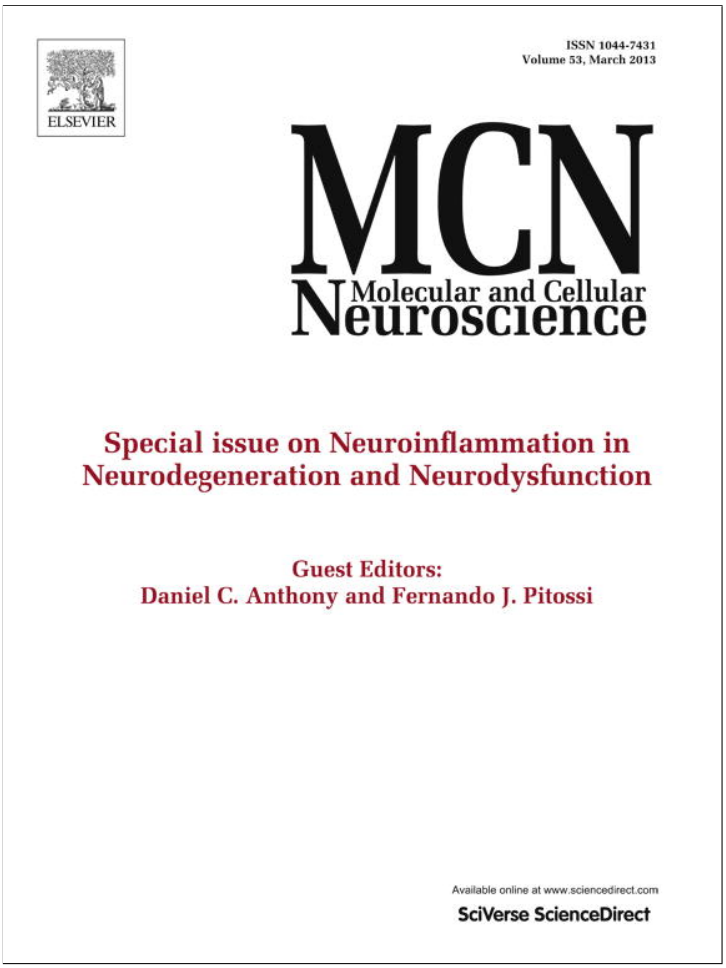

Molecular and Cellular Neuroscience 53 (2013) 77–85

Contents lists available at SciVerse ScienceDirect

Molecular and Cellular Neuroscience

journal homepage: www.elsevier.com/locate/ymcne

Adverse neuro-immune–endocrine interactions in patients with active tuberculosis

Oscar Bottasso [a,*], María Luisa Bay [a], Hugo Besedovsky [b], Adriana del Rey [b]

[a] Instituto de Inmunología, Facultad de Ciencias Médicas, Universidad Nacional de Rosario, Argentina
[b] Institute für Physiologie und Pathophysiologie, Marburg, Germany

ARTICLE INFO

Article history:
Received 14 March 2012
Accepted 2 November 2012
Available online 10 November 2012

Keywords:
Neuroendocrine regulation
Sickness behavior
Depression
Tuberculosis
Adaptive immunity
Metabolism
Weight loss
Chronic inflammation

ABSTRACT

The nervous, endocrine and immune systems play a crucial role in maintaining homeostasis and interact with each other for a successful defensive strategy against injurious agents. However, the situation is different in long-term diseases with marked inflammation, in which defensive mechanisms become altered. In the case of tuberculosis (TB), this is highlighted by several facts: an imbalance of plasma immune and endocrine mediators, that results in an adverse environment for mounting an adequate response against mycobacteria and controlling inflammation; the demonstration that dehidroepiandrosterone (DHEA) secretion by a human adrenal cell line can be inhibited by culture supernatants from *Mycobacterium tuberculosis*-stimulated peripheral blood mononuclear cells – PBMC – of TB patients, with this effect being partly reverted when neutralizing transforming growth factor-β in such supernantants; the *in vitro* effects of adrenal steroids on the specific immune response of PBMC from TB patients, that is a cortisol inhibition of mycobacterial antigen-driven lymphoproliferation and interferon-γ production as well as a suppression of TGF-β production in DHEA-treated PBMC; and lastly the demonstration that immune and endocrine compounds participating in the regulation of energy sources and immune activity correlated with the consumption state of TB patients. Collectively, immune-endocrine disturbances of TB patients are involved in critical components of disease pathology with implications in the impaired clinical status and unfavorable disease outcome. This article is part of a Special Issue entitled 'Neuroinflammation in neurodegeneration and neurodysfunction'.

The integrated response against pathogenic insults, the case of tuberculosis

Introduction

It is well established that the endocrine, immune and nervous systems engage in multiple interactions during the host response to acute and chronic dangerous stimuli, sharing functional responses to such threats (Besedovsky and del Rey, 1996; Chrousos, 1995; Elenkov et al., 2000; Eskandari and Sternberg, 2002). Neural and hormonal systems activated by stressful conditions, for instance, can modify the response of immune cells, whereas the immune system communicates to the central nervous system (CNS), regulating its function. There are also anatomical connections because of the presence of immune cells within the nervous system and the innervation by the autonomous system of lymphatic organs. Communication between the neuro-endocrine and immune systems occurs mainly via chemical messengers, while cytokines released by immune cells represent the critical signal for communicating with the CNS (Besedovsky and del Rey, 1996; Chrousos, 1995; Elenkov et al., 2000; Eskandari and Sternberg, 2002). Inflammation can be described as a host response to damaged tissues and cells by pathogens, or other noxious stimuli. The inflammatory response may be acute, as a transitory physical injury or infection that usually results in healing, thus removing the stimulus and repairing the tissue. Alternatively, a low grade and chronic response that is prolonged and maladaptive involving active inflammation, tissue destruction and attempts at tissue repair, as seen in long-term infections and autoimmune diseases, may be established. A low grade inflammatory profile has also been associated recently with diseases encompassing metabolic alterations like aging and obesity (De Nardo and Latz, 2011; Medzhitov, 2008).

Chronic, low-level inflammation, as it may happen in infections due to mycobacteria, i.e., *Mycobacterium tuberculosis*, encompasses a two- to fourfold elevation in circulating levels of pro-inflammatory cytokines and acute-phase proteins such as C-reactive protein (CRP), together with minor increases in neutrophil count. Within pro-inflammatory cytokines, tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6 are powerful and synergistic cytokines produced by immune cells in response to danger signals. At the same time, they can also either reach the brain via the circumventricular organs, which are devoided of the blood brain barrier (BBB) like the median eminence, or by transport across the BBB, or signaling via the vagus nerve, or through the activation of second messengers like nitric oxide and prostaglandins (Turnbull and Rivier, 1999). Whatever the case, these cytokines constitute a major pathway for activating the hypothalamo-pituitary adrenal (HPA) axis and the sympathetic nervous system. The hypothalamus

* Corresponding author at: Instituto de Inmunología, Facultad de Ciencias Médicas UNR, Santa Fe 3100, Rosario 2000, Argentina. Fax: +54 341 4804569.
E-mail address: bottasso@uolsinectis.com.ar (O. Bottasso).

1044-7431/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.mcn.2012.11.002

produces corticotropin-releasing hormone (CRH) and arginine vasopressin. From the parvo-ventricular nucleous, CRH-containing neurons have efferent pathways to the median eminence and projections to noradrenergic centers in the brainstem and spinal cord. Release of CRH into the hypophyseal portal blood stimulates the secretion of corticotrophin (ACTH) from the anterior pituitary gland. Circulating ACTH reaches the adrenal glands, where it induces the synthesis and release of glucocorticoids (GCs) and adrenal androgens like dehydroepiandrosterone (DHEA) (Besedovsky and del Rey, 1996; Chrousos, 1995; Elenkov et al., 2000; Eskandari and Sternberg, 2002; Turnbull and Rivier, 1999). On the other hand, activation of noradrenergic pathways by CRH results in secretion of norepinephrine (NE) by the peripheral sympathetic nervous system and release of NE and epinephrine by the adrenal medulla.

The immune and inflammatory responses that follow an injurious insult may be local and limited or systemic, involving a broad range of clinical and biochemical alterations, designated as the "sickness syndrome" (Baumann and Gauldie, 1994; Besedovsky and del Rey, 1996; Elenkov et al., 2000; Eskandari and Sternberg, 2002; Hart, 1990). The episode is characterized by the acute-phase reaction together with a sickness behavior including increased sleep, and decreased food and water intake as well as decreased social and sexual behavior. Most of these changes require information about the infection/inflammation induced by peripheral immune activation that reaches the CNS and is followed by the "de novo" synthesis of compounds within the CNS that, in turn, modify essential homeostatic functions. Distinct regions of the CNS regulate various aspects of energy balance, including food intake. This regulation involves several neuropeptides localized in neurons within the hypothalamus, where information from various neural inputs, endocrine factors and changes in the nutrient and metabolite milieu are integrated to regulate energy balance. These molecules include the orexigenic neuropeptide Y (NPY), promoting increased food intake, and the anorexigenic neuropeptide proopiomelanocortin (POMC) which is involved in reducing energy expenditure and food intake. Peripheral signals, such as the adipose tissue-derived hormone leptin, are also involved in the regulation of energy balance. Its receptors are particularly expressed in neurons within the hypothalamus containing NPY and POMC, and facilitate its action by inhibiting orexigenic neuropeptides and stimulating anorexigenic peptides (Hotamisligil and Erbay, 2008). In addition to leptin another adipocytokine, like adiponectin, and the orexigenic hormone ghrelin are known to play a role in the neuroendocrine regulation of food intake (Beltowski, 2003; Chan et al., 2003; Cummings et al., 2005; Neary et al., 2004).

The sickness syndrome which is also characterized by activation of both the HPA axis and sympathetic nervous system (Straub et al., 2010) intends to be beneficial for the host, at least during the early phase of the process. Nevertheless, when the response becomes excessive or prolonged it may be detrimental favoring the establishment of a pathological situation and the accompanying clinical expression. For instance, anorexia which reduces the energy expenditure and decreases the growth of pathogens by reducing the availability of nutrients essential for bacterial proliferation (Weinberg, 1984) will reduce body weight to affect the metabolic status, if persistent. On the other hand, the establishment of an infectious process implies a new metabolic set point in order to achieve an adequate immune response (Hotamisligil and Erbay, 2008; Pearce, 2010; Straub et al., 2010), without affecting the needs for some often competing and essential functions. Since energy is not an unlimited resource, increased energy dedicated to immune responses, likely adaptive in the initial phase of infection, may ultimately lead to a metabolic deficit and decreased fitness when prolonged. Firm evidence for the link between energy supply and the immune response derives from a recent study in Africa demonstrating that the metabolic requirement to cope with measles further impaired body weight in undernourished children (Phillips et al., 2004).

This metabolic dependence of the functionality of immune cells (Schwartz et al., 2000), is in turn affected by neuroendocrine factors and products released by the adipose tissue. In addition to regulating energy balance, the adipose tissue is now regarded as an active secretory organ also involved in the regulation of several processes like appetite, insulin sensitivity, endocrine and reproductive systems, metabolism, inflammation and immunity. In this sense a reduction of body fat is linked to an impaired immunity in a broad range of species, including humans (Norgan, 1997; Ouchi et al., 2011; Spurlock et al., 1997).

As will be commented in the following sections, TB constitutes a natural model in which the essential processes employed to maintain homeostasis and successful defensive strategies turn out to be harmful when the infection becomes chronic. Catabolic changes as a result of neuro-immune-endocrine alterations, decreased food intake and the consequent reduction of body weight are involved in the consumption state, which is usually seen in patients with active TB.

The infection with M. tuberculosis and the defensive response

Tuberculosis has been a blight on the humanity since its origins and surely was present before the initiation of the recorded history (Daniel, 2006). It constitutes a leading cause of death throughout the world, and still widely affects low-income and middle-income countries where poverty, political disorganization, and access to care remain major obstacles to global TB control. Approximately 8.8 million new TB cases emerge and 1.6 million people die of this disease every year (WHO, 2008).

The disease is a typical example, if not the most salient, of a consumptive state due to an infectious cause, for which it was also designed phthisis because of its wasting consequences.

The infection is acquired through the inhalation of air-borne particles containing *M. tuberculosis*. Within the lungs, *M. tuberculosis* mainly infects and resides in alveolar macrophages and dendritic cells, or in monocytes recruited from peripheral blood. Macrophages generally constitute an effective first line of defense against mycobacteria, although *M. tuberculosis* can adapt to survive and reside within these cells for years. Individuals who are able to mount an immune response adequate enough to contain *M. tuberculosis* bacilli will control this primary infection preventing bacillary proliferation and limiting the spreading of the organism. Most cases of primary tuberculous infection are clinically and radiologically unapparent; with a positive tuberculin test being the only indication of the occurrence of the infection. These individuals remain persistently infected by *M. tuberculosis* constituting non-contagious carriers of the bacillus.

Subsequent to the initial phase of infection, due to a rupture of the host-parasite balance, 5–10% of individuals with latent infection develop post-primary TB (Flynn, 2004). The existence of post-primary TB, also known as secondary TB, means that the infection can progress after the development of an adequate specific immune response, which may occur by inhalation of new bacilli or by reactivation of the primary focus. Pulmonary TB is the most common form of post-primary disease. In individuals with HIV/AIDS the involvement of the central nervous system is more frequent, and factors like malnutrition and recent measles in children, or alcoholism, malignancies, and the use of immunosuppressive agents in adults may favor this situation. The compromise of the central nervous system occurs in two fundamental forms: meningoencephalitis and intracranial tuberculoma. The clinical manifestations are due to the inflammatory process induced by the mycobacterial infection, and the symptoms depend on the site and intensity of inflammation. Meningoencephalitis generally has an insidious onset and a slowly progressive course, with symptoms including apathy, lethargy, fever, and mental disturbances such as irritability, understanding difficulties, personality alterations, disorientation, and progressive mental confusion. Vertigo, migraine and vomiting can also be observed. In the case of intracranial tuberculoma, the clinical manifestations depend on the location of the lesion, which generally grows slowly. When there is no compromise of the sub-arachnoid space, the cerebrospinal fluid is normal and the computerized tomography

exhibits a mass, which is generally difficult to differentiate from neoplasia (Rock et al., 2008).

The fundamental mechanism responsible for the immune containment of *M. tuberculosis* growth and dissemination is the granuloma, which is an organized aggregate of immune cells that surround foci of infected cells. Initial granulomas are composed of immature mononuclear phagocytes surrounded by lymphoid effector cells including CD4+ and CD8+ T cells. Mature granulomas present neovascularization, highly activated macrophages, epithelioid and giant multinucleated cells. An extensive fibrotic capsule develops constituting a restraining barrier. Tubercle bacilli tend to locate in the center of the granuloma, in which necrotic material containing high amounts of fat as a result of lipids released from bacillary catabolism can be seen (Russell et al., 2009). This material is known as caseous necrosis, but macrophages may also be destroyed partly because of the lysing effect of cytotoxic CD8+ cells (Dannenberg and Rook, 1994). Caseous necrosis may progress to liquefaction leading to subsequent cavitation. Tubercle bacilli, whose multiplication had been until then inhibited by granuloma formation, find favorable conditions for growth after that. The development of tuberculous cavities in the lung is a typical feature of postprimary TB allowing the spreading of infectious material through bronchi and continuous elimination through sputum. In this way, the clinical spectrum of pulmonary TB may range from a few foci affecting the upper parts of the lungs to intense tissue destruction and multiple lobe affectation. Such different disease outcomes are thought to be the result of complex interactions between *M. tuberculosis* and the defensive response.

While resistance to *M. tuberculosis* is known to be conferred by T cell-mediated immune mechanisms, a strict distinction on whether they belong to a particular T helper cytokine pattern is not observed in the human infection, given the wide spectrum of cytokines produced in response to this mycobacterial infection. Cytokines like interferon gamma (IFN-γ) are relevant in controlling bacillary load, given its ability to recruit and activate monocyte/macrophage cells for microbicidal activity. Studies in humans indicate that more severe and even fatal mycobacterial infections are seen in patients with defects in IFN-γ receptor (Boom, 1996; Cooper, 2009; Cooper et al., 2002; Flynn, 2004), although there is a growing awareness of additional contributing factors. Analysis of Th2 cytokines has been less convincing respect their involvement in disease immunopathology. Several groups showed an increased production of IL-4 in TB patients, particularly in cases with cavitary disease (Sanchez et al., 1994; Schauf et al., 1993; Surcel et al., 1994; van Crevel et al., 2000). Nevertheless, this finding could not be corroborated in other studies (Lai et al., 1997; Lin et al., 1996). Thus, it is unclear whether IL-4 exerts a role in disease susceptibility or simply reflects disease activity. Such differences in cytokine production in TB patients may partly depend on variations in the type and extent of the clinical disease. In fact, our studies in TB patients with different degrees of pulmonary involvement indicated that increased IL-4 production predominates in advanced stages of the disease, whereas patients with mild forms display an important degree of IFN-γ production that gradually declines with disease progression (reviewed in Bottasso et al., 2007).

An appraisal of the circulating pattern of immune-endocrine mediators in human tuberculosis

Tuberculosis offers an attractive model to investigate the pathological processes occurring during an infectious disease. On the one hand, the existence of metabolic-related manifestations (Bottasso et al., 2007) provides an extraordinary opportunity to study the immune-endocrine component that may underlie these alterations, considering the energy supply that is necessary to maintain the immune response (Hotamisligil and Erbay, 2008; Straub, 2011). On the other hand, the variation in the immune response of TB patients according to disease severity, may reflect a different kind of host-pathogen interactions involving a dynamic intersection of many signaling and response networks. We have learned a great deal about the adaptive immune response, but there is also a need to get a comprehensive idea of the nature of the overall defensive response which also involves the neuroendocrine system. As commented, the neuroendocrine and immune systems are quite intertwined and have evolved in parallel, sharing regulatory and mediatory molecules and mutually influencing each other's activities. When both systems are activated during inflammation, the hypothalamus, the pituitary gland, and any of several target glands, including the adrenal gland and the thyroid are committed in the regulatory processes. Because the anterior pituitary gland secretes at least six key hormones: ACTH, growth hormone (GH), prolactin (PRL), thyrotropin, and the gonadotropins, changes in the stress and immune responses, development, reproduction, and energy homeostasis are all likely to occur. In addition, largely because of the dominant role of the HPA axis, inflammation and immunity are also influenced by a great number of hormones that are under the control of this axis.

In general, activation of the HPA axis influences the activity of certain important facets of the immune system, mostly through the activity of glucocorticoids and DHEA. The former exerts diverse actions, both inhibitory and stimulatory, on nearly all features of the immune reaction, including the innate and adaptive responses. For instance, GCs inhibit the production of proinflammatory cytokines as well as other mediators of inflammation and stimulate the production of antiinflammatory cytokines, providing antiinflammatory control during an inflammatory reaction (Besedovsky and del Rey, 1996; Elenkov and Chrousos, 1999; Turnbull and Rivier, 1999; Webster et al., 2002). These systemic end-effector hormones interact with the ubiquitous glucocorticoid receptors (GRs) in target tissues, including the immune system (Barnes and Adcock, 2009). On the other hand, DHEA counteracts the above described promoting effects of GCs on cytokine production, but also exerts itself potent anti-inflammatory effects (Dillon, 2005).

Within this conceptual framework context, we analyzed the circulating levels of IFN-γ, IL-10, and IL-6 along with pituitary, adrenal, gonadal and thyroid hormones in newly diagnosed male TB patients with different lung affectation and free from any other treatment. Compared to healthy controls TB patients showed increased plasma levels of IFN-γ, IL-10, and IL-6, in presence of markedly decreased levels of testosterone and DHEA. At the same time, GH concentrations were noticeably augmented in patients, with no significant differences in insulin-like growth factor-1, in parallel to slightly increased amounts of cortisol, estradiol, PRL, and thyroid hormones (del Rey et al., 2007). These results deviate from the alterations seen during chronic stress, in which stress hormones like cortisol, PRL, thyroid hormones and GH, are usually reduced (Van den Berghe, 2003). Such bias may be partly due to immune-derived products released during the specific immune response mounted by TB patients, in view of the reported effects of cytokines on endocrine functions (Besedovsky and del Rey, 1996; Turnbull and Rivier, 1999; van den Berghe, 2003).

Considering that during infections GCs favor Th2 responses, whereas DHEA counteracts this Th2-promoting effect of GCs (Besedovsky and del Rey, 1996; Dillon, 2005; Turnbull and Rivier, 1999), increased levels of GCs and reduced DHEA concentrations would not favor the development of appropriate cell-mediated immune response against mycobacteria. In support of this assumption, a relation between the circulating levels of cortisol and DHEA and the mycobacterial-driven immune response mounted by PBMCs from TB patients was found. In fact, plasma DHEA levels were positively correlated with the amount of IFN-γ present in culture supernatants, whereas the cortisol/DHEA ratio correlated inversely with the *in vitro* production of this cytokine (Bozza et al., 2007). Hormonal changes may also result in a deficient control of inflammation, considering that the moderately increased cortisol levels that may not be sufficient to compensate for the limited anti-inflammatory effect of reduced amounts of DHEA. The increased levels of thyroid

hormones along with diminished values of testosterone may also favor the inflammatory situation, since the former promote pro-inflammatory cytokine production (Foster et al., 2000), whereas the latter displays anti-inflammatory activities (Malkin et al., 2004).

At first sight, the modestly increased levels of PRL, together with a several fold increase in GH blood levels may seem beneficial in view of their CMI-stimulating capacities (Dorshkind and Horseman, 2000). Nevertheless, increased GH levels were not paralleled by increased insulin-like growth factor-1 (IGF-1) concentrations, which is normally induced by GH and mediates many of its effects (Dorshkind and Horseman, 2000), suggesting a certain degree of GH resistance in TB patients. As such, the effect of increased levels of GH and PRL can be viewed as an unsuccessful attempt to improve cell mediated immune responses, which are required for coping with mycobacterial infections.

Collectively, the hormonal profile of TB patients seems to be inappropriate for the development of protective immune responses and the control of persistent inflammation.

The reciprocal effects between adrenal steroids and the specific immune response mounted by TB patients

Because of the immunomodulatory effects of cortisol and DHEA, the potential influence of these steroids on the response of PBMC from untreated TB patients stimulated *in vitro* with *M. tuberculosis* antigens was explored. Treatment of cortisol, at slightly supraphysiological levels, resulted in a decreased mycobacterial antigen-driven proliferation and IFN-γ production, more pronounced in patients with advanced disease (Mahuad et al., 2004). As reported in other studies wherein GC suppressed the production of TNF-α, IFN-γ and IL-1, but caused no major alterations in IL-4 and IL-10 synthesis (Elenkov and Chrousos, 1999; Wilckens and de Rijk, 1997), IL-10 production which was easily detectable in all cultures remained unaffected by cortisol (Mahuad et al., 2004). Lymphoproliferation as well as IL-10 and IFN-γ production were unchanged by DHEA, while causing a significant decrease of TGF-β production by PBMCs from patients with advanced TB. TGF-β is a cytokine well known for its suppressive and detrimental effects in TB (Toossi and Ellner, 1998). In essence, both adrenal steroids can partly account for the abnormal specific immune response observed during TB, which may have implications not only in disease pathology but also for delineation of potential immunointervention strategies.

In a further study we also tested the effect of adrenal steroids in cells from household contacts of contagious TB patients (HHCs). These individuals are quite likely to course a latent tuberculosis infection (LTBI), in which a robust defensive response ensures the formation of a granulomatous lesion that apparently restrains the infection and prevents active disease from occurring (Morrison et al., 2008). Antigen-stimulated IFN-γ production showed the highest levels among HHCs and significantly different from TB patients and healthy controls (HCo). Treatment with cortisol significantly reduced IFN-γ in culture supernatants from all groups respect to their untreated counterparts, although HHCs continued to present the higher IFN-γ concentrations than in all other groups. Furthermore, treatment of cells from HHCs with lower concentrations of DHEA resulted in increased amounts of IFN-γ, which were the highest concentrations of the cytokine obtained under the experimental conditions tested there (Bozza et al., 2009). This DHEA-dependent increment of IFN-γ levels confirms the facilitating effects of DHEA on its synthesis (Dillon, 2005), and adds novel evidence of a differential effect related to the host status.

As part of this bidirectional communication between the endocrine and immune system, we also analyzed whether mediators released during the anti-tuberculous immune response modulate differentially steroid production by adrenal cells. In a first set of studies we demonstrated that culture supernatants (SN) from *M. tuberculosis* antigen-stimulated PBMC of TB patients inhibit DHEA secretion by the human adrenal cell line NCI-H295-R (del Rey et al., 2007). In a more recent study, we have also shown that TGF-β is implicated in such inhibition of DHEA production. In fact, treatment with anti-TGF-β antibodies abrogated the inhibitory effects of SN of *M. tuberculosis*-stimulated PBMC from TB patients on DHEA release by the adrenal cells. Conversely, treatment of these cells with the same SN increased the production of cortisol that remained unaffected when adding anti-TGF-β antibodies. Nevertheless, when neutralizing TGF-β in supernatants of *M. tuberculosis*-stimulated PBMC from HCo cortisol production by adrenal cells was even more augmented suggesting that HCo triggers the production of soluble factors capable to increase cortisol production. This observation adds an extra level of complexity to the intricate network of influences underlying the immune-endocrine regulation particularly at the level of adrenal steroid production and immune mediators, in which effects vary depending on the source of culture supernatants and the steroid hormone under analysis (D'Attilio et al., 2012).

The relation of systemic immuno-endocrine alterations with the clinical status and immunological abnormalities

As commented, the consumption state, whose most salient symptom is the profound decrease in body weight is a complex process that cannot be fully explained by the reduction of appetite resulting in anorexia. Possibly, it is related with the imbalance of catabolic and anabolic processes in peripheral tissues, particularly in the adipose tissue. While being opposed to obesity, the conception of the consumption state as being linked to chronic inflammation may be considered. This not only applies to infectious processes but also for cancer cachexia. A striking manifestation characterized by a depletion of skeletal muscle and white adipose tissue mass, affecting around half of all patients with cancer (Bing and Trayhurn, 2008), in which the chronic inflammatory state, mostly due to the host's reaction to the presence of the tumor seems to be involved (Argiles et al., 2003, 2009; Besedovsky et al., 1985, 2000; Bing and Trayhurn, 2008; Deans and Wigmore, 2005; Delano and Moldawer, 2006).

Maintenance of the chronic inflammatory condition is a result of the production of humoral factors, mainly cytokines, or products secreted by the host's cells and tissues like hormones. Such mediators may act at through a direct action on the CNS and/or pathways activated from the periphery to modulate a complex cascade of biological responses leading to a series of alterations that ultimately result in body weight loss. Cytokines which seem to be involved in this condition are TNF-α, IL-1β, IL-6 and IFN-γ. For instance, intracerebroventricular injection of IL-6 stimulates energy expenditure (Rothwell et al., 1991), and reduces retroperitoneal fat and circulating levels of leptin (Wallenius et al., 2002), whereas a negative correlation between IL-6 levels in cerebral-spinal fluid, body weight and subcutaneous and total body fat, has been observed (Stenlof et al., 2003). TNF-α is regarded as an important mediator of catabolism (Morley et al., 2006). Increased levels of TNF-α were found in patients with both malaria (Scuderi et al., 1986) and visceral leishmaniasis (Pearson et al., 1990), which was associated with death and cachexia. In rats infected with *Escherichia coli*, pentoxifylline, which inhibits TNF-α secretion, decreased the anorexia, loss of body weight and muscle protein seen during such infection (Breuille et al., 1993). Studies in a rat model of cancer-induced cachexia, showed that pharmacological inhibition of TNF-α and IL-1β was effective in ameliorating anorexia (Laviano et al., 2000; Torelli et al., 1999). Moreover, mice deficient in the IL-1β-converting enzyme are also resistant to the anorectic effect of intracerebroventricular injection of LPS (Burgess et al., 1998; Yao et al., 1999). In the same sense, IFN-γ knockout mice are insensitive to the anorectic effect of LPS, suggesting that IFN-γ is necessary for the suppression of feeding by LPS (Arsenijevic et al., 2000). Weight loss in mice bearing the Lewis lung tumor is associated with IFN-γ production, and administration of an anti-IFN-γ antibody

reduced the depletion of body fat but had no effect on total body protein (Matthys et al., 1991).

In addition, these cytokines share similar metabolic effects, and their biological activities are interrelated, most notably in regard to the modulation of immune response and inflammation (Langhans, 2000; Pond, 2005).

Within this context, we have demonstrated that the weight loss of TB patients was related to the immune and endocrine disturbances, since the body mass index (BMI) was negatively associated with IL-6 circulating levels, whereas the levels of this cytokine correlated positively with cortisol concentrations (Mahuad et al., 2007). To expand studies on the disturbed metabolism during TB, we recently explored several mediators participating in the immune-endocrine-metabolic unit and examined whether there was a relation between certain immune-endocrine patterns and the clinical status of patients, particularly weight loss. Assessment focused on circulating levels of leptin, adiponectin, IL-6, IL-1β, ghrelin, CRP, cortisol and DHEA (Santucci et al., 2011). We also studied HHCs, because they constitute a protected group capable of containing the infection, only 5–10% of them may develop TB disease during their lifetime (Bates, 1980; Comstock, 1982), showed no weight loss and shared the same socio-economic and environmental conditions. In other words, TB patients and their HHCs constitute "natural models" for analyzing this type of immune-endocrine-metabolic relation.

Patients had a lower BMI, reduced levels of leptin and DHEA, and increased concentrations of CRP, IL-6, cortisol, IL-1β and nearly significant adiponectin values than HHCs and a group of HCo. Within TB patients the BMI and leptin levels were positively correlated and decreased with increasing disease severity, whereas higher concentrations of IL-6, CRP, IL-1β, cortisol, and ghrelin were seen in cases with moderate to severe tuberculosis. Household contacts had lower DHEA and higher IL-6 levels than controls.

Leptin is involved in the control of energy storage by decreasing food intake and increasing energy expenditure (Kelesidis et al., 2010; Martin et al., 2008). As regards TB, circulating leptin levels were found to be increased (Yuksel et al., 2003), unchanged (Kim et al., 2010) or reduced together with decreased body fat and loss of appetite (van Crevel et al., 2002). The positive association of leptin levels with BMI (Maffei et al., 1995), also detected in our TB patients, and the relation of leptin with the adipose tissue mass (Considine et al., 1996), suggest that reduced leptin levels seen in our study may be linked to the weight loss that accompanies the disease. At the same time, it is known that chronic stimulation with pro-inflammatory cytokines, as is the case of TB, suppresses leptin production (La Cava and Matarese, 2004; Matarese et al., 2005). The fact that HHCs, undergoing a LTBI without weight loss, had normal leptin plasma levels, favors the view of reduced leptin levels in TB as being due to an energy imbalance. As components participating in the regulation of food consumption, adiponectin is related to increase in appetite, central fat distribution and multiple metabolic disorders (Lara-Castro et al., 2006), whereas ghrelin is a potent circulating orexigen and controls energy expenditure (Lorenzi et al., 2009; Taub, 2008). This complementary activity of leptin, ghrelin and adiponectin in providing information to the CNS about the energy balance to maintain homeostasis, seems to be disrupted in TB since their circulating pattern is compatible with an orexigenic effect.

At variance with our results, Kim et al. (2010) reported no differences in leptin and ghrelin levels in TB patients, although further separation into well-nourished or malnourished cases revealed lower amounts of ghrelin in the latter subgroup. Reasons for such differences may be of different nature i.e, genetic and environmental factors may be also implied. Also, our sample population was composed of untreated patients whereas in the Korean study patients were bled within 3 days following treatment initiation. In distinguishing prior malnutrition from the consumption state that accompanies progressive disease, the preserved nutritional status of close HHCs of present TB patients adds support to the latter possibility.

Within the complex network of mediators accounting for the consumption state during TB, IL-6 seems to be also involved in light on the negative association of IL-6 circulating levels and BMI (Mahuad et al., 2007) and the increased levels of this cytokine seen in our former studies in TB patients (del Rey et al., 2007; Mahuad et al., 2007; Santucci et al., 2011). The inverse correlation between IL-6 levels in cerebral-spinal fluid, body weight and serum leptin concentrations found in obese patients (Stenlof et al., 2003), is in line with present findings of IL-6 being negatively associated with leptin and BMI. In a similar way IL-1β may also take part in the catabolic state, since this cytokine was not only increased during TB but was also negatively associated with the BMI.

Although GCs may have some anti-lipolytic effects in obesity-related situations (Peckett et al., 2011), increased cortisol in TB patients may favor the loss of body mass, since the hormone mobilizes lipid stores by inducing lipolysis in fat cells inhibiting protein synthesis and stimulating proteolysis in muscle cells (Dallman et al., 1993). In addition increased cortisol may also inhibit food intake and hence induce body weight loss (Kellendonk et al., 2002). Highlighting the important degree of nonspecific systemic inflammation seen during TB that is surely implied in cortisol abnormalities, TB patients displayed increased amounts of CRP, which is in line with other studies reporting increased levels of CRP in patients with TB (Breen et al., 2008; Choi et al., 2007; Wallis et al., 2010).

The negative correlation of leptin with IL-6 and CRP deviates from the reported effects of this adipocytokine, which is known to increase the production of several pro-inflammatory cytokines by monocytes/macrophages (Raso et al., 2002) as well as displaying some pro-inflammatory effects (La Cava and Matarese, 2004; Matarese et al., 2005). Also, in contrast with a recent demonstration of an inverse relation between plasma adiponectin levels and a number of inflammatory markers (Bahceci et al., 2007), in our case changes in adiponectin, IL-6 and IL-1β were in the same direction. To some extent, this skewed profile of associations may be related to a dysregulation of a defensive response of TB patients, more evident in the case of leptin. Since hormones and adipocytokines are influential in the orchestration of the cellular immune response, we have next explored the potential relation between plasma levels of such compounds and the *in vitro* immune response mounted by TB patients. The analysis revealed that leptin plasma levels positively correlated with *ex vivo* basal production of IFN-γ and ConA-driven proliferation by cells from TB patients. Considering the Th1-favoring effects of leptin (La Cava and Matarese, 2004; Matarese et al., 2005), the low endogenous levels of this adipocytokine seen in TB patients may partly account for the impaired specific cellular immune responses we have typically observed in them (Dlugovitzky et al., 1999, 2000).

Because of the need to understand the defensive response in an integrated fashion, an approach enabling to analyze several variables simultaneously was employed. Linear discriminant analysis is a statistical method for studying the differences between classes of objects. Broadly speaking, the method is appropriated to find an additive combination of variables that shows the best separation of the individuals and hence classifying subjects into a correct group. Inherent in this procedure is the identification of the most suitable variables which contribute significantly to the discrimination within the whole set of them. Group classification by means of discriminant analysis and the k-nearest neighbor non-parametric method showed that TB patients were clearly different from the other groups. In the discriminant stepwise procedure the higher levels of CRP together with lower amounts of DHEA and reduced BMI emerged as having significant discriminative power among TB patients (Santucci et al., 2011).

The implications of weight loss and the BMI in TB were already commented. As regards DHEA our results are in line with data from patients with chronic disabling inflammatory diseases in whom a prolonged immune aggression coexist with a deficient production of this adrenal steroid (Straub and Besedovsky, 2003). As discussed

decreased DHEA levels in TB patients are unfavorable for the course of the disease, in terms of the disturbed anti-infective immune response and control of tissue damage. Supporting this view, treatment with a synthetic DHEA derivative improved the course of experimental tuberculosis in mice (Hernández-Pando et al., 2005). Also, administration of DHEA sulphate improved IgG and IFN-γ production in mice immunized with heat shock proteins from Mtb (Ribeiro et al., 2007). Extending this view, in recent years there has been strong assumption that DHEA may play some role in inducing resistance during infection with *Schistosoma mansoni*, both in humans and experimentally infected hosts (Abebe et al., 2003; Fulford et al., 1998; Morales-Montor et al., 2001).

Discrimination methods were less effective in distinguishing HHCs from healthy controls, for which the evaluation of additional variables may be required to achieve a clear-cut separation. Nevertheless, a trend of HHCs to display increased adipocytokines levels, together with lower amounts of DHEA and higher IL-6 concentrations was found. Although clinical and radiological evaluation gave no indication of an overt disease, close contacts of TB patients are likely to course a subclinical TB infection (Bozza et al., 2009; Morrison et al., 2008), for which increased levels of IL-6 may reflect a subclinical inflammation.

Cytokines, chronic inflammation and psychiatric disorders in tuberculosis

Considering that the immune and nervous systems co-evolved to protect individuals from noxious stimuli, it seems sensible that exposure to immune stressors could distort this protective system affecting neurological functions (Besedovsky and del Rey, 1996; Chrousos, 1995; Elenkov et al., 2000; Eskandari and Sternberg, 2002). The sickness response is a clear example of such immune-to brain communication pathway triggering the production of a constellation of CNS-mediated phenomena together with the release of pro-inflammatory cytokines. In line with the behavioral effects of cytokines, depression was found to be associated with augmented concentrations of pro-inflammatory cytokines including TNF-α, IL-1β and IL-6 in the peripheral blood and cerebrospinal fluid as well as increases in the circulating levels of acute phase proteins (Dantzer et al., 2008; Miller et al., 2009). Several pieces of evidence indicate that elevated cytokines are linked to major depressive disorders and that inflamation may take part in the network of causal events leading to such disturbances (Dantzer et al., 2008; Miller et al., 2009).

Within this context, studies have shown that the prevalence of depression and other psychiatric disorders, i.e., anxiety, is significant among patients with TB (Aghanwa and Erhabor, 1998; Moussas et al., 2008; Westaway and Wolmarans, 1992). Some studies searching for the presence of common mental disorders in TB patients in low and middle income countries have found high rates of affective disorders (Aydin and Uluşahin, 2001; Deribew et al., 2010; Husain et al., 2008; Issa et al., 2009; Peltzer et al., 2012; Westaway and Wolmarans, 1992). Also, specific treatment was shown to improve health status of TB patients including some scores related with depression (Kruijshaar et al., 2010).

Exposure to psychological stress leads to an increased production of pro-inflammatory cytokines (Maes et al., 1998), and this ability of stress to drive inflammatory responses is exaggerated in depressed individuals (Pace et al., 2006). Since TB is accompanied by depression and the disease represents, to some extent, a form of psychological stress, a mental-associated extra level of influence accounting for the protracted inflammatory response during TB seems likely.

Future directions and concluding remarks

The neuroendocrine and immune systems play crucial roles in maintaining integrity against external/internal threats. The former is relatively nonspecific, in the sense that it is activated by any threat to general homeostasis, whereas the latter is reasonably specific as it detects the presence of potentially harmful invading microorganisms and reacts to them. As commented, there is a bidirectional signaling pathway between these systems to optimize effectiveness of both, with the purpose of a successful defense against and intending adaptation of the host to injury.

Nevertheless, the situation is completely different in long-term disease with marked inflammation, in which defensive mechanisms become altered and the subsequent disease outcome, as seen in TB (summarized in Fig. 1). This is highlighted by several facts: an imbalance

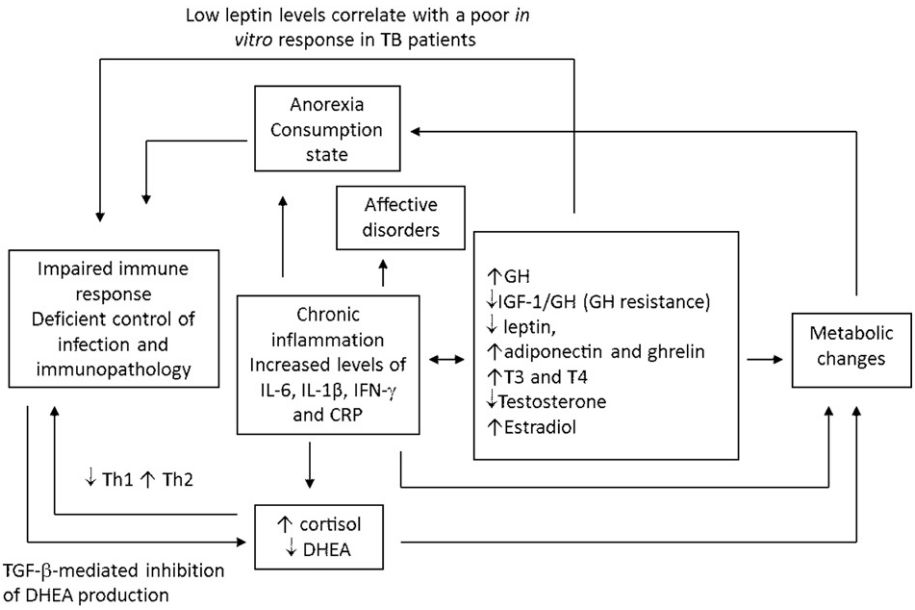

Fig. 1. Immune–endocrine disturbances in tuberculosis and its clinical and immunological consequences. The chronic presence of pro-inflammatory cytokines are likely to be involved in anorexia and affective disorders, in addition to modulating the production of cortisol and DHEA, by acting on the hypothalamus, on the pituitary or even directly on the adrenal glands. The increased cortisol/DHEA ratio, changes in the concentration of gonadal steroids, the consumption state and low leptin levels may also affect the development of an effective response for controlling the infection. In turn, synthesis of TGF-β by immune competent cells from TB patients decreases DHEA production by adrenal cells. Although the levels of GH are also increased in patients with TB, a state of GH resistance seems to be present in these patients. This process together with the hormonal changes would further contribute to the catabolic status.

of plasma immune and endocrine mediators, that results adverse for mounting an adequate response against mycobacteria and controlling inflammation; the inhibition of DHEA secretion by a human adrenal cell line when exposed to culture supernatants from *M. tuberculosis*-stimulated PBMC of TB patients, and its partial reversion by TGF-β neutralization; the *in vitro* effects of adrenal steroids on the specific immune response of PBMC from TB patients, that is a cortisol inhibition of mycobacterial antigen-driven lymphoproliferation and IFN-γ production together with the DHEA suppression of TGF-β production; more recently, the demonstration that immune and endocrine compounds participating in the regulation of energy sources and immune activity correlated with the consumption state of TB patients.

On a theoretical basis, our studies also raise a series of questions worth exploring. For instance, the influence that genetic and environmental component may exert in reinforcing or dissociating the link between metabolic and immune-endocrine abnormalities. Whether weight loss and inflammation are triggered in parallel or in sequence is also interesting but cannot be assessed since studying the establishment of an overt TB disease in humans is unethical. Nevertheless, investigating the presence of common initiating signals linking both processes is more amenable. The importance of white adipose tissue physiology and the role of adipocyte-secreted adipocytokines in the regulation of body composition and adiposity are deserving increased interest (Hauner, 2010; Trayhurn et al., 2006). It is known that peroxisome proliferator activated receptor gamma (PPARγ) has a central role in adipogenesis and adipocyte function (Okuno et al., 1998). As a member of a superfamily of nuclear receptors participating in the control of a large number of physiological processes (Farmer, 2005), PPARγ is thought to play a role in chronic inflammatory conditions. Also, inhibition of PPARγ function by inflammatory cytokines may contribute to the pathogenesis of several pathological situations, like insulin resistance, atherosclerosis, and consumption states (Lehrke and Lazar, 2005; Sharma and Staels, 2007; Stienstra et al., 2008). It follows that PPARγ may exert a possible contributory role in the chronic inflammation and disturbed metabolism during TB. Work in mice showed that airway challenge with Mtb triggered the expression of PPARγ in broncho-alveolar lavage cells (Korf et al., 2009).

From a translational standpoint, the finding that immune-endocrine disturbances are involved in the pathological consequences of TB raises the hope of delineating novel adjuvant therapies for a better treatment of the disease.

Acknowledgments

The present study received financial support from FONCYT research grants (BID 1728/OC-AR 5-25462 and PID160 PAE 37245) and the German Research Council (DFG, RE 1451/2-2).

References

Abebe, F., Birkeland, K.I., Gaarder, P.I., Petros, B., Gundersen, S.G., 2003. The relationships between dehydroepiandrosterone sulphate (DHEAS), the intensity of *Schistosoma mansoni* infection and parasite-specific antibody responses. A cross-sectional study in residents of endemic communities in north-east Ethiopia. APMIS 111, 319–328.

Aghanwa, H.S., Erhabor, G.E., 1998. Demographic/socioeconomic factors in mental disorders associated with TB in southwest Nigeria. J. Psychosom. Res. 45, 353–360.

Argiles, J.M., Moore-Carrasco, R., Busquets, S., Lopez-Soriano, F.J., 2003. Catabolic mediators as targets for cancer cachexia. Drug Discov. Today 8, 838–844.

Argiles, J.M., Busquets, S., Toledo, M., Lopez-Soriano, F.J., 2009. The role of cytokines in cancer cachexia. Curr. Opin. Support. Palliat. Care 3, 263–268.

Arsenijevic, D., Garcia, I., Vesin, C., Vesin, D., Arsenijevic, Y., Seydoux, J., Girardier, L., Ryffel, B., Dulloo, A., Richard, D., 2000. Differential roles of tumor necrosis factor-alpha and interferon-gamma in mouse hypermetabolic and anorectic responses induced by LPS. Eur. Cytokine Netw. 11, 662–668.

Aydin, I.O., Uluşahin, A., 2001. Depression, anxiety comorbidity, and disability in tuberculosis and chronic obstructive pulmonary disease patients: applicability of GHQ-12. Gen. Hosp. Psychiatry 23, 77–83.

Bahceci, M., Gokalp, D., Bahceci, S., Tuzcu, A., Atmaca, S., Arikan, S., 2007. The correlation between adiposity and adiponectin, tumor necrosis factor alpha, interleukin-6 and high sensitivity C-reactive protein levels. Is adipocyte size associated with inflammation in adults? J. Endocrinol. Invest. 30, 210–214.

Barnes, P.J., Adcock, I.M., 2009. Glucocorticoid resistance in inflammatory diseases. Lancet 373, 1905–1917.

Bates, J.H., 1980. Transmission and pathogenesis of tuberculosis. Clin. Chest Med. 1, 167–174.

Baumann, H., Gauldie, J., 1994. The acute phase response. Immunol. Today 15, 74–80.

Beltowski, J., 2003. Adiponectin and resistin—new hormones of white adipose tissue. Med. Sci. Monit. 9, RA55–RA61.

Besedovsky, H., del Rey, A., 1996. Immune-neuro–endocrine interactions: facts and hypothesis. Endocr. Rev. 17, 64–95.

Besedovsky, H.O., del Rey, A., Schardt, M., Sorkin, E., Normann, S., Baumann, J., Girard, J., 1985. Changes in plasma hormone profile after tumor transplantation into syngeneic and allogeneic rats. Int. J. Cancer 86, 457–461.

Besedovsky, H.O., Normann, S., Schardt, M., del Rey, A., 2000. Endocrine host responses during early and late phases of tumor development. Int. J. Cancer 86, 457–461.

Bing, C., Trayhurn, P., 2008. Regulation of adipose tissue metabolism in cancer cachexia. Curr. Opin. Clin. Nutr. Metab. Care 11, 201–207.

Boom, W.H., 1996. The role of T-cell subsets in *Mycobacterium tuberculosis* infection. Infect. Agents Dis. 5, 73–81.

Bottasso, O., Bay, M.L., Besedovsky, H., del Rey, A., 2007. The immuno-endocrine component in the pathogenesis of tuberculosis. Scand. J. Immunol. 66, 166–175.

Bozza, V.V., D'Attilio, L., Mahuad, C.V., Giri, A.A., del Rey, A., Besedovsky, H., Bottasso, O., Bay, M.L., 2007. Altered cortisol/DHEA ratio in tuberculosis patients and its relationship with abnormalities in the mycobacterial-driven cytokine production by peripheral blood mononuclear cells. Scand. J. Immunol. 66, 97–103.

Bozza, V., D´Attilio, L., Didoli, G., Santucci, N., Nannini, L., Bogue, C., del Rey, A., Besedovsky, H., Bay, M.L., Bottasso, O., 2009. The adrenal steroid response during tuberculosis and its effects on the mycobacterial-driven IFN-γ production of patients and their household contacts. Ann. N. Y. Acad. Sci. 1153, 247–255.

Breen, R.A., Leonard, O., Perrin, F.M.R., Smith, C.J., Bhagani, S., Cropley, I., Lipman, M.C., 2008. How good are systemic symptoms and blood inflammatory markers at detecting individuals with tuberculosis? Int. J. Tuber. Lung Dis. 12, 44–49.

Breuille, D., Farge, M.C., Rose, F., Arnal, M., Attaix, D., Obled, C., 1993. Pentoxifylline decreases body weight loss and muscle protein wasting characteristic of sepsis. Am. J. Physiol. 265, E660–E666.

Burgess, W., Gheusi, G., Yao, J.H., Johnson, R.W., Dantzer, R., Kelley, K.W., 1998. Interleukin-1 beta-converting enzyme deficient mice resist central but not systemic endotoxin-induced anorexia. Am. J. Physiol. 274, R1829–R1833.

Chan, J.L., Heist, K., DePaoli, A.M., Veldhuis, J.D., Mantzoros, C.S., 2003. The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. J. Clin. Invest. 111, 1409–1421.

Choi, C.M., Kang, C.I., Jeung, W.K., Kim, D.H., Lee, C.H., Yim, J.J., 2007. Role of the C-reactive protein for the diagnosis of TB among military personnel in South Korea. Int. J. Tuber. Lung Dis. 11, 233–236.

Chrousos, G.P., 1995. The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. N. Engl. J. Med. 332, 1351–1362.

Comstock, G., 1982. Epidemiology of tuberculosis. Am. Rev. Respir. Dis. 125, 8–15.

Considine, R.V., Sinha, M.K., Heiman, M.L., Kriauciunas, A., Stephens, T.W., Nyce, M.R., Ohannesian, J.P., Marco, C.C., McKee, L.J., Bauer, T.L., et al., 1996. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N. Engl. J. Med. 334, 292–295.

Cooper, A.M., 2009. Cell mediated immune responses in tuberculosis. Annu. Rev. Immunol. 27, 393–422.

Cooper, A.M., Adams, L.B., Dalton, D.K., Appelberg, R., Ehlers, S., 2002. IFN-gamma and NO in mycobacterial disease: new jobs for old hands. Trends Microbiol. 10, 221–226.

Cummings, D.E., Foster-Schubert, K.E., Overduin, J., 2005. Ghrelin and energy balance: focus on current controversies. Curr. Drug Targets 6, 153–169.

D'Attilio, L., Bozza, V., Santucci, N., Bongiovanni, B., Dídoli, G., Radcliffe, S., Besedovsky, H., del Rey, A., Bottasso, O., Bay, M.L., 2012. Inhibition of DHEA production by factors released from *M. tuberculosis*-stimulated peripheral blood mononuclear cells is abrogated by transforming growth factor-β neutralization. Ann. N. Y. Acad. Sci. 1262, 1–9.

Dallman, M., Strack, A., Akana, S., Bradbury, M.J., Hanson, E.S., Scribner, K.A., Smith, M., 1993. Feast and famine: critical role of glucocorticoids with insulin in daily energy flow. Front. Neuroendocrinol. 14, 303–347.

Daniel, T.M., 2006. The history of tuberculosis. Respir. Med. 100, 1862–1870.

Dannenberg Jr., A.M., Rook, G.A., 1994. Pathogenesis of pulmonary tuberculosis: an interplay between tissue-damaging and macrophage-activating immune responses: dual mechanisms that control bacillary multiplication. In: Bloom, B.R. (Ed.), Tuberculosis: Pathogenesis, Protection, and Control. ASM Press, Washington, DC, pp. 459–484.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56.

De Nardo, D., Latz, E., 2011. NLRP3 inflammasomes link inflammation and metabolic disease. Trends Immunol. 32, 373–379.

Deans, C., Wigmore, S.J., 2005. Systemic inflammation, cachexia and prognosis in patients with cancer. Curr. Opin. Clin. Nutr. Metab. Care 8, 265–269.

del Rey, A., Mahuad, C.V., Bozza, V., Bogue, C., Farroni, M.A., Bay, M.L., Bottasso, O.A., Besedovsky, H.O., 2007. Endocrine and cytokine responses in humans with pulmonary tuberculosis. Brain Behav. Immun. 21, 171–179.

Delano, M.J., Moldawer, L.L., 2006. The origins of cachexia in acute and chronic inflammatory diseases. Nutr. Clin. Pract. 21, 68–81.

Deribew, A., Tesfaye, M., Hailmichael, Y., Apers, L., Abebe, G., Duchateau, L., Colebunders, R., 2010. Common mental disorders in TB/HIV co-infected patients in Ethiopia. BMC Infect. Dis. 10, 201.

Dillon, J., 2005. Dehydroepiandrosterone, dehydroepiandrosterone sulfate and related steroids: their role in inflammatory, allergic and immunological disorders. Curr. Drug Targets Inflamm. Allergy 4, 377–385.
Dlugovitzky, D., Bay, M.L., Rateni, L., Urízar, L., Rondelli, F.M., Largacha, C., Farroni, M.A., Molteni, O., Bottasso, O.A., 1999. In vitro synthesis of interferon-γ, interleukin-4, transforming growth factor-β, and interleukin 1-β by peripheral blood mononuclear cells from tuberculosis patients. Relationship with the severity of pulmonary involvement. Scand. J. Immunol. 49, 210–217.
Dlugovitzky, D., Bay, M.L., Rateni, L., Fiorenza, G., Vietti, L., Farroni, M.A., Bottasso, O.A., 2000. Influence of disease severity on nitrite and cytokine production by peripheral blood mononuclear cells from patients with pulmonary tuberculosis. Clin. Exp. Immunol. 122, 343–349.
Dorshkind, K., Horseman, N.D., 2000. The roles of prolactin, growth hormone, insulin-like growth factor-I, and thyroid hormones in lymphocyte development and function: insights from genetic models of hormone and hormone receptor deficiency. Endocr. Rev. 21, 292–312.
Elenkov, I.J., Chrousos, G.P., 1999. Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. Trends Endocrinol. Metab. 10, 359–368.
Elenkov, I.J., Wilder, R.L., Chrousos, G.P., Vizi, E.S., 2000. The sympathetic nerve-an integrative interface between two supersystems: the brain and the immune system. Pharmacol. Rev. 52, 595–638.
Eskandari, F., Sternberg, E.M., 2002. Neural–immune interactions in health and disease. Ann. N. Y. Acad. Sci. 966, 20–27.
Farmer, S.R., 2005. Regulation of PPAR gamma activity during adipogenesis. Int. J. Obes. (Lond.) 29 (Suppl. 1), S13–S16.
Flynn, J.L., 2004. Immunology of tuberculosis and implications in vaccine development. Tuberculosis 84, 93–101.
Foster, M.P., Jensen, E.R., Montecino-Rodriguez, E., Leathers, H., Horseman, N., Dorshkind, K., 2000. Humoral and cell-mediated immunity in mice with genetic deficiencies of prolactin, growth hormone, insulin-like growth factor-I, and thyroid hormone. Clin. Immunol. 96, 140–149.
Fulford, A.J.C., Webster, M., Ouma, J.H., Kimani, G., Dunne, D.W., 1998. Puberty and age-related changes in susceptibility to schistosome infection. Parasitol. Today 14, 23–26.
Hart, B.L., 1990. Behavioral adaptations to pathogens and parasites: five strategies. Neurosci. Biobehav. Rev. 14, 273–294.
Hauner, H., 2010. Adipose tissue inflammation: are small or large fat cells to blame? Diabetologia 53, 223–225.
Hernández-Pando, R., Aguilar-Leon, D., Orozco, H., Serrano, A., Ahlem, C., Trauger, R., Schramm, B., Reading, C., Frincke, J., Rook, G.A., 2005. 16alpha-Bromoepiandrosterone restores T helper cell type 1 activity and accelerates chemotherapy-induced bacterial clearance in a model of progressive pulmonary tuberculosis. J. Infect. Dis. 191, 299–306.
Hotamisligil, G., Erbay, E., 2008. Nutrient sensing and inflammation in metabolic diseases. Nat. Rev. Immunol. 8, 923–934.
Husain, M.O., Dearman, S.P., Chaudhry, I.B., Rizvi, N., Waheed, W., 2008. The relationship between anxiety, depression and illness perception in tberculosis patients in Pakistan. Clin. Pract. Epidemiol. Mental Health 26, 4.
Issa, B.A., Yussuf, A.D., Kuranga, S.I., 2009. Depression comorbidity among patients with tuberculosis in a university teaching hospital outpatient clinic in Nigeria. Mental Health Family Med. 6, 133–138.
Kelesidis, T., Kelesidis, I., Chou, S., Mantzoros, C.S., 2010. Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann. Intern. Med. 152, 93–100.
Kellendonk, C., Eiden, S., Kretz, O., Schütz, G., Schmidt, I., Tronche, F., Simon, E., 2002. Inactivation of the GR in the nervous system affects energy accumulation. Endocrinology 143, 2333–2340.
Kim, J.H., Lee, C.T., Yoon, H.I., Song, J., Shin, W.G., Lee, J.H., 2010. Relation of ghrelin, leptin and inflammatory markers to nutritional status in active pulmonary tuberculosis. Clin. Nutr. 29, 512–518.
Korf, H., Vander Beken, S., Romano, M., Steffensen, K.R., Stijlemans, B., Gustafsson, J.A., Grooten, J., Huygen, K., 2009. Liver X receptors contribute to the protective immune response against *Mycobacterium tuberculosis* in mice. J. Clin. Invest. 119, 1626–1637.
Kruijshaar, M.E., Lipman, M., Essink-Bot, M.L., Lozewicz, S., Creer, D., Dart, S., Maguire, H., Abubakar, I., 2010. Health status of UK patients with active tuberculosis. Int. J. Tuber. Lung Dis. 14, 296–302.
La Cava, A., Matarese, G., 2004. The weight of leptin in immunity. Nat. Rev. Immunol. 4, 371–379.
Lai, C.K., Ho, S., Chan, C.H., Chan, J., Choy, D., Leung, R., Lai, K.N., 1997. Cytokine gene expression profile of circulating CD4 + T cells in active pulmonary tuberculosis. Chest 111, 606–611.
Langhans, W., 2000. Anorexia of infection: current prospects. Nutrition 16, 996–1005.
Lara-Castro, C., Luo, N.L., Wallace, P., Klein, R.L., Garvey, W.T., 2006. Adiponectin multimeric complexes and the metabolic syndrome trait cluster. Diabetes 55, 249–259.
Laviano, A., Gleason, J.R., Meguid, M.M., Yang, Z.J., Cangiano, C., Rossi-Fanelli, F., 2000. Effects of intra-VMN mianserin and IL-1ra on meal number in anorectic tumor-bearing rats. J. Investig. Med. 48, 40–48.
Lehrke, M., Lazar, M.A., 2005. The many faces of PPARgamma. Cell 123, 993–999.
Lin, Y., Zhang, M., Hofman, F.M., Gong, J., Barnes, P.F., 1996. Absence of a prominent Th2 cytokine response in human tuberculosis. Infect. Immun. 64, 1351–1356.
Lorenzi, T., Meli, R., Marzioni, D., Morroni, M., Baragli, A., Castellucci, M., Gualillo, O., Muccioli, G., 2009. Ghrelin: a metaboilic signal affecting the reproductive system. Cytokine Growth Factor Rev. 20, 137–152.
Maes, M., Song, C., Lin, A., De Jongh, R., Van Gastel, A., Kenis, G., Bosmans, E., De Meester, I., Benoy, I., Neels, H., Demedts, P., Janca, A., Scharpé, S., Smith, R.S., 1998. The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. Cytokine 10, 313–318.
Maffei, M., Halaas, J., Ravussin, E., Pratley, R.E., Lee, G.H., Zhang, Y., Fei, H., Kim, S., Lallone, R., Ranganathan, S., et al., 1995. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat. Med. 1, 1155–1161.
Mahuad, C., Bay, M.L., Farroni, M.A., Bozza, V., del Rey, A., Besedovsky, H., Bottasso, O.A., 2004. Cortisol and dehydroepiandrosterone affect the response of peripheral blood mononuclear cells to mycobacterial antigens during tuberculosis. Scand. J. Immunol. 60, 639–646.
Mahuad, C., Bozza, V., Pezzotto, S.M., Bay, M.L., del Besedovsky, H., Rey, A., Bottasso, O., 2007. Impaired immune responses in tuberculosis patients are related to weight loss that coexists with an immunoendocrine imbalance. Neuroimmunomodulation 14, 193–199.
Malkin, J., Pugh, P.J., Jones, R.D., Kapoor, D., Channer, K.S., Jones, T.H., 2004. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. J. Clin. Endocrinol. Metab. 89, 3313–3318.
Martin, S.S., Qasim, A., Reilly, M.P., 2008. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. J. Am. Coll. Cardiol. 52, 1201–1210.
Matarese, G., Moschos, S., Mantzoros, C.S., 2005. Leptin in immunology. J. Immunol. 174, 3137–3142.
Matthys, P., Heremans, H., Opdenakker, G., Billiau, A., 1991. Anti-interferon-γ antibody treatment, growth of Lewis lung tumours in mice and tumour-associated cachexia. Eur. J. Cancer 27, 182–187.
Medzhitov, R., 2008. Origin and physiological roles of inflammation. Nature 454, 428–435.
Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. Psychiatry 65, 732–741.
Morales-Montor, J., Newhouse, E., Mohamed, F., Bagdadi, A., Damain, R.T., 2001. Altered levels of hypothalamic–pituitary–adrenal axis hormones in baboons and mice during the course of infection with *Schistosoma mansoni*. J. Infect. Dis. 183, 313–320.
Morley, J.E., Thomas, D.R., Wilson, M.M., 2006. Cachexia: pathophysiology and clinical relevance. Am. J. Clin. Nutr. 83, 735–743.
Morrison, J., Pai, M., Hopewell, P.C., 2008. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Infec. Dis. 8, 359–368.
Moussas, G., Tselebis, A., Karkanias, A., Stamouli, D., Ilias, I., Bratis, D., Vassila-Demi, K.A., 2008. Comparative study of anxiety and depression in patients with bronchial asthma, chronic obstructive pulmonary disease and tuberculosis in a general hospital of chest diseases. Ann. Gen. Psychiatry 7, 7.
Neary, N.M., Goldstone, A.P., Bloom, S.R., 2004. Appetite regulation: from the gut to the hypothalamus. Clin. Endocrinol. 60, 153–160.
Norgan, N.G., 1997. The beneficial effects of body fat and adipose tissue in humans. Int. J. Obes. Relat. Metab. Disord. 21, 738–746.
Okuno, A., Tamemoto, H., Tobe, K., Ueki, K., Mori, Y., Iwamoto, K., Umesono, K., Akanuma, Y., Fujiwara, T., Horikoshi, H., Yazaki, Y., Kadowaki, T., 1998. Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. J. Clin. Invest. 101, 1354–1361.
Ouchi, N., Parker, J.L., Lugus, J.J., Walsh, K., 2011. Adipokines in inflammation and metabolic disease. Nat. Rev. Immunol. 11, 85–97.
Pace, T.W., Mletzko, T.C., Alagbe, O., Musselman, D.L., Nemeroff, C.B., Miller, A.H., Heim, C.M., 2006. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am. J. Psychiatry 163, 1630–1633.
Pearce, E.L., 2010. Metabolism in T cell activation and differentiation. Curr. Opin. Immunol. 22, 314–320.
Pearson, R.D., Cox, G., Evans, T., Smith, D.L., Weidel, D., Castracane, J., 1990. Wasting and macrophage production of tumor necrosis factor/cachectin and interleukin 1 in experimental visceral leishmaniasis. Am. J. Trop. Med. Hyg. 43, 140–149.
Peckett, A.J., Wright, D.C., Riddell, M.C., 2011. The effects of glucocorticoids on adipose tissue lipid metabolism. Metab. Clin. Exp. 60, 1500–1510.
Peltzer, K., Naidoo, P., Matseke, G., Louw, J., Mchunu, G., Tutshana, B., 2012. Prevalence of psychological distress and associated factors in tuberculosis patients in public primary care clinics in South Africa. BMC Psychiatry 12, 89.
Phillips, R.S., Enwonwu, C.O., Okolo, S., Hassan, A., 2004. Metabolic effects of acute measles in chronically malnourished Nigerian children. J. Nutr. Biochem. 15, 281–288.
Pond, C.M., 2005. Adipose tissue and the immune system. Prostaglandins Leukot. Essent. Fat. Acids 73, 17–30.
Raso, G.M., Pacilio, M., Esposito, E., Coppola, A., Di Carlo, R., Meli, R., 2002. Leptin potentiates IFN-gamma-induced expression of nitric oxide synthase and cyclo-oxygenase-2 in murine macrophage J774A. 1. Br. J. Pharmacol. 137, 799–804.
Ribeiro, F., Lopes, R.P., Nunes, C.P., Maito, F., Bonorino, C., Bauer, M.E., 2007. Dehydroepiandrosterone sulphate enhances IgG and interferon-gamma production during immunization to tuberculosis in young but not aged mice. Biogerontology 8, 209–220.
Rock, R.B., Olin, M., Baker, C.A., Molitor, T.W., Peterson, P.K., 2008. Central nervous system tuberculosis: pathogenesis and clinical aspects. Clin. Microbiol. Rev. 21, 243–261.
Rothwell, N.J., Busbridge, N.J., Lefeuvre, R.A., Hardwick, A.J., Gauldie, J., Hopkins, S.J., 1991. Interleukin-6 is a centrally acting endogenous pyrogen in the rat. Can. J. Physiol. Pharmacol. 69, 1465–1469.
Russell, D.G., Cardona, P.J., Kim, M.J., Allain, S., Altare, F., 2009. Foamy macrophages and the progression of the human tuberculosis granuloma. Nat. Immunol. 10, 943–948.

Sanchez, F.O., Rodriguez, J.I., Garcia, L.F., 1994. Immune responsiveness and lymphokine production in patients with tuberculosis and healthy controls. Infect. Immun. 62, 5673–5678.
Santucci, N., D'Attilio, L., Kovalevski, L., Bozza, V., Besedovsky, H., del Rey, A., Bay, M.L., Bottasso, O., 2011. A multifaceted analysis of immune–endocrine-metabolic alterations in patients with pulmonary tuberculosis. PLoS One 6 (10), e26363.
Schauf, V., Rom, W.N., Smith, K.A., Sampaio, E.P., Meyn, P.A., Tramontana, J.M., Cohn, Z.A., Kaplan, G., 1993. Cytokine gene activation and modified responsiveness to interleukin-2 in the blood of tuberculosis patients. J. Infect. Dis. 168, 1056–1059.
Schwartz, M.W., Woods, S.C., Porte Jr., D., Seeley, R.J., Baskin, D.G., 2000. Central nervous system control of food intake. Nature 404, 661–671.
Scuderi, P., Sterling, K.E., Lam, K.S., Finley, P.R., Ryan, K.J., Ray, C.G., Petersen, E., Slymen, D.J., Salmon, S.E., 1986. Raised serum levels of tumour necrosis factor in parasitic infections. Lancet 2, 1364–1365.
Sharma, A.M., Staels, B., 2007. Review: Peroxisome proliferator-activated receptor gamma and adipose tissue—understanding obesity-related changes in regulation of lipid and glucose metabolism. J. Clin. Endocrinol. Metab. 92, 386–395.
Spurlock, M.E., Frank, G.R., Willis, G.M., Kuske, J.L., Cornelius, S.G., 1997. Effect of dietary energy source and immunological challenge on growth performance and immunological variables in growing pigs. Anim. Sci. 75, 720–726.
Stenlof, K., Wernstedt, I., Fjallman, T., Wallenius, V., Wallenius, K., Jansson, J.O., 2003. Interleukin-6 levels in the central nervous system are negatively correlated with fat mass in overweight/obese subjects. J. Clin. Endocrinol. Metab. 88, 4379–4383.
Stienstra, R., Duval, C., Keshtkar, S., van der Laak, J., Kersten, S., Muller, M., 2008. Peroxisome proliferator-activated receptor gamma activation promotes infiltration of alternatively activated macrophages into adipose tissue. J. Biol. Chem. 283, 22620–22627.
Straub, R.H., 2011. Concepts of evolutionary medicine and energy regulation contribute to the etiology of systemic chronic inflammatory diseases. Brain Behav. Immun. 25, 1–5.
Straub, R.H., Besedovsky, H.O., 2003. Integrated evolutionary, immunological, and neuroendocrine framework for the pathogenesis of chronic disabling inflammatory diseases. FASEB J. 17, 2176–2183.
Straub, R.H., Cutolo, M., Buttgereit, F., Pongratz, G., 2010. Energy regulation and neuroendocrine–immune control in chronic inflammatory diseases. J. Intern. Med. 267, 543–560.
Surcel, H.M., Troye Blomberg, M., Paulie, S., Andersson, G., Moreno, C., Pasvol, G., Ivanyi, J., 1994. Th1/Th2 profiles in tuberculosis, based on the proliferation and cytokine response of blood lymphocytes to mycobacterial antigens. Immunology 81, 171–176.
Taub, D., 2008. Novel connections between the neuroendocrine and immune systems: the ghrelin immunoregulatory network. Vitam. Horm. 77, 325–346.
Toossi, Z., Ellner, J.J., 1998. The role of TGF beta in the pathogenesis of human tuberculosis. Clin. Immunol. Immunopathol. 87, 107–114.
Torelli, G.F., Meguid, M.M., Moldawer, L.L., Edwards III, C.K., Kim, H.J., Carter, J.L., Laviano, A., Rossi-Fanelli, F., 1999. Use of recombinant human soluble TNF receptor in anorectic tumor-bearing rats. Am. J. Physiol. 277, R850–R855.
Trayhurn, P., Bing, C., Wood, I.S., 2006. Adipose tissue and adipokines—energy regulation from the human perspective. J. Nutr. 136, 1935S–1939S.
Turnbull, A.V., Rivier, C.L., 1999. Regulation of the hypothalamic–pituitary–adrenal axis by cytokines: actions and mechanisms of action. Physiol. Rev. 79, 1–71.
van Crevel, R., Karyadi, E., Preyers, F., Leenders, M., Kullberg, B.J., Nelwan, R.H., van der Meer, J.W., 2000. Increased production of interleukin 4 by CD4+ and CD8+ T cells from patients with tuberculosis is related to the presence of pulmonary cavities. J. Infect. Dis. 181, 1194–1197.
van Crevel, R., Karyadi, E., Netea, M.G., Verhoef, H., Nelwan, R.H., West, C.E., van der Meer, J.W., 2002. Decreased plasma leptin concentrations in tuberculosis patients are associated with wasting and inflammation. J. Clin. Endocrinol. Metab. 87, 758–763.
Van den Berghe, G., 2003. Endocrine evaluation of patients with critical illness. Endocrinol. Metab. Clin. North. Am. 32, 385–410.
Wallenius, V., Wallenius, K., Ahren, B., Rudling, M., Carlsten, H., Dickson, S.L., Ohlsson, C., 2002. Interleukin-6-deficient mice develop mature-onset obesity. Nat. Med. 8, 75–79.
Wallis, R.S., Pai, M., Menzies, D., Doherty, T.M., Walzl, G., Perkins, M.D., Zumla, A., 2010. Biomarkers and diagnostics for tuberculosis: progress, needs and translation into practice. Lancet 375, 1920–1937.
Webster, J., Tonelli, J., Sternberg, E.M., 2002. Neuroendocrine regulation of immunity. Annu. Rev. Immunol. 20, 125–163.
Weinberg, E.D., 1984. Iron withholding: a defense against infection and neoplasia. Physiol. Rev. 64, 65–102.
Westaway, M.S., Wolmarans, L., 1992. Depression and self-esteem: rapid screening for depression in black, low literacy, hospitalized TB patients. Soc. Sci. Med. 35, 1311–1315.
WHO, 2008. Global Tuberculosis Control — Surveillance, Planning, Financing. WHO/HTM/TB. World Health Organization, Geneva, p. 393.
Wilckens, T., de Rijk, R., 1997. Glucocorticoids and immune function: unknown dimensions and new frontiers. Immunol. Today 19, 418–424.
Yao, J.H., Ye, S.M., Burgess, W., Zachary, J.F., Kelley, K.W., Johnson, R.W., 1999. Mice deficient in interleukin-1beta converting enzyme resist anorexia induced by central lipopolysaccharide. Am. J. Physiol. 277, R1435–R1443.
Yuksel, I., Sencan, M., Dokmetas, H.S., Dokmetas, I., Ataseven, H., Yönem, O., 2003. The relation between serum leptin levels and body fat mass in patients with active lung tuberculosis. Endocr. Res. 29, 257–264.