Neurohormonal-cytokine interactions: Implications for inflammation, common human diseases and well-being

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Abstract

The neuroendocrine system affects the immune system through the neuroendocrine humoral outflow via the pituitary, and through direct neuronal influences via the sympathetic, parasympathetic (cholinergic) and peptidergic/sensory innervation of peripheral tissues. Circulating hormones or locally released neurotransmitters and neuropeptides regulate major immune functions, such as antigen presentation, antibody production, lymphocyte activity, proliferation and traffic, and the secretion of cytokines including the selection of T helper (Th1) or Th2 cytokine responses. During inflammation, the activation of the stress system, through induction of a Th2 shift protects the organism from systemic "overshooting" with Th1/pro-inflammatory cytokines. Under certain conditions, however, stress hormones, substance P, ATP and the activation of the corticotropin-releasing hormone/substance P-histamine axis may actually facilitate inflammation, through induction of interleukin (IL)-1, IL-6, IL-8, IL-18, tumor necrosis factor (TNF)-α and CRP production. Thus, a dysfunctional neuroendocrine-immune interface associated with abnormalities of the 'systemic anti-inflammatory feedback' and/or 'hyperactivity' of the local pro-inflammatory factors may play a role in the pathogenesis of atopic/allergic and autoimmune diseases, obesity, depression and atherosclerosis. Better understanding of the neuroendocrine control of inflammation may provide critical insights into mechanisms underlying a variety of common human immune-related diseases.

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Homeostasis within the immune system is largely dependent on cytokines, the chemical messengers between immune cells, which play crucial roles in mediating inflammatory and immune responses. These diverse groups of proteins may be regarded as hormones of the immune system. Pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α, released during an immune response and inflammation activate the central components of the stress system, alter neurotransmitter networks activity and induce fever, sleepiness, fatigue, loss of appetite and decreased libido. In addition, they activate the hepatic synthesis of acute phase proteins—changes referred to as 'sickness behavior' and 'acute-phase response', respectively (Fig. 1).

Cytokines act in an autocrine, paracrine or endocrine fashion to control the proliferation, differentiation and activity of immune cells. For instance, T helper (Th)1 cells primarily secrete interferon (IFN)-γ, interleukin (IL-2) and tumor necrosis factor (TNF)-β, which promote cellular immunity, whereas Th2 cells secrete a different set of cytokines, primarily IL-4, IL-10 and IL-13, which promote humoral immunity (Fearon and Locksley, 1996; Mosmann and Sad, 1996; Trinchieri, 2003) (Fig. 1). Naïve CD4+ (antigen-inexperienced) Th0 cells are bipotential and serve as precursors of Th1 and Th2 cells. IL-12, produced by antigen-presenting cells (APC), such as monocytes/macrophages and dendritic cells (DCs), is the major inducer of Th1 differentiation and, hence, cellular immunity. IL-12 also synergizes with IL-18 to induce the production of IFN-γ by natural killer (NK) cells. Thus, IL-12 in concert with IL-18, IFN-α and IFN-γ promote the differentiation of Th0 cells towards the Th1 phenotype. IL-1, IL-12, TNF-α and IFN-γ also stimulate the functional activity of T cytotoxic cells (Tc), NK cells and activated macrophages, which are the major components of cellular immunity. The type 1 cytokines IL-12, TNF-α and IFN-γ also stimulate the synthesis of nitric oxide (NO) and other inflammatory mediators that drive chronic delayed type inflammatory
responses. Because of their synergistic roles in stimulating inflammation IL-12, TNF-α and IFN-γ are considered the major pro-inflammatory cytokines (Fearon and Locksley, 1996; Mosmann and Sad, 1996; Trinchieri, 2003).

Th1 and Th2 responses are mutually inhibitory. Thus, IL-12 and IFN-γ inhibit Th2, while IL-4 and IL-10 inhibit Th1 cell activities. IL-4 and IL-10 promote humoral immunity by stimulating the growth and activation of mast cells and eosinophils (Eo), the differentiation of B cells into antibody-secreting B cells and B cell immunoglobulin switching to IgE. Importantly, these cytokines also inhibit macrophage activation, T-cell proliferation and the production of pro-inflammatory cytokines (Fearon and Locksley, 1996; Mosmann and Sad, 1996; Trinchieri, 2003). Therefore, the Th2 (type 2) cytokines IL-4 and IL-10 are the major anti-inflammatory cytokines.

1. Cytokines and common human diseases

1.1. Cytokines and allergy/atopy

Allergic diseases, such as asthma, seasonal and perennial allergic rhinitis, eczema and IgE-mediated food allergy, are
characterized by dominant Th2 responses, overproduction of histamine and a shift to IgE production (Humbert et al., 1999; Wills-Karp, 2001). The Th2 cytokines IL-4 and IL-13 induce B lymphocytes to express the $\varepsilon$-germeline gene transcript, an essential precursor for immunoglobulin heavy chain rearrangement and IgE antibody (Ab) production. IL-5 is selective for eosinophils (Eo) and promotes maturation, activation and priming for mediator release. Atopic eczema presents a mixed Th2/Th1 pattern, although Th2 responses are considered important during the evolution of eczematous lesions. Thus, asthma, rhinitis and eczema should be regarded as systemic diseases in view of their multiple manifestations. These diseases are associated with a marked negative impact on quality of life, manifested as absence from work/school, impairment of leisure time and sleep disturbances.

Mast cells and Eo play an important role in allergic reactions, where tissue mast cell activation triggers a local inflammatory response, with the Eo being the principal recruited cell. By far, the most common mechanism of activation of the mast cells is the interaction of antigen with antigen-specific IgE fixed on the surface of mast cells. There is a significant subset of the general population that may form antigen-specific IgE to environmental agents, and these individuals are generally referred to as ‘atopic’. Tissue-based mast cells are the most important cells in the genesis of mast cell-Eo-based disorders. Their activation leads to the generation of arachidonic acid metabolites, the release of histamine and proteases, and the generation and release of cytokines, such as TNF-α. These substances cause increased vascular permeability, and attract inflammatory cells, including neutrophils, Eo, monocytes and lymphocytes (Metcalfe et al., 1997; Prussin and Metcalfe, 2001; Taylor and Metcalfe, 2001).

Asthma is an inflammatory disease in which the lung is populated by CD4+ T-cells belonging to the Th2 phenotype producing IL-4, IL-5, IL-9 and IL-13. The over-expression of these cytokines results in recruitment and activation of mast cells and eosinophils that mediate local inflammation and consequently airway obstruction and hyperresponsiveness (Wills-Karp, 2001). An impaired IL-12 production coupled to an overproduction of IL-13 by alveolar macrophages may underlie to a great extent the Th2-biased response in asthma (Naseer et al., 1997; Wills-Karp, 2001).  

1.2. Cytokines and Th1-related autoimmunity

Several autoimmune diseases are characterized by common alterations of the Th1 versus Th2 and pro-versus anti-inflammatory cytokine balance. In rheumatoid arthritis (RA), multiple sclerosis (MS), type 1 diabetes mellitus and autoimmune thyroid disease (ATD) the balance is skewed towards Th1 and an excess of IL-12 and TNF-α production, whereas Th2 activity and the production of IL-10 appear to be deficient. This may be a critical factor that determines the proliferation and differentiation of Th1-related autoreactive cellular immune responses in these disorders (Segal et al., 1998). Similarly, in Crohn’s disease (CD), the inflammation is due to a Th1 T-cell abnormality involving overproduction of IL-12, IFN-γ and TNF-α production, whereas ulcerative colitis is probably driven by the production of IL-13 (Bouma and Strober, 2003). A second checkpoint of Th1 T-cell-mediated inflammation involves its down-regulation by the suppressor cytokine TGF-β.

1.3. Cytokines in depression and atherosclerosis

Recent evidence indicates that pro-inflammatory cytokines contribute to the biology of depression. First, treatment of patients with chronic hepatitis C and malignant melanoma with high doses of INF-α is often accompanied by symptoms of depression, such as abnormal sleep patterns, irritability, anxiety, low mood, cognitive impairment, in addition to mild to severe fatigue, apathy, loss of appetite as common adverse effects. Second, behavioral changes, resembling the vegetative symptoms of depression are observed in rodents after acute administration of proinflammatory cytokines. Third, recent evidence indicates increased serum levels of pro-inflammatory cytokines, such as IL-6 in subjects with depressive symptoms and syndromes. Fourth, the involvement of pro-inflammatory cytokines and specifically IL-6 is further substantiated by reports showing increased plasma levels of acute-phase proteins, such as haptoglobin and C-reactive protein in major depression (Corcos et al., 2002; Kronfol and Remick, 2000; Wichers and Maes, 2002).

One of the paradigm shifts in our understanding about atherosclerosis in the last decade is the development of the concept that it is potentially caused by a chronic inflammation most likely linked to infection(s) with Chlamydia pneumoniae and/or the human cytomegalovirus (CMV). When considering the role of cytokines in inflammation related to atherosclerosis it is important to distinguish between local inflammation within the plaque microenvironment and systemic inflammation, as evident by acute-phase protein production and circulating pro-inflammatory mediators. Locally produced pro-inflammatory mediators with atherogenic activity include IFN-γ, TNF-α, IL-1β, IL-8, IL-12, IL-18 and monocyte chemotactic protein (MCP)-1. Systemic mediators and markers of inflammation include IL-6, IL-8 and C-reactive protein. Increased IL-6 is associated with elevated fibrinogen levels, which leads to an increased tendency to thrombosis, independent of the effects of IL-6 (Greaves and Channon, 2002).

2. Neurohormonal regulation of cytokine production

The brain affects the immune system through the neuroendocrine humoral outflow via the pituitary, and through direct neuronal influences via the sympathetic, parasympathetic (cholinergic) and peptidergic/sensory innervation of peripheral tissues including lymphoid organs and blood vessels (Fig. 1). Cytokine regulation is traditionally linked to the effects of immuno-genetic factors operating exclusively within the immune system. Evidence accumulated over the last 2–3 decades indicates, however, that neurohormonal messages from the brain superimpose upon and interweave with these factors. Thus, systemic and local concentrations of neurohormonal mediators together with the local cytokine milieu shape
the individual’s cytokine responsiveness and phenotypes, and disease susceptibility and activity.

2.1. Systemic effects of glucocorticoids (GCs) and catecholamines (CAs)

Recent evidence indicates that both GCs and CAs systemically mediate a Th2 shift by suppressing APCs- and Th1- and up-regulating Th2-cytokine production (Elenkov and Chrousos, 1999). Thus, GCs and the two major CAs, norepinephrine (NE) and epinephrine (EPI), through stimulation of classic cytoplasmic/nuclear GR and β2-ARs, respectively, suppress the production by APCs of IL-12, the main inducer of Th1 responses (Blotta et al., 1997; Elenkov et al., 1996; Hasko et al., 1998; Panina-Bordignon et al., 1997). Since IL-12 is extremely potent in enhancing IFN-γ and inhibiting IL-4 synthesis by T-cells, this is also associated with decreased IFN-γ but increased production of IL-4 by T-cells (Blotta et al., 1997; DeKruyff et al., 1998; Wu et al., 1998) (see Fig. 1). GCs also have a direct effect on Th2 cells by up-regulating their IL-4, IL-10 and IL-13 production (Blotta et al., 1997; Ramierz et al., 1996). GCs do not affect the production of IL-10 by monocytes (Elenkov et al., 1996; van der Poll et al., 1996a); yet, lymphocyte-derived IL-10 production is up-regulated by GCs (Ramierz et al., 1996). This could be the result of a direct stimulatory effect of GCs on T-cell IL-10 production and/or a block on the restraining inputs of IL-12 and IFN-γ on lymphocyte IL-10 production. Both GCs and CAs inhibit the production of IL-1, TNF-α and IFN-γ, while CAs inhibit the production of TNF-α by monocytes, microglial cells and astrocytes, and suppress the production of IL-1, an effect that is mostly indirect via inhibition of TNF-α and potentiation of IL-10 production (Elenkov et al., 1995; Hetter et al., 1991; Koff et al., 1986; Nakamura et al., 1998; Severn et al., 1992; van der Poll and Lowry, 1997). Since β2-ARs are expressed on Th1 cells, but not on Th2 cells (Sanders et al., 1997) CAs do not affect directly the cytokine production by Th2 cells—in murine and human systems β2-AR agonists inhibit IFN-γ production by Th1 cells, but do not affect IL-4 production by Th2 cells (Borger et al., 1998; Sanders et al., 1997). However, CAs through stimulation of β2-AR up-regulate the production of the anti-inflammatory cytokine IL-6 and IL-10 by APCs (Elenkov et al., 1996; Hasko et al., 1995; Maimone et al., 1993; Norris and Benveniste, 1993; van der Poll et al., 1996b).

2.2. ATP and adenosine

ATP through stimulation of P2Y11 receptors and subsequent increase of cAMP inhibit IL-12 and TNF-α, and stimulate IL-10 production by APCs (Hasko et al., 2000; Wilkin et al., 2002). As a result, T-cells produce lower amounts of IFN-γ and higher amounts of IL-4, IL-5 and IL-10 (la Sala et al., 2001). Through these mechanisms, ATP favors Th2 responses. However, monocytes, macrophages, microglial cells and some lymphocytes and cancer cells also express the P2X7 receptor that belongs to the 2PX family of ligand-gated ion channels. Binding of ATP to the P2X7 receptor activates proIL-1β post-translational processing resulting in increased release of IL-1β by monocytes and microglial cell (Chakfe et al., 2002; Perregaux et al., 2000). IL-18, like IL-1β is produced as a propolypeptide that requires cleavage by caspase-1 to generate an active mature cytokine. Thus, it appears that ATP via stimulation of P2X7 receptor can act as an extracellular initiator of the post-translational processing of certain pro-inflammatory cytokines, such as IL-1β and IL-18, and thus favor inflammation (Chakfe et al., 2002; Perregaux et al., 2000).

Inflammation, ischemia and tissue injury represent pathologic states in which intracellular ATP metabolism is accelerated, resulting in an enhanced release of the endogenous purine nucleoside adenosine (ADO). Postganglionic sympathetic nerve terminals also release ATP that is rapidly degraded to ADO, which induces vasodilation mediated by A2 receptors. ADO exerts potent anti-inflammatory and immunosuppressive effects mediated mainly by A2 receptors: diminished leukocyte accumulation, inhibition of complement (C2) production and reduction of superoxide anion generation (Cronstein et al., 1985, 1993; Lappin et al., 1984). ADO through stimulation of A2a receptor-cAMP/PKA pathway also inhibits IL-12 and TNF-α and stimulates the production of IL-10 by APCs (Hasko et al., 1996; Le Moine et al., 1996; Link et al., 2000; Prabhakar et al., 1995).

2.3. Histamine

Histamine, through activation of H1 histamine receptors is one of the major mediators of acute inflammation and allergic reactions. Histamine, however, via stimulation of H2 receptors expressed on immune cells also exerts important immunoregulatory functions (Fatus and Meretey, 1992). Thus, histamine inhibits IL-12 and TNF-α, but potentiates IL-10 and IL-6 production by human monocytes and DCs (Elenkov et al., 1998; Idzko et al., 2002; Vannier et al., 1991; Vannier and Dinarello, 1994). In addition, histamine, via H2 receptors inhibits IFN-γ production by Th1 cells, but has no effect on IL-4 production from Th2 clones (Lagier et al., 1997). Thus, histamine, similarly to CAs and ADO appears to drive a Th2 shift at the level of both APCs and Th1 cells. Through this mechanism, allergen/antigen-IgE-induced-release of histamine might participate in a positive feedback loop that promotes and sustains a shift to IgE production in atopic/allergic conditions.

2.4. Peptidergic/sensory nerves

Lymphoid organs and blood vessels receive predominantly sympathetic and peptidergic/sensory innervation. The most abundant peptides are substance P (SP) and cacinotin gene-related peptide (CGRP) closely overlapping anatomically, but not necessarily co-localized in all sensory nerves, and vasoactive intestinal polypeptide (VIP), present in cholinergic nerves (see below). Whereas SP stimulates most macrophage functions and upregulates TNF-α and IL-12 production by monocytes and macrophages, CGRP down-regulates pro-inflammatory TNF-α and IL-12 production and potentiates IL-6 and IL-10 secretion through the CGRP1 receptor-cAMP/PKA pathway (Fox et al.,
specific compartments of the body. Thus, steroid treatment may not pertain to certain conditions or local responses in 2.6. Local versus systemic effects

vasodilation in most vascular beds. (Ganea and Delgado, 2001). However, VIP induces marked 10, primarily through VPAC1 receptors on immune cells stimulates the secretion of the anti-inflammatory cytokine IL-12, activating immune cells (Broug-Holub et al., 1998; Le Tulzo et al., 1997). These

was not demonstrated. Thus, stress-induced changes in alveolar macrophage activity might result from alveolar type II epithelial cell activation, leading to release of surfactant and/ or other factors (Broug-Holub et al., 1998).

CAs also potentiate the production of IL-8 (a chemokine that promotes the recruitment of polymorphonuclear cells to an inflammatory site) by monocytes, epithelial cells of the lung and endothelial cells, indirectly, via an effect on platelets (Engstad et al., 1999; Kaplanski et al., 1993; Kavelaars et al., 1997; Linden, 1996). Furthermore, CAs (through β2/β3-ARs) and insulin up-regulate IL-6 production by human adipocytes (Mohamed-Ali et al., 2001; Vicennati et al., 2002). IL-6 is the major inducer of C-reactive protein (CRP) production by the liver and both GCs and CAs enhance this induction (Baumann and Gauldie, 1994). Interestingly, histamine induces the production of both IL-6 and IL-8 by coronary artery endothelial cells, whereas chronic β-AR stimulation induces myocardial, but not systemic, production of TNF-α, IL-1β and IL-6 (Li et al., 2001; Murray et al., 2000)(Fig. 2).

2.7. CRH/SP-mast cell-histamine interactions

Corticotropin-releasing hormone (CRH) is also secreted peripherally at inflammatory sites (peripheral or immune CRH) (Karalis et al., 1991). Immunoreactive CRH is identified locally in tissues from patients with RA, ATD and ulcerative colitis. CRH in early inflammation is of peripheral postganglionic sympathetic and sensory afferent nerve rather than immune cell origin (Elenkov et al., 1999; Karalis et al., 1991). Peripheral CRH has vascular permeability-enhancing and vasodilatory actions. An intradermal CRH injection induces a marked increase of vascular permeability and mast cell degranulation, mediated through CRH type 1 receptors (Theoharides et al., 1998). It appears that the mast cell is a major target of immune CRH. Peripheral CRH and SP, released from sensory peptidergic neurons, are two of the most potent mast cell secretagogues (Church et al., 1989; Foreman, 1987; Theoharides et al., 1995, 1998). Thus, peripheral CRH and SP activate mast cells via a CRH type 1 and NK1 receptor-dependent mechanism leading to release of histamine and other contents of the mast cell granules that cause vasodilatation, increased vascular permeability and other manifestations of inflammation (Fig. 2).

3. Implications for inflammation, common human diseases and well-being

Complex interactions exist between cytokines, inflammation and the adaptive responses in maintaining homeostasis, health and well-being. The inflammatory reaction, like the stress response is crucial for survival of the self and species. Also, like the stress response, inflammation is meant to be tailored to the stimulus and time-limited. A fully fledged systemic inflammatory reaction results in stimulation of four major programs: (1) the acute phase reaction, (2) the sickness syndrome, (3) the pain program, mediated by the afferent sensory and autonomic systems and (4) the stress program, mediated by the hypothalamic–pituitary–adrenal (HPA) axis and the locus ceruleus–NE/sympathetic nervous system (SNS). The main
effector substances of the systemic inflammatory response are inflammatory cytokines; the acute phase reactants, mostly of hepatic origin, such as CRP; the effectors of the sensory afferent system, such as substance P; of the stress system, namely hypothalamic CRH and vasopressin, cortisol, the CAs NE and EPI, and peripheral neuronal CRH (Chrousos, 1995, 1998; Clauw and Chrousos, 1997).

Whether it is an inflammatory focus with spillover of inflammatory effector molecules into the systemic circulation or a truly generalized, systemic inflammatory reaction, the programs that are activated during inflammation have both synergistic and antagonistic actions. For instance, the inflammatory cytokines and, particularly IL-6 stimulate the hepatic synthesis of acute phase proteins, such as CRP and this effect is potentiated by GCs and CAs, which, however, also inhibit the secretion of inflammatory cytokines, bringing inflammation to a close. The sickness syndrome consists of fever, anorexia/nausea, fatigue, somnolence or sleep disturbances, decreased physical, social and sexual activity, hyperalgesia and an increased metabolic rate; almost all manifestations are suppressed by GCs. Yet, peripheral neuronal CRH activated by stress or the inflammatory reaction, and SP activated by the inflammatory reaction potentiate inflammation. In fact, through the former mechanism stress may trigger and/or exacerbate an inflammatory condition, such as asthma or rheumatoid arthritis (Chrousos, 1995, 1998; Clauw and Chrousos, 1997).

Chronic systemic inflammation, depending upon its degree, varies from asymptomatic to mildly, to severely symptomatic. Regardless of the presence of overt symptomatology of sickness syndrome manifestations, chronic elevations of circulating inflammatory cytokines and/or activation of the stress system result in a combination of immune and metabolic disturbances, including endothelial inflammation, changes in the Th1/Th2 balance, osteoporosis, hypercoagulability of the blood, dyslipidemia, insulin resistance, carbohydrate intolerance and/or diabetes type 2. The non-immune manifestations constitute the visceral fat syndrome which deteriorates with time in patients with chronic inflammation and/or stress; this represents an exacerbation of a phenomenon that naturally occurs with advancing age in both men and women. These immune and metabolic changes increase all cause mortality, primarily cardiovascular due to atherosclerosis, but also cancer- and infection-related; they also cause significant morbidity, potentially including clinically significant osteoporosis. Chronic or intermittent but frequent inflammation due to presence of inflammatory foci, such as those in allergic rhinitis, bronchial asthma, periodontitis, *Helicobacter pylori* infection or multiple sclerosis, may be responsible for varying degrees and patterns of sickness syndrome manifestations and may be associated with the chronic immune, metabolic and cardiovascular complications of inflammation mentioned above (Chrousos, 1995, 1998; Crofford et al., 1997; Elenkov and Chrousos, 1999; Papanicolaou et al., 1998).

Interestingly, adipose tissue secretes large amounts of TNF-α and IL-6 in a neurologically, hormonally and metabolically regulated fashion. The plasma levels of these cytokines are proportional to the body mass index and are further elevated in patients with visceral obesity. The secretion of inflammatory cytokines has a circadian pattern, with elevations in the evening and in the early morning hours. This pattern is maintained in patients with inflammatory diseases and in obese subjects, albeit at a higher level, is affected by the quality of sleep, and correlates with manifestations of the sickness syndrome. In obesity, the hypercytokinemia is associated frequently with some manifestations of the sickness syndrome, such as fatigue.

**Fig. 2.** Simplified scheme of the complex interactions between CAs, neuropeptides and the CRH/SP-mast cell-histamine axis, and their pro- and anti-inflammatory effects in certain local responses (see text; from reference Elenkov, 2003). Solid lines represent stimulation, while dashed lines inhibition. *Abbreviations:* CGRP, Calcitonin gene-related peptide; CRH, corticotropin-releasing hormone (peripheral); EPI, epinephrine; IL, interleukin; NE, norepinephrine; SP, substance P; TNF, tumor necrosis factor.
and somnolence, and of the other programs that may be activated during the inflammatory reaction. Thus, obesity and, especially the visceral type, can be considered as a chronic inflammatory state, with many of the behavioral, immune, metabolic and cardiovascular sequelae of such a state (Vgontzas et al., 1999, 2000).

3.1. Atopy/allergy

The effects of stress hormones on atopic/allergic reactions are complex, at multiple levels and can be in either direction (Elenkov and Chrousos, 1999; Marshall and Agarwal, 2000; von Hertzen, 2002). In this context, a clear distinction should be made between susceptibility to disease and effects on already established chronic Th2-mediated inflammatory disease. Stress episodes preceding the development of the disease through induction of the Th2-potential may increase the susceptibility of the individual (von Hertzen, 2002). When the disease is already established, stress may induce a Th2 shift and also can activate the CRH-mast cell-histamine axis (see above) and, thus may facilitate or sustain atopic reactions; however, these effects can be antagonized by the effects of stress hormones on the mast cell (Elenkov and Chrousos, 1999). GCs and CAs (through \(\beta_2\)-ARs) suppress the release of histamine by mast cells, thus abolishing its pro-inflammatory, allergic and bronchoconstrictor effects. Consequently, reduced levels of EPI and cortisol at night could contribute to nocturnal wheezing and have been linked to high circulating histamine levels in asthmatics (Barnes et al., 1980). This may also explain the beneficial effect of GCs and \(\beta_2\)-agonists in asthma. It is noteworthy that infusion of high doses of adrenaline (epinephrine), however, causes a rise in circulating histamine levels that may be due to an \(\alpha\)-adrenergic-mediated increase in mediator release (cf. ref. Barnes et al., 1980). Thus, severe acute stress associated with high EPI concentrations and/or high local secretion of CRH could lead to mast cell degranulation. As a result, a substantial amount of histamine could be released, which consequently would not antagonize, but rather amplify the Th2 shift through H2 receptors, while in parallel, by acting on H1 receptors, it could initiate a new episode or exacerbate a chronic allergic condition (Table 1).

GCs alone or in combination with \(\beta_2\)-AR-agonists are broadly used in the treatment of atopic reactions, and particularly asthma. \textit{In vivo, ex vivo} and \textit{in vitro} exposure to GCs and \(\beta_2\)-agonists result in a reduction of IL-12 production, which persists at least several days (DeKruyff et al., 1998; Table 1.

**Table 1**

<table>
<thead>
<tr>
<th>Disease group/condition</th>
<th>Disease or condition</th>
<th>Cytokines and Th profile</th>
<th>Comments</th>
<th>Role of stress hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy/atopy</td>
<td>Asthma</td>
<td>Deficit of IL-12, overproduction of IL-4, IL-13, Th2 shift</td>
<td>The systemic Th2-inducing effects of stress hormones are antagonized by the local effects of GCs on Th2 cells and mast cell mediator release</td>
<td>Stress hormones and histamine may contribute to the deficit of IL-12 and overproduction of Th2 cytokines; stress may also activate the CRH-mast-cell-histamine axis. This overall may induce/facilitate allergic reactions</td>
</tr>
<tr>
<td>Th1-related autoimmunity</td>
<td>RA, MS, ATD, Diabetes type 1, CD</td>
<td>Overproduction of IL-12, TNF-(\alpha), IFN-(\gamma), deficit of IL-10, Th1 shift</td>
<td>Stress may exacerbate RA through the activation of the CRH-mast-cell-histamine axis (see text for details)</td>
<td>A hypoactive stress system may facilitate or sustain the Th1 shift (see text for details)</td>
</tr>
<tr>
<td>Major depression</td>
<td>Melancholic depression</td>
<td>Increased serum levels of IL-1, IL-6 and CRP</td>
<td>Depression is associated with an increased risk of cardiovascular diseases</td>
<td>IL-1 and IL-6 induce hypercortisolemic and hypernoradrenergic state; alternatively CAs up-regulate IL-6 production, and thus increase its systemic levels</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Myocardial infarction, unstable angina, stroke</td>
<td>Local overproduction of IFN-(\gamma), TNF-(\alpha), IL-1(\beta), IL-8, IL-12, IL-18; systemic elevation of IL-6, IL-8, IL-1(\beta) and CRP</td>
<td>The effect of stress hormones on adipose tissue and lipid metabolism may facilitate their local pro-inflammatory effects</td>
<td>Stress hormones and histamine may induce the production of pro-inflammatory cytokines by myocardium, endothelium and adipose tissues</td>
</tr>
</tbody>
</table>

Modified from reference Elenkov et al. (2005).
Elenkov et al., 1996; Panina-Bordignon et al., 1997). Thus, glucocorticoid and/or β2-AR-agonist therapy is likely to reduce the capacity of APC to produce IL-12, to greatly suppress type 2 cytokine synthesis in activated, but not resting T-cells, and to abolish eosinophilia (DeKruyff et al., 1998). If, however, resting (cytokine-uncommitted) T-cells are subsequently activated by APCs preexposed to GCs and/or β2-AR agonists, enhanced IL-4 production, but limited IFN-γ synthesis, could be induced (DeKruyff et al., 1998). Thus, while in the short term, the effect of GCs and β2-AR agonists may be beneficial; their long-term effects might be to sustain the increased vulnerability of the patient to the allergic condition. This is further substantiated by the observations that both GCs and β2-AR agonists potentiate the IgE production in vitro and in vivo (Coqueret et al., 1994; Zieg et al., 1994).

3.2. Th1-related autoimmunity

A hypoactive stress system may facilitate or sustain the Th1 shift in Th1-mediated RA or MS (Elenkov and Chrousos, 1999, 2002; Sternberg, 2001). Recent studies suggest that suboptimal production of cortisol is involved in the onset and/or progression of RA (Straub and Cutole, 2001; Wilder, 1995; Wilder and Elenkov, 1999). Patients with RA have “inappropriately normal” or low cortisol levels in plasma in the setting of severe, chronic inflammation, characterized by increased production of TNF-α, IL-1 and IL-6. This may actually facilitate or sustain the pro-inflammatory shift in this disease. Whether this abnormality is primary or secondary has not been established (Wilder and Elenkov, 1999). Several lines of evidence indicate that the sympathetic-immune interface might also be defective in MS and RA (Arnason et al., 1988a,b; Elenkov et al., 2000; Karaszewski et al., 1990, 1993). Interestingly, patients with long-term RA have a highly significant reduction of sympathetic nerve fibers in synovial tissues with preponderance of about 10:1 for primary sensory, SP positive fibers as compared with sympathetic fibers (Miller et al., 2000). Thus, the reduction of sympathetic nerve fibers in the chronic disease may lead to uncoupling of the local inflammation from the anti-inflammatory input of sympathetic nerves. Since SP is powerful pro-inflammatory agent, via release of histamine, TNF-α and IL-12, such preponderance may lead to an unfavorable pro-inflammatory state, supporting the disease process of RA (see Fig. 3). Clinical observations also indicate that RA and MS, frequently remit during pregnancy but exacerbate, or have their onset, in the postpartum period. Recent evidence suggests that a cortisol-, NE- and 1,25-dihydroxyvitamin D3 induced inhibition and subsequent rebound of IL-12 and TNF-α production may represent a major mechanism by which pregnancy and postpartum alter the course of or susceptibility to RA and MS (Elenkov et al., 2001).

3.3. Depression and cardiovascular diseases

In melancholic depression, the stress response seems hyperactive, and patients are anxious, dread the future, lose responsiveness to the environment, have insomnia, lose their appetite and have a diurnal variation with depression at its worst in the morning. Patients with melancholic depression have significantly higher CSF NE and plasma cortisol levels that are
increased around the clock, with inappropriately high plasma ACTH and CSF CRH levels, considering the degree of their hypercortisolism. These data suggest mutually reinforcing bi-directional links between a central hypernoradrenergic state and the hyperfunctioning of specific central CRH pathways that each are driven and sustained by hypercortisolism (Wong et al., 2000). On the other hand, the hypersonnia, hypophagia, lethargy, fatigue and relative apathy of the syndrome of atypical depression are most likely associated with concomitant hypofunctioning of the CRH and LC-NE systems (Gold and Chrousos, 1999, 2002). Abnormalities of the neuroendocrine system in major depression (melancholic), particularly the hypercortisolism and the central hypernoradrenergic state might be accentuated by the ‘low-grade’ systemic inflammation, and specifically the increase of plasma IL-1 and IL-6 (Corcos et al., 2002). Alternatively, since CAs up-regulate IL-6 production, the chronic hypernoradrenergic state may drive the increase in systemic IL-6 levels (Fig. 2; Table 1). Stress hormones-induced local pro-inflammatory effects may play important role in the pathogenesis of atherosclerosis (Table 1), whereas autonomic dysfunction after myocardial infarction and brain stroke may contribute to the impaired immune homeostasis in these conditions (Prass et al., 2003; Riese et al., 2000).

4. Conclusions

The CNS and the immune system are the two major adaptive systems of the body (Elenkov et al., 2000). Inflammation, and particularly chronic inflammation of varying types, as a result of the failure of these two major adaptive systems to respond and resolve it, affect the well-being of the individual, including behavioral parameters, such as cognitive ability, performance, affect and sleep, as well as indices of metabolic and cardiovascular health that are known to influence human life expectancy both in absolute terms and adjusted for disability. During an immune and inflammatory responses, the activation of the stress system, through induction of a Th2 shift, in conjunction with the increase of the ‘anti-inflammatory’ efferent vagus activity in visceral organs, may actually protect the organism from systemic “overshooting” with type 1/pro-inflammatory cytokines and other products of activated macrophages with tissue damaging potential (see also references Chrousos, 1995; Elenkov et al., 2000; Elenkov and Chrousos, 1999; Tracey, 2002; Wilder, 1995). On the other hand, in certain local responses, and under certain conditions, stress hormones, may actually facilitate inflammation, through induction of IL-1, IL-6, IL-8, IL-18, TNF-α and CRP production and through activation of the CRH/SP-histamine axis. Thus, a dysfunctional neuroendocrine-immune interface associated with abnormalities of the ‘systemic anti-inflammatory feedback’ and/or ‘hyperactivity’ of the local pro-inflammatory factors, may play a role in the pathogenesis of atopic/allergic and autoimmune diseases, obesity and depression, and their complications, and atherosclerosis and infections (not discussed here, see references Altare et al., 1998; Cohen et al., 1991; Cole et al., 1998, 2001; Elenkov et al., 1996; Elenkov and Chrousos, 1999; Kino et al., 1999; Lerner, 1996; Levenstein et al., 1999; Mirani et al., 2002; Rook et al., 2002). Clearly, these hypotheses require further investigation, but the answers should provide critical insights into mechanisms underlying a variety of common human immune-related diseases.

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