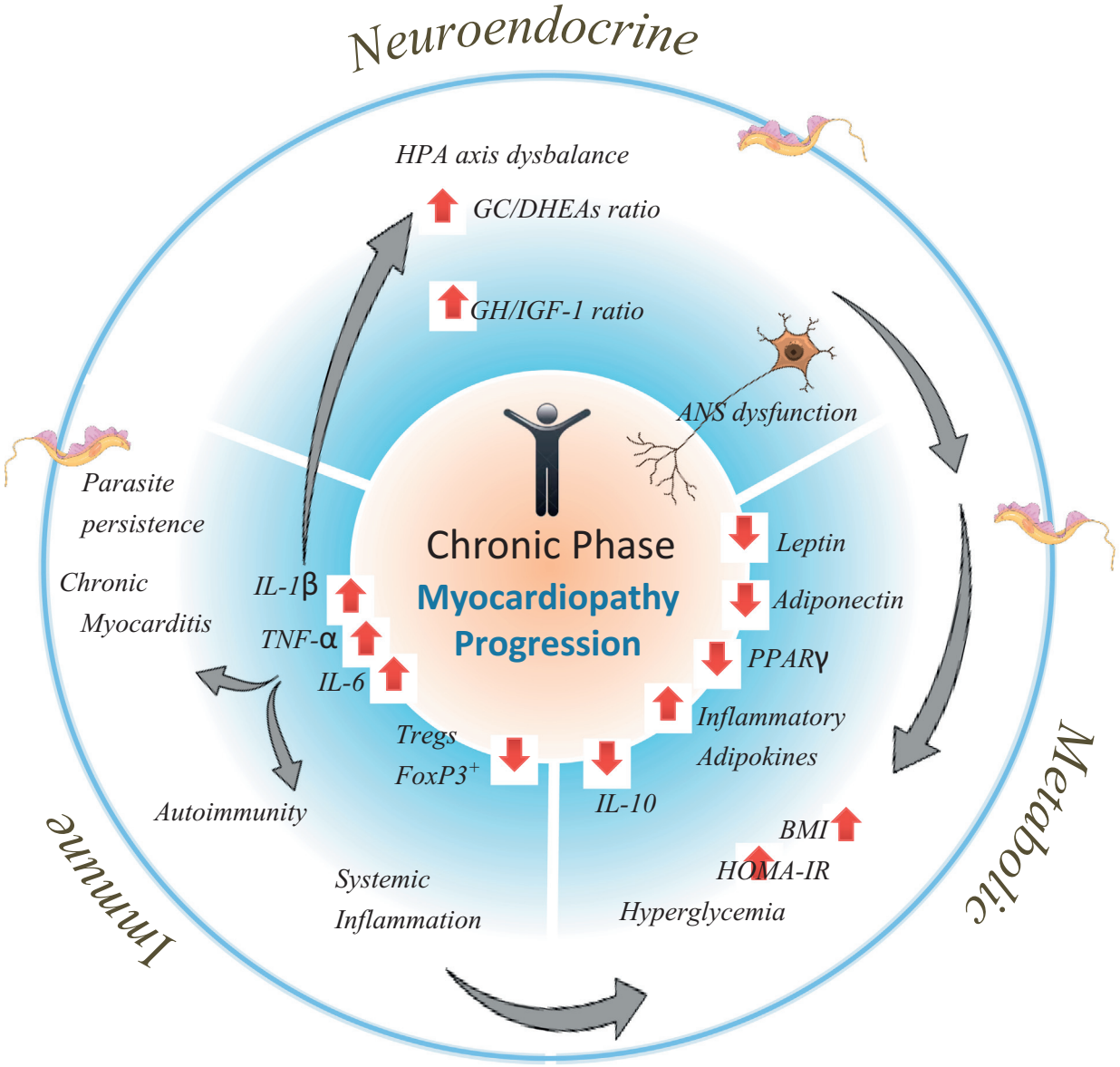

Fig. 7. Immune, neuroendocrine and metabolic changes associated to human chronic Chagas disease.
Schematic illustration showing the main immune-neuroendocrine disturbances and metabolic disorders detected in patients with symptomatic human chronic Chagas disease. Note that parasites or their antigens have been detected in different organs and tissues of the three systems. The center of the graph (with blue background) points to the main alterations from different immune-neuroendocrine and metabolic mediators during this stage, while systemic and clinical repercussions are indicated in the outer area of the graph (in white background). ANS: autonomic nervous system; BMI: body mass index; DHEAs: dehydroepiandrosterone sulfate; GC: glucocorticoids; GH: growth hormone; HPA axis: hypothalamus-pituitary-adrenal axis; HOMA-IR: model assessment of insulin resistance; INF-γ: interferon gamma; IL-1: interleukin 1 beta; IL-6: interleukin 6; IL-10: interleukin 10; IGF-1: insulin growth factor 1; PPAR-γ: peroxisome proliferator-activated receptor gamma; PRL: prolactin; TNF-α: tumor necrosis factor alfa; Tregs Foxp3^{+}: regulatory T cells expressing the transcription factor FoxP3. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in this sense, *T. cruzi* can recognize extracellular matrix proteins like laminin or fibronectin to invade diverse cells [131].Coincidently, an increase in the deposition of both extracellular matrix protein was observed in central areas of the brain, particularly in the hypothalamus, as well as pituitary and adrenal glands, accompanied by an accumulation of local inflammatory infiltrates and presence of parasites or their kinetoplastid DNA [32]. Likewise, pituitary dysfunction is also observed in animals infected with *T. congolense*, whereas alterations in the microvasculature of the gland, greater deposition of extracellular matrix and presence of parasites in situ were found [132]. Data from viral infections suggest that neural disorders may be related to a remodeling of the extracellular matrix in the hypothalamus and other brain areas, caused by an imbalance of enzymes involved in their synthesis and degradation. Another possible mechanism of inflammation at the neuroendocrine level was related to the existence of autoimmunity. In this regard, it is worth noting that both human and experimental CD is characterized by cellular and humoral autoreactivity towards nerve structures [133]. Overall, these findings indicate that alterations in the content of the extracellular matrix, coupled with greater tissue inflammation and autoreactivity, may play a role in the neuroendocrine dysfunction seen in this trypanosomiasis.

8. Final comments

Studies reviewed here support the view that proinflammatory cytokines are closely related to neuroendocrine and metabolic

disturbances observed in Chagas disease, highlighting the pathological consequences from the neuro-immune-endocrine and metabolic interactions required to mount a defensive reaction against *T. cruzi*. A schematic and integrative representation of those changes is summarized in Figs. 6 and 7, showing the main abnormalities observed in acute models of *T. cruzi* infection and in the human chronic phase, respectively. These immune-neuroendocrine and metabolic changes are highly relevant in evolutionary terms since they adjust the fine-tuning of the protective response redirecting resources towards the establishment of a well-balanced situation, which ultimately avoids an energy-costly process. Such alterations may be a part of an adaptative immune-neuroendocrine and metabolic regulatory circuitry tending to modulate host defense or, alternatively, or secondary to disease-associated dysfunctions. Whatever the case, future studies will be needed to define whether immune-neuroendocrine and metabolic alterations help to shape the diverse manifestations of chronic Chagas disease. In addition to its intrinsic value, this knowledge is critical when attempting to delineate new intervention strategies for better control of disease and their life-threatening disorders.

Transparency document

The Transparency document associated with this article can be found, in online version.

Declaration of competing interest

The authors declare that they have no conflicts of interest to disclose.

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