

# Cytokine Dysregulation, Inflammation and Well-Being

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## Key Words

Autoimmune diseases · Cytokines · Inflammation · Interleukins · Stress · Tumor necrosis factor

## Abstract

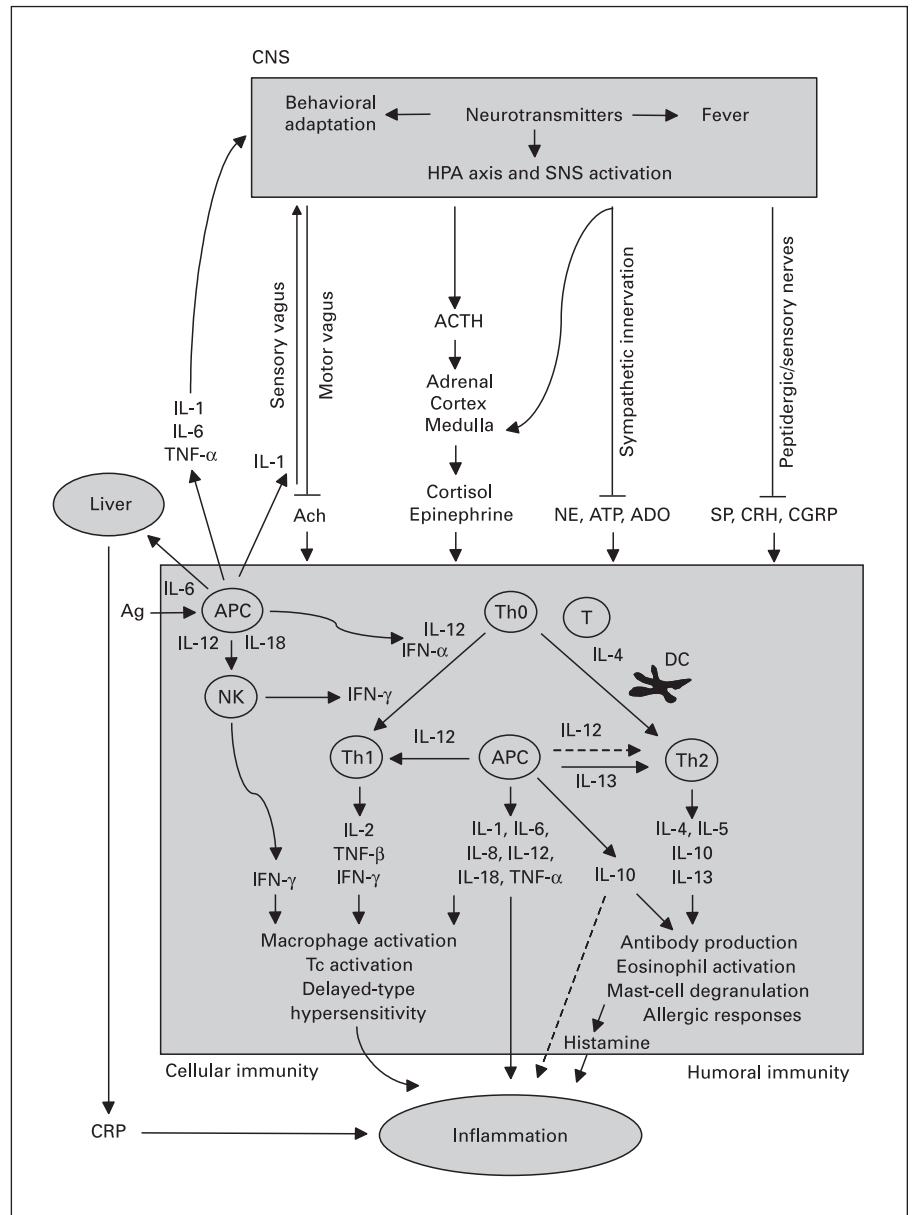
Cytokines mediate and control immune and inflammatory responses. Complex interactions exist between cytokines, inflammation and the adaptive responses in maintaining *homeostasis*, health, and well-being. Like the stress response, the inflammatory reaction is crucial for survival and is meant to be tailored to the stimulus and time. A full-fledged systemic inflammatory reaction results in stimulation of four major programs: the acute-phase reaction, the sickness syndrome, the pain program, and the stress response, mediated by the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Common human diseases such as atopy/allergy, autoimmunity, chronic infections and sepsis are characterized by a dysregulation of the pro- versus anti-inflammatory and T helper (Th)1 versus Th2 cytokine balance. Recent evidence also indicates the involvement

of pro-inflammatory cytokines in the pathogenesis of atherosclerosis and major depression, and conditions such as visceral-type obesity, metabolic syndrome and sleep disturbances. 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 may actually facilitate inflammation through induction of interleukin (IL)-1, IL-6, IL-8, IL-18, tumor necrosis factor- $\alpha$  and C-reactive protein production and through activation of the corticotropin-releasing hormone/substance P-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, depression, and atherosclerosis. These abnormalities and the failure of the adaptive systems to resolve inflammation affect the well-being of the individual, including behavioral parameters, quality of life and sleep, as well as indices of metabolic and cardiovascular health. 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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**Fig. 1.** A simplified scheme of the bidirectional communication between the brain and the immune system; role of cytokines in the regulation of cellular and humoral immunity, and the role of neuroendocrine and immune adaptive responses in inflammation. Lymphoid organs, and particularly their parenchyma, similar to smooth muscles of the vasculature, receive predominantly sympathetic/noradrenergic and peptidergic/sensory innervation; the heart and the gastrointestinal tract receive both sympathetic and parasympathetic (cholinergic) innervation. Cellular immunity provides protection against intracellular bacteria, protozoa, fungi and several viruses, while humoral immunity provides protection against multicellular parasites, extracellular bacteria, some viruses, soluble toxins and allergens (see text). Ach = Acetylcholine; ADO = adenosine; APC = antigen-presenting cells; Ag = antigen; ACTH = adrenocorticotropic hormone; CGRP = calcitonin gene-related peptide; CRH = corticotropin-releasing hormone; HPA = hypothalamic-pituitary-adrenal axis; NK = natural killer cells; NE = norepinephrine; SNS = sympathetic nervous system; SP = substance P; Tc = T-cytotoxic cells.



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. 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)- $\gamma$ , interleukin (IL)-2 and tumor necrosis factor (TNF)- $\beta$ , 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 [1–3] (fig. 1).

Naive CD4<sup>+</sup> (antigen-inexperienced) Th0 cells are bi-potential and serve as precursors of Th1 and Th2 cells. IL-12, produced by antigen-presenting cells (APC), such as monocytes/macrophages and dendritic cells, is the major inducer of Th1 differentiation and, hence, cellular immunity. IL-12 also synergizes with IL-18 to induce the production of IFN- $\gamma$  by natural killer (NK) cells. Thus, IL-12 in concert with IL-18, IFN- $\alpha$  and IFN- $\gamma$  promote the differentiation of Th0 cells towards the Th1 pheno-

type. IL-1, IL-12, TNF- $\alpha$  and IFN- $\gamma$  also stimulate the functional activity of T-cytotoxic cells, NK cells and activated macrophages, which are the major components of cellular immunity. The type 1 cytokines IL-12, TNF- $\alpha$  and IFN- $\gamma$  also stimulate the synthesis of nitric oxide and other inflammatory mediators that drive chronic delayed-type inflammatory responses. Because of their synergistic roles in stimulating inflammation IL-12, TNF- $\alpha$  and IFN- $\gamma$  are considered the major pro-inflammatory cytokines [1–3].

Th1 and Th2 responses are mutually inhibitory. Thus, IL-12 and IFN- $\gamma$  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, 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 [1–3]. Therefore, the Th2 (type 2) cytokines IL-4 and IL-10 are the major anti-inflammatory cytokines.

### **Cytokines and Common Human Diseases**

#### *Cytokines and Allergy/Atopy*

Dr. Stephen Durham (National Heart and Lung Institute, London, UK) summarized recent evidence that allergic diseases, e.g. 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 [4, 5]. The Th2 cytokines IL-4 and IL-13 induce B lymphocytes to express the  $\epsilon$ -germline gene transcript, an essential precursor for immunoglobulin heavy-chain rearrangement and IgE antibody production. IL-5 is selective for eosinophils 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.

Dr. Dean Metcalfe (National Institutes of Health, Bethesda, Md., USA) emphasized the importance of mast cells and eosinophils in allergic reactions, where tissue mast cell activation triggers a local inflammatory re-

sponse, with the eosinophils 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'. The antigen-specific IgEs become rapidly fixed to high-affinity receptors on the surface of mast cells and basophils that bear Fc $\epsilon$ R1. This can also trigger circulating basophils to degranulate, and such reactions may contribute to systemic allergic reactions. However, tissue-based mast cells are the most important cells in the genesis of mast-cell/eosinophil-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- $\alpha$ . These substances cause increased vascular permeability, and attract inflammatory cells, including neutrophils, eosinophils, monocytes and lymphocytes [6–8].

Drs. Giovanni Passalacqua and Giorgio Canonica (University of Genoa, Genoa, Italy) presented evidence that adhesion molecules play a substantial role for the selective recruitment of inflammatory cells and that ICAM-1 (CD54) is one of the most reliable markers of ongoing allergic inflammation at the nasal and bronchial level. Furthermore, a weak inflammatory infiltration is present in the mucosae, even in the absence of symptoms, when a sub-threshold exposure to the allergen persists – this is referred to as minimal persistent inflammation and has been demonstrated in both mite- and pollen-induced allergy. The minimal persistent inflammation also involves a weak and persistent expression of the ICAM-1 molecule, which is the major receptor for human rhinoviruses. Minimal persistent inflammation and ICAM-1 expression in symptom-free allergic subjects is of relevance because, especially in children, asthma exacerbations are frequently related to upper-respiratory rhinoviral infections [9–11].

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 overexpression of these cytokines results in recruitment and activation of mast cells and eosinophils that mediate local inflammation and consequently airway obstruction and hyperresponsiveness [5]. Recent studies indicate that when compared with control subjects, reduced numbers of IL-12-expressing cells, and elevated IL-13 mRNA and protein levels exist in bronchial biopsy specimens and bronchial lavage cells from asthmatic patients [12]. Inter-

estingly, elevations in IL-13 appear to have a closer association with asthma than with atopy. Furthermore, the major source of IL-13 in bronchial lavage fluid appears to be the alveolar macrophage. Thus, 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 [5, 12].

#### *Cytokines and Th1-Related Autoimmunity*

Several autoimmune diseases are characterized by common alterations in 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, the balance is skewed towards Th1 and an excess of IL-12 and TNF- $\alpha$  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 [13].

Dr. Warren Strober (National Institutes of Health, Bethesda, Md., USA) presented evidence from studies in murine models that resemble Crohn's disease (CD), as well as studies of CD in humans, demonstrating that inflammation in CD is due to a Th1 T-cell abnormality involving overproduction of IL-12, IFN- $\gamma$  and TNF- $\alpha$ , whereas ulcerative colitis is probably driven by the production of IL-13 [14]. Importantly, in murine models, treatment with anti-IL-12 or other agents that down-regulate the level of IL-12 secretion can have a dramatic effect on the inflammation, resolving it within days in some cases. The success of these agents in murine models of inflammation has led to a clinical trial of anti-IL-12 treatment in patients with CD. A second checkpoint of Th1 T-cell-mediated inflammation involves its down-regulation by the suppressor cytokine transforming growth factor (TGF)- $\beta$ . Dr. Strober reported that he and his team have successfully treated mice with experimental intestinal inflammation with intranasally administered DNA encoding TGF- $\beta$  [15, 16].

#### *Cytokines in Depression and Atherosclerosis*

Drs. Philip Gold and George Chrousos (National Institutes of Health, Bethesda, Md., USA) addressed the recent evidence suggesting 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 IFN- $\alpha$  is often accompanied by symptoms of depression, such as abnormal sleep patterns, irritability, anxiety, low mood, cognitive impair-

ment, in addition to mild-to-severe fatigue, apathy and loss of appetite as common adverse effects [17–19]. A full-blown depressive disorder is reported in up to 36% of cases. 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, e.g. IL-6, in subjects with depressive symptoms and syndromes. Interestingly, decreased levels of the anti-inflammatory cytokine TGF- $\beta$ <sub>2</sub> were recently described in depressed bulimic patients, while in some clinical studies it has been reported that antidepressants may attenuate the effects of pro-inflammatory cytokines by increasing the production of the anti-inflammatory cytokine IL-10. 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 (CRP) in major depression [17–19].

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 [20]. 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- $\gamma$ , TNF- $\alpha$ , IL-1 $\beta$ , IL-8, IL-12, IL-18 and monocyte chemoattractant protein-1. Systemic mediators and markers of inflammation include IL-6, IL-8 and CRP. Increased IL-6 is associated with elevated fibrinogen levels, which leads to an increased tendency to thrombosis, independent of the effects of IL-6 [20].

#### *Cytokines and Life-Threatening Systemic Inflammation*

Dr. Umberto Meduri (University of Tennessee, Memphis, Tenn., USA) stressed that dysregulated systemic inflammation with persistent elevation in circulating inflammatory cytokines over time is an important pathogenetic mechanism for pulmonary and extrapulmonary organ dysfunction in patients with severe sepsis and acute respiratory distress syndrome (ARDS). Sepsis, however, may not be attributable solely to an 'immune system gone haywire' but may also indicate an immune system that is severely compromised and unable to eradicate pathogens [21].

It is now appreciated that at cellular level, transcription factors [nuclear factor- $\kappa$ B (NF- $\kappa$ B)] – activated by inflammatory signals – and glucocorticoid receptor  $\alpha$  (GR $\alpha$ ) – activated by endogenous or exogenous glucocorticoids (GCs) – have diametrically opposed functions (stimulatory vs. inhibitory) in regulating inflammation. NF- $\kappa$ B is recognized as the principal driver of the inflammatory response, being responsible for the transcription of >100 genes, including TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 [22]. Once activated, NF- $\kappa$ B and GR $\alpha$  can mutually repress each other through a protein-protein interaction that prevents their DNA binding and subsequent transcriptional activity. Activation of one transcription factor in excess of the binding (inhibitory) capacity of the other shifts cellular responses toward increased (dysregulated) or decreased (regulated) transcription of inflammatory mediators over time [23]. Recent data indicate that failure to improve in sepsis and ARDS is frequently associated with failure of the activated GRs to downregulate the transcription of inflammatory cytokines despite elevated levels of circulating cortisol, a condition defined as systemic inflammation-associated acquired GC resistance which is potentially reversible with prolonged GC supplementation [24].

### **Neuroendocrine 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).

#### *Systemic Effects of Glucocorticoids and Catecholamines*

Dr. Ilia Elenkov (Georgetown University Medical Center, Washington, D.C., USA) summarized recent evidence indicating that both GCs and catecholamines (CAs) systemically mediate a Th2 shift by suppressing APCs and Th1 and up-regulating Th2 cytokine production [25]. Thus, GCs and the two major CAs, norepinephrine (NE) and epinephrine (EPI), through stimulation of classic cytoplasmic/nuclear GR and  $\beta_2$ -adrenergic receptors (ARs), respectively, suppress the production by APCs of IL-12, the main inducer of Th1 responses [26–29]. Since IL-12 is extremely potent in enhancing IFN- $\gamma$  and inhibiting IL-4 synthesis by T cells, this is also associated with decreased IFN- $\gamma$  but increased production of IL-4

by T cells [29–31] (fig. 1). GCs also have a direct effect on Th2 cells by up-regulating their IL-4, IL-10 and IL-13 production [29, 32]. GCs do not affect the production of IL-10 by monocytes [26, 33]; yet, lymphocyte-derived IL-10 production is up-regulated by GCs [32]. 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- $\gamma$  on lymphocyte IL-10 production. Both GCs and CAs inhibit the production of IL-1, TNF- $\alpha$  and IFN- $\gamma$ , while CAs inhibit the production of TNF- $\alpha$  by monocytes, microglial cells and astrocytes, and suppress the production of IL-1, an effect that is mostly indirect via inhibition of TNF- $\alpha$  and potentiation of IL-10 production [34–38]. Since  $\beta_2$ -ARs are expressed on Th1 cells, but not on Th2 cells [39], CAs do not directly affect the cytokine production by Th2 cells – in murine and human systems  $\beta_2$ -AR agonists inhibit IFN- $\gamma$  production by Th1 cells, but do not affect IL-4 production by Th2 cells [39, 40]. However, through stimulation of  $\beta_2$ -AR CAs up-regulate the production of the anti-inflammatory cytokines IL-10 and IL-6 by APCs [26, 41–43].

#### *ATP and Adenosine*

ATP through stimulation of P2Y<sub>11</sub> receptors and the subsequent increase in cAMP inhibit IL-12 and TNF- $\alpha$ , and stimulate IL-10 production by APCs [44, 45]. As a result, T cells produce lower amounts of IFN- $\gamma$  and higher amounts of IL-4, IL-5, and IL-10 [46]. Through these mechanisms, ATP favors Th2 responses. However, monocytes, macrophages, microglial cells, and some lymphocytes and cancer cells also express the P2X<sub>7</sub> receptor that belongs to the 2PX family of ligand-gated ion channels. Binding of ATP to the P2X<sub>7</sub> receptor activates pro-IL-1 $\beta$  post-translational processing resulting in increased release of IL-1 $\beta$  by monocytes and microglial cells [47, 48]. IL-18, like IL-1 $\beta$ , is produced as a propeptide that requires cleavage by caspase-1 to generate an active mature cytokine. Thus, it appears that ATP via stimulation of the P2X<sub>7</sub> receptor can act as an extracellular initiator of the post-translational processing of certain pro-inflammatory cytokines, such as IL-1 $\beta$  and IL-18, and thus favors inflammation [47, 48].

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 A<sub>2</sub> 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 [49–51]. ADO, through stimulation of A2a receptor-cAMP/PKA pathway, also inhibits IL-12 and TNF- $\alpha$  and stimulates the production of IL-10 by APCs [52–55].

### *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 [56]. Thus, histamine inhibits IL-12 and TNF- $\alpha$ , but potentiates IL-10 and IL-6 production by human monocytes and dendritic cells [57–60]. In addition, via H2 receptors, histamine inhibits IFN- $\gamma$  production by Th1 cells, but has no effect on IL-4 production from Th2 clones [61]. 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.

### *Peptidergic/Sensory Nerves*

Lymphoid organs and blood vessels receive predominantly sympathetic and peptidergic/sensory innervation. The most abundant peptides are substance P (SP) and calcitonin gene-related peptide (CGRP), which are closely overlapping anatomically, but not necessarily colocalized in all sensory nerves, and vasoactive intestinal polypeptide (VIP), present in cholinergic nerves (see below). Whereas SP stimulates most macrophage functions and upregulates TNF- $\alpha$  and IL-12 production by monocytes and macrophages, CGRP down-regulates pro-inflammatory TNF- $\alpha$  and IL-12 production and potentiates IL-6 and IL-10 secretion through the CGRP1 receptor-cAMP/PKA pathway [62–67]. In addition, both SP and CGRP are strong vasodilators, CGRP being the most potent vasodilator yet discovered.

### *Parasympathetic (Cholinergic) System*

Recent evidence indicates that the efferent vagus nerve signaling is involved in immunoregulation. Thus, exposure of human macrophages, but not peripheral blood monocytes to acetylcholine, the principal vagal neurotransmitter, or to nicotine inhibits the release of pro-inflammatory cytokines TNF- $\alpha$ , IL-1 and IL-18, without affecting the anti-inflammatory cytokine IL-10 in re-

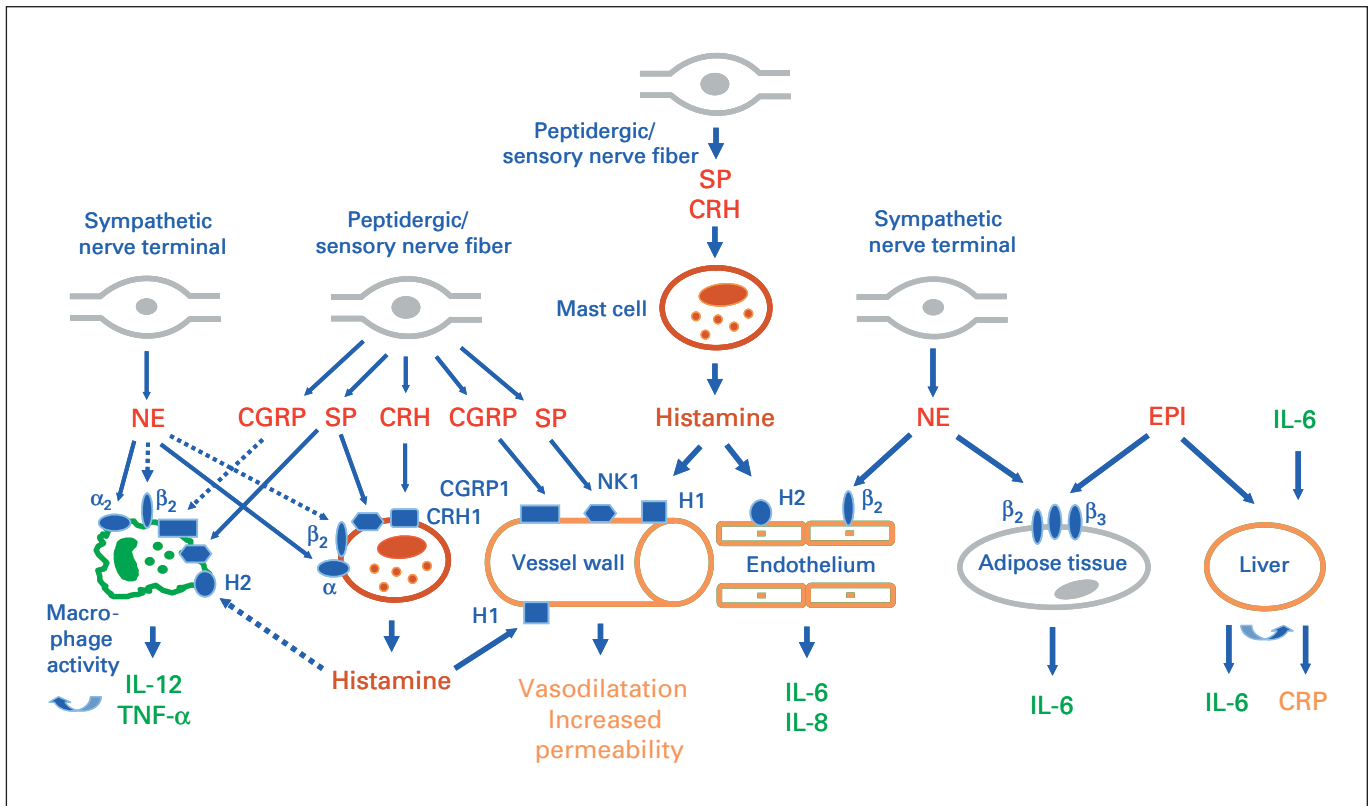
sponse to endotoxin [68, 69]. Moreover, direct electrical stimulation of the peripheral vagus nerve, in vivo, during experimental endotoxemia in rats suppresses TNF- $\alpha$  synthesis in liver and heart, attenuates peak serum TNF- $\alpha$  levels, and prevents the development of endotoxic shock [68, 69]. In addition to the VIPergic innervation of the lymphoid organs, activated T cells, and particularly Th2 cells, are the major VIP source in the immune system [67]. VIP inhibits TNF- $\alpha$  and IL-12 production, and stimulates the secretion of the anti-inflammatory cytokine IL-10, primarily through VPAC1 receptors on immune cells [67]. However, VIP induces marked vasodilation in most vascular beds.

### *Local versus Systemic Effects*

The systemic Th2-inducing properties of several hormones may not pertain to certain conditions or local responses in specific compartments of the body. Thus, steroid treatment results in a significant increase in the number of IL-12+ cells with concurrent reduction in the number of IL-13+-expressing cells in bronchial biopsy specimens of asthmatics. Interestingly, this occurs only in steroid-sensitive but not steroid-resistant asthmatic subjects [12]. The number of IL-4+ cells in the bronchial and nasal mucosa is also reduced by GC treatment [70, 71]. Furthermore, the synthesis of TGF- $\beta$ , another cytokine with potent anti-inflammatory activities, is enhanced by GCs in human T cells but suppressed in glial cells [72], and low doses of GCs can indeed activate alveolar macrophages, leading to increased lipopolysaccharide-induced IL-1 $\beta$  production [73].

NE, via stimulation of  $\alpha_2$ -ARs, can augment lipopolysaccharide-stimulated production of TNF- $\alpha$  by mouse peritoneal macrophages [74]. In rodents, induction of hemorrhage, a condition associated with elevations of systemic CA concentrations, or exposure of animals to mild inescapable electrical foot shock stress results in increased IL-1 $\beta$  and TNF  $\alpha$  production by alveolar macrophages and lung mononuclear cells [75, 76]. These effects are most likely indirect – in vitro, a direct modulatory effect of CAs on lipopolysaccharide-induced IL-1 $\beta$  by alveolar macrophages was not demonstrated. Thus, stress-induced changes in alveolar macrophage activity might result from alveolar type II epithelial cell activation, leading to the release of surfactant and/or other factors [76].

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 [77–80]. Furthermore, CAs (through



**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 Elenkov [146]). Solid lines represent stimulation and dashed lines inhibition.

$\beta_2$ -/ $\beta_3$ -ARs) and insulin up-regulate IL-6 production by human adipocytes [81, 82]. IL-6 is the major inducer of CRP production by the liver and both GCs and CAs enhance this induction [83]. Interestingly, histamine induces the production of both IL-6 and IL-8 by coronary artery endothelial cells, whereas chronic  $\beta$ -AR stimulation induces myocardial, but not systemic, production of TNF- $\alpha$ , IL-1 $\beta$  and IL-6 [84, 85] (fig. 2).

#### *Corticotropin-Releasing Hormone/Substance P-Mast Cell-Histamine Interactions*

Dr. George Chrousos emphasized that corticotropin-releasing hormone (CRH) is also secreted peripherally at inflammatory sites (*peripheral or immune CRH*) [86]. Immunoreactive CRH is identified locally in tissues from patients with RA, autoimmune thyroid disease and ulcerative colitis. CRH in early inflammation is of peripheral postganglionic sympathetic and sensory afferent nerve rather than immune cell origin [86, 87]. Peripheral CRH has vascular-permeability-enhancing and vasodilatory

actions. An intradermal CRH injection induces a marked increase in vascular permeability and mast cell degranulation, mediated through CRH type 1 receptors [88]. 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 [88–91]. Thus, peripheral CRH and SP activate mast cells via a CRH type 1 and NK1 receptor-dependent mechanism leading to the release of histamine and other contents of the mast cell granules that cause vasodilatation, increased vascular permeability and other manifestations of inflammation (fig. 2).

#### **Inflammation, Stress, Common Human Diseases and Well-Being**

Dr. George Chrousos addressed the complex interactions between inflammation and the adaptive responses in maintaining homeostasis, health, and well-being. He

stated that 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. A full-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 axis and the locus ceruleus-NE/sympathetic nervous system. The main effector substances of the systemic inflammatory response are inflammatory cytokines, such as TNF- $\alpha$ , IL-1 and IL-6, chemokines, such as IL-8, and other mediators of inflammation; the acute-phase reactants, mostly of hepatic origin, such as CRP, fibrinogen and plasminogen activator inhibitor 1; the effectors of the sensory afferent system, such as SP, and, of the stress system, namely hypothalamic CRH and vasopressin, cortisol, the CAs NE and EPI, and peripheral neuronal CRH [92–94].

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, 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 RA [25, 92, 95].

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 dia-

betes 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 complications due to atherosclerosis, but also those related to cancer and infection; they also cause significant morbidity, potentially including clinically significant osteoporosis. Chronic or intermittent but frequent inflammation due to the presence of inflammatory foci, such as those in allergic rhinitis, bronchial asthma, periodontitis, *Helicobacter pylori* infection or MS, 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 [25, 92, 93, 95, 96].

Interestingly, adipose tissue secretes large amounts of TNF- $\alpha$  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 frequently associated with some manifestations of the sickness syndrome, such as fatigue 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 [97, 98].

Dr. Alexandros Vgontzas (Milton S. Hershey Medical Center, Hershey, Pa., USA) noted that it is only in the last 15 years that there has been systematic study on changes in sleep during infection/inflammation. Recent studies in humans demonstrate the association between the pro-inflammatory cytokines IL-1, IL-6 and TNF- $\alpha$ , and sleep and sleep disturbances. These cytokines increase during nocturnal sleep, whereas their exogenous administration is associated with sleepiness and fatigue. Excessive daytime sleepiness and fatigue are a major public health concern but the mechanisms are not entirely clear. Levels of IL-6 and TNF- $\alpha$  are elevated in patients with disorders of excessive daytime sleepiness, and sleep disturbances

**Table 1.** Cytokines, dysfunction of the neural-immune interface and role of stress hormones in common human immune-related diseases

Disease group/condition	Disease or condition	Cytokines and Th profile	Comments	Role of stress hormones	References
Allergy/atopy	asthma	deficit in IL-12, overproduction of IL-4, IL-13, Th2 shift	the systemic Th2-inducing effects of stress hormones are antagonized by the local effects of GCs on Th2 cells and mast cell-mediator release	stress hormones and histamine may contribute to the deficit in IL-12 and overproduction of Th2 cytokines; stress may also activate the CRH-mast cell-histamine axis; this overall may induce/facilitate allergic reactions	25, 101, 102
Th1-related autoimmunity	RA, MS, autoimmune thyroid disease, diabetes type 1, CD	overproduction of IL-12, TNF- $\alpha$ , IFN- $\gamma$ ; deficit in IL-10, Th1 shift	stress may exacerbate RA through the activation of the CRH-mast cell-histamine axis (see text for details)	a hypoactive stress system may facilitate or sustain the Th1 shift (see text for details)	25, 107, 108, 111–113, 120
Major depression	melancholic depression	increased serum levels of IL-1, IL-6 and CRP	depression is associated with an increased risk of cardiovascular diseases	IL-1 and IL-6 induce hypercortisolemic and hypernoradrenergic state; alternatively CAs up-regulate IL-6 production, and thus increase its systemic levels	17–19, 121–123
Atherosclerosis	myocardial infarction, unstable angina, stroke	local overproduction of IFN- $\gamma$ , TNF- $\alpha$ , IL-1 $\beta$ , IL-8, IL-12, IL-18; systemic elevation in IL-6, IL-8, IL-1 $\beta$ and CRP	the effect of stress hormones on adipose tissue and lipid metabolism may facilitate their local pro-inflammatory effects	stress hormones and histamine may induce the production of pro-inflammatory cytokines by myocardium, endothelium and adipose tissues	20, 144, 145
Major injury	infection complications	suppressed cellular immunity and IL-12, and IFN- $\gamma$ production, overproduction of IL-10	major injury induces an overstimulation of the stress system followed by massive release of GCs, CAs and histamine	stress hormones and histamine may contribute to the deficit in IL-12 and cellular immunity and overproduction of Th2 cytokines, and thus contribute to severe immunosuppression and infection complications	25, 127–129
Sepsis		overproduction of TNF- $\alpha$ , IL-1 ?deficit in IL-10		inappropriate and defective systemic and local anti-inflammatory effects of stress hormones; CA and GC desensitization and resistance	23, 118, 124–126, 132–134

and obesity are the primary underlying factors of this elevation. Thus, hypercytokinemia is present in obese, otherwise healthy individuals, whereas it is highest in obese patients with sleep apnea. These results indicate that hypercytokinemia, particularly elevation of plasma IL-6 and TNF- $\alpha$  levels related to low-grade systemic inflammation, may play a role in mediating both excessive daytime sleepiness and cardiovascular complications associated with obesity and sleep disorders, such as sleep apnea. On the other hand, poor sleep or sleep deprivation in healthy individuals leads to a significant increase in daytime plasma concentrations of IL-6, and the circadian pattern of this cytokine correlates with daytime sleepiness and fatigue [97–100].

#### *Atopy/Allergy*

Drs. Gailen Marshall (University of Texas, Houston Medical School, Houston, Tex., USA), Ilia Elenkov and

George Chrousos noted that the effects of stress on atopic/allergic reactions are complex, at multiple levels and can be in either direction [25, 101, 102]. 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 [102]. 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 [25]. 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 [103]. This may also explain the beneficial effect of GCs and  $\beta_2$ -agonists on asthma. It is noteworthy that infusion of high doses of adrenaline (EPI), however, causes a rise in circulating histamine levels that may be due to an  $\alpha$ -adrenergic-mediated increase in mediator release [103]. 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. In vivo, ex vivo and in vitro exposure to GCs and  $\beta_2$ -agonists result in a reduction in IL-12 production, which persists at least several days [26, 30, 104]. Thus, GC and/or  $\beta_2$ -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 [30]. If, however, resting (cytokine-uncommitted) T cells are subsequently activated by APCs pre-exposed to GCs and/or  $\beta_2$ -AR agonists, enhanced IL-4 production, but limited IFN- $\gamma$  synthesis, could be induced [30]. Thus, while in the short term, the effect of GCs and  $\beta_2$ -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  $\beta_2$ -AR agonists potentiate the IgE production in vitro and in vivo [105, 106].

#### *Th1-Related Autoimmunity*

Drs. Esther Sternberg (National Institutes of Health, Bethesda, Md., USA), Ilia Elenkov and George Chrousos discussed the role of the neuroendocrine system in autoimmunity. It was postulated that a hypoactive stress system might facilitate or sustain the Th1 shift in Th1-mediated RA or MS [25, 107, 108]. Animal studies and certain clinical observations support this hypothesis. Thus, Fischer rats, which have a hyperactive stress system, are extremely resistant to experimental induction of Th1-mediated autoimmune states, including collagen- and adjuvant-induced arthritis and experimental allergic encephalomyelitis. Conversely, Lewis rats, which exhibit a hypoactive stress system, are extremely prone to develop the above-mentioned experimentally induced Th1-mediated disease models [109, 110]. Recent studies suggest that

suboptimal production of cortisol is involved in the onset and/or progression of RA [111–113]. 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- $\alpha$ , 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 [112]. Several lines of evidence indicate that the sympathetic-immune interface might also be defective in MS and RA [114–118]. Interestingly, patients with long-term RA have a highly significant reduction in sympathetic nerve fibers in synovial tissues with preponderance of about 10:1 for primary sensory, SP-positive fibers as compared with sympathetic fibers [119]. Thus, the reduction in sympathetic nerve fibers in chronic diseases may lead to uncoupling of the local inflammation from the anti-inflammatory input of sympathetic nerves. Since SP is a powerful pro-inflammatory agent, via release of histamine, TNF- $\alpha$  and IL-12, such preponderance may lead to an unfavorable pro-inflammatory state, supporting the disease process of RA. 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-D<sub>3</sub>-induced inhibition and subsequent rebound of IL-12 and TNF- $\alpha$  production may represent a major mechanism by which pregnancy and postpartum alter the course of or susceptibility to RA and MS [120].

#### *Depression and Atherosclerosis*

Dr. Philip Gold pointed out that 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 adrenocorticotropic hormone and CSF CRH levels, considering the degree of their hypercortisolism. These data suggest mutually reinforcing bidirectional links between a central hypernoradrenergic state and the hyperfunctioning of specific central CRH pathways that are driven and sustained by hypercortisolism, respectively [121]. On the other hand, Drs. Gold and Chrousos addressed advanced data indicating that the hypersomnia, hyperphagia, lethargy, fatigue, and relative apathy of the syndrome of atypical depression are associ-

ated with concomitant hypofunctioning of the CRH and locus ceruleus-NE systems [122, 123]. Drs. Gold and Chrousos also emphasized the strong association that exists between depression (melancholic) and osteoporosis. Endocrine factors such as depression-induced hypersecretion of CRH and hypercortisolism, hypogonadism, growth hormone deficiency and increased concentration of circulating IL-6, might play a crucial role in the bone loss observed in subjects suffering from major depression (melancholic). 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 in plasma IL-1 and IL-6 [18]. 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).

### *Sepsis*

Severe sepsis is a pathologic state in which organs distant from a site of infection do not function normally. Although pulmonary dysfunction, ARDS, is most common, hepatic dysfunction, renal failure, CNS derangement and cardiovascular dysfunction also occur. These phenomena may occur most often when systemic forces fail to control local inflammation. Although CNS dysfunction, including autonomic and hypothalamic-pituitary-adrenal axis dysfunction, undoubtedly plays a substantial role in the development of sepsis, the detailed mechanisms remain poorly understood. To complicate this further, the plasma compartment of the septic patient contains abnormal concentrations of more than 50 mediators, and disruption of normal pathways for interorgan and intercellular communication could contribute to a loss of physiologic complexity that may be a functional cause of multiple organ dysfunction [124–126].

Nevertheless, it appears that stress hormones interfere with the pro-/anti-inflammatory cytokine balance critical for maintaining homeostasis and the outcome during sepsis (see text above). Thus, a massive release of stress hormones and histamine triggered by major injury (serious traumatic injury, major burns or major surgical procedures), via inhibition of Th1 cytokines and induction of a Th2 shift, may contribute to the severe immunosuppression and infection complications, and, in some cases to sepsis, observed in these conditions [25, 127–129]. On the other hand, in established sepsis, an inappropriate low stress hormone release in response to the pro-inflammatory reaction would favor the overproduction of in-

flammatory mediators at local sites: first, by insufficient inhibition of pro-inflammatory cytokine production, and, second by insufficient induction of anti-inflammatory cytokines such as IL-10. Most importantly, efferent, inflammation-suppressing output from the CNS, including stress hormones, might be rendered insufficient to prevent systemic inflammation in several ways [25, 126].

The available evidence strongly suggests that there is an additional inadequate responsiveness to CNS-derived signals, which is caused by peripheral desensitization or tachyphylaxis. First, this is manifested by subnormal pressor response to NE most likely due to down-regulation of vascular endothelial and smooth muscle cell responsiveness to CAs. Interestingly, normalization of pressor response by the administration of hydrocortisone may reflect a GC-mediated increase in AR expression and sensitivity to cAMP. Second, the stimulation of cAMP production by circulating leukocytes is reduced in septic patients, which may determine diminution of IL-10 production.

In this context, the role of GC supplementation in patients with systemic inflammation is undergoing a cyclical reassessment stirred by the new understanding of the role of GC in modulating inflammation and immunity [130] and the positive results of recent randomized studies [131]. Dr. G. Umberto Meduri emphasized the role of GC inadequacy and/or resistance as an important pathophysiologic component of a dysregulated protracted systemic inflammatory response in ARDS. He presented evidence that prolonged GC therapy may be useful, not as an anti-inflammatory treatment per se, but as hormonal supplementation necessary to compensate for the host's inability to produce appropriately elevated levels of cortisol and/or for the inability of target organs to respond to endogenous cortisol. Thus, prolonged methylprednisolone administration in patients with unresolved ARDS enhanced GR-mediated activity, and thereby reduced NF- $\kappa$ B DNA binding and the consequent transcription of pro-inflammatory cytokines. As a result, patients treated with methylprednisolone, contrary to controls, had progressive and sustained reductions in plasma TNF- $\alpha$ , IL-1 $\beta$  and IL-6 levels over time and better survival rate. These findings provide support for the presence of systemic-inflammation-induced GC resistance in ARDS, underscore the central role played by activated GR $\alpha$  in regulating inflammation, and justify the pharmacological efficacy of prolonged methylprednisolone treatment in unresolved ARDS [23, 131–134].

## Conclusions

During an immune and inflammatory response, the brain and the immune system communicate with each other, and this process is essential for maintaining *homeostasis*. Thus, the CNS and the immune system are major *adaptive* systems of the body. 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 immune and inflammatory responses, the activation of the stress system, through induction of a Th2 shift, in conjunction with the increase in the ‘anti-inflammatory’ efferent vagus activity in visceral organs, may actually protect the organism from sys-

temic ‘overshooting’ with type 1/pro-inflammatory cytokines and other products of activated macrophages with tissue-damaging potential [25, 69, 92, 111, 118]. 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- $\alpha$  and CRP production and through activation of the CRH/SP-histamine axis. Thus, a dysfunctional neuroendocrine-immune interface associated with abnormalities in 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, as well as atherosclerosis and infections (not discussed here [25, 26, 135–143]). 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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