Stress Hormones, Th1/Th2 patterns, Pro/Anti-inflammatory Cytokines and Susceptibility to Disease

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George Chrousos
Aghia Sophia Children's Hospital

Stress Hormones, Th1/Th2 patterns, Pro/Anti-inflammatory Cytokines and Susceptibility to Disease

Ilia J. Elenkov and George P. Chrousos

In general, stress has been regarded as immunosuppressive. Recent evidence, however, indicates that acute, subacute or chronic stress might suppress cellular immunity but boost humoral immunity. This is mediated by a differential effect of stress hormones, the glucocorticoids and catecholamines, on T helper 1 (Th1)/Th2 cells and type 1/type 2 cytokine production. Furthermore, acute stress might induce pro-inflammatory activities in certain tissues through neural activation of the peripheral corticotropin-releasing hormone–mast cell–histamine axis. Through the above mechanisms, stress might influence the onset and/or course of infectious, autoimmune/inflammatory, allergic and neoplastic diseases.

The neuroendocrine and immune systems play major roles in adaptation. Any 'stressor' or threat to the stability of the internal milieu is counteracted by responses of the organism: 'the adaptive responses'. The effectors of these responses are the corticotropin-releasing hormone (CRH) and locus ceruleus-noradrenaline (LC-NA)/autonomic (sympathetic) neurons of the hypothalamus and brain stem, which regulate the peripheral activities of the hypothalamic–pituitary–adrenal (HPA) axis and the systemic/adrenomedullary sympathetic nervous systems (SNS), respectively. Activation of the HPA axis and LC-NA/autonomic system result in systemic elevations of glucocorticoids and catecholamines (CAs), respectively, which act in concert to maintain the steady state or homeostasis[1].

Any immune challenge that threatens the stability of the internal milieu can be regarded as a stressor. The past 15 years have provided evidence that certain cytokines, especially tumor necrosis factor α (TNF-α?, interleukin 1 (IL-1), IL-6 and leukemia inhibitory factor (LIF) activate the stress system *in vivo*[1–4]. Moreover, these cytokines, either alone or in conjunction with components of the stress system and the classic stress hormones, induce fever, sleepiness, fatigue, loss of appetite and decreased libido, and activate the hepatic synthesis of acute phase proteins – changes referred to as 'sickness behavior' and 'acute-phase response', respectively. Stress that is associated with an immune challenge has been called immune or inflammatory stress[1] and, like other forms of stress, is coordinated by the central stress system and its peripheral arms (Fig. 1).

For more than 20 years, stress hormones, particularly glucocorticoids, have been known to inhibit lymphocyte/leukocyte proliferation, migration and cytotoxicity, as well as the secretion of certain cytokines, such as IL-2 and interferon γ (IFN-γ??. These early observations, in the context of the broad clinical use of glucocorticoids as potent anti-inflammatory drugs in the past 50 years, initially led to the conclusion that stress was, in general, immunosuppressive. Recently, however, there has been convincing evidence that glucocorticoids and CAs, at levels that can be achieved during stress, influence the immune response in a less monochromatic way. This new understanding helps explain some well-known, but often contradictory, effects of stress on the immune system and on the onset and course of infections, as well as infectious complications after major injury and autoimmune/inflammatory, allergic and neoplastic diseases. It is our intention to provide a brief up-to-date review of this understanding.

• Role of Th1 and Th2 Cells and Type 1 and Type 2 Cytokines in the Regulation of Cellular and Humoral Immunity

Immune responses are regulated by antigen-presenting cells (APCs), such as monocytes/macrophages, dendritic cells and other phagocytic cells, which are components of innate immunity, and by the recently described T helper (Th) lymphocyte subclasses Th1 and Th2, which are components of acquired (adaptive) immunity[5,6] (Fig. 2). Th1 cells primarily secrete IFN-γ, IL-2 and 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.

Naive CD4$^{\lessgtr}$ (antigen-inexperienced) Th0 cells are clearly bipotential and serve as precursors of Th1 and Th2 cells. Among the factors currently known to influence the differentiation of these cells towards the Th1 or Th2 subsets, cytokines produced by cells of the innate immune system are the most important. Thus, IL-12, produced by activated monocytes/macrophages or other APCs, is a major inducer of Th1 differentiation and hence cellular immunity; this cytokine acts in concert with natural killer (NK)-cell-derived IFN-γ to promote Th1 responses[7]. APC-derived IL-12 and TNF-α, in concert with NK- and Th1-cell-derived IFN-γ??stimulate the functional activity of T cytotoxic (Tc) cells, NK cells and activated macrophages, which constitute the major components of cellular

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I.J. Elenkov and G.P. Chrousos are at the Pediatric Endocrinology Section, Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, USA; I.J. Elenkov is also at the Inflammatory Joint Diseases Section, Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892, USA.

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immunity. All three 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 these crucial and synergistic roles in inflammation, IL-12, TNF-α and IFN-γ are considered the major pro-inflammatory cytokines[5–7].

Th1 and Th2 responses are mutually inhibitory. Thus, IL-12 and IFN-γ inhibit Th2, and IL-4 and IL-10 inhibit Th1 responses. 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 inhibit macrophage activation, T-cell proliferation and the production of pro-inflammatory cytokines[5,6]. Thus, IL-4 and IL-10 are the major anti-inflammatory cytokines[5,6] (Fig. 1).

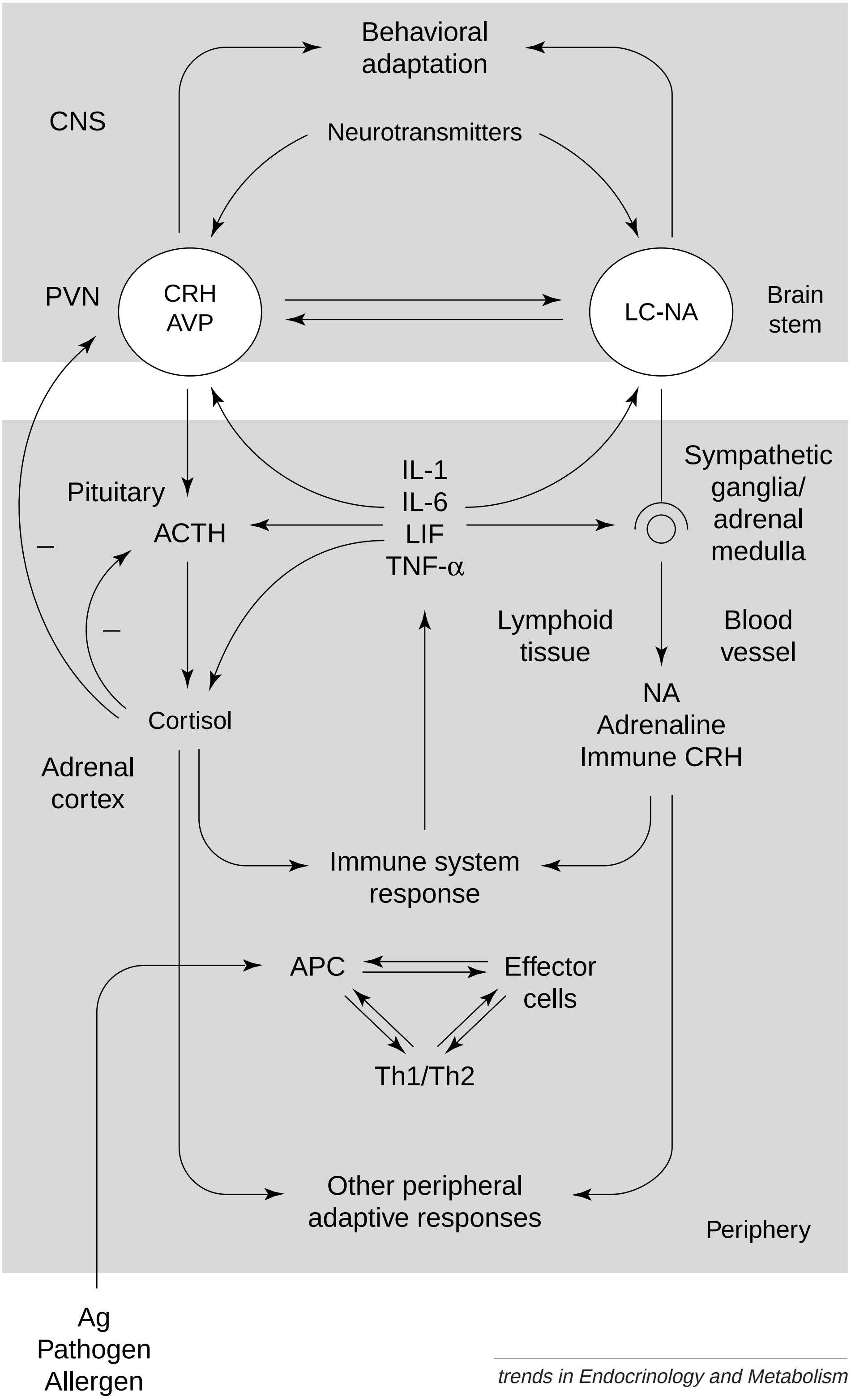

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Figure 1. Simplified representation of the CRH and LC-NA/autonomic (sympathetic) systems, their peripheral components, their role in central and peripheral adaptive responses, and their relationships to functions of the immune system (see text). Abbreviations: –, inhibition; ACTH, adrenocorticotropic hormone; Ag, antigen; APC, antigen-presenting cell; AVP, arginine vasopressin; CNS, central nervous system; CRH, corticotropin-releasing hormone; IL, interleukin; LC-NA, locus ceruleus-noradrenaline/autonomic (sympathetic) system; LIF, leukemia inhibitory factor; NA, noradrenaline; PVN, paraventricular nucleus; Th, T helper cell; TNF-α, tumor necrosis factor α.

Stress Hormones Suppress Cellular and Potentiate Humoral Immunity

Effects of Glucocorticoids

Previous studies have shown that glucocorticoids suppress the production of TNF-α??IFN-γ and IL-2 *in vitro* and *in vivo* in animals and humans[1]. As recently shown, glucocorticoids also act through their classic cytoplasmic/nuclear receptors on APCs to suppress the production of the main inducer of Th1 responses, IL-12, *in vitro* and *ex vivo*[8,9]. Because IL-12 is extremely potent in enhancing IFN-γ and inhibiting IL-4 synthesis by T cells, the inhibition of IL-12 production might be a major mechanism by which glucocorticoids affect the Th1/Th2 balance. Thus, glucocorticoid-treated monocytes/macrophages produce significantly less IL-12, leading to a decreased capacity of these cells to induce IFN-γ production by antigen-primed $CD4^{\leqslant}$ T cells. The same treatment of monocytes/macrophages is also associated with an increased production of IL-4 by T cells, probably as a result of blocking the suppressive effects of IL-12 on Th2 activity[10] (Fig. 3). Furthermore, glucocorticoids potently downregulate the expression of IL-12 receptors on T and NK cells. This explains why human peripheral blood mononuclear cells (PBMCs) stimulated with immobilized anti-CD3 antibody lose their ability to produce IFN-γ? in the presence of glucocorticoids[11]. Thus, although glucocorticoids might have a direct suppressive effect on Th1 cells, the overall inhibition of IFN-γ production by these cells appears to result mainly from the inhibition of IL-12 production by APCs and from the loss of IL-12 responsiveness in NK and Th1 cells.

It is particularly noteworthy that glucocorticoids have no effect on the production of the potent anti-inflammatory cytokine IL-10 by monocytes[8,12]; yet, lymphocyte-derived IL-10 production appears to be upregulated by glucocorticoids. Thus, rat $CD4^{\lessgtr}$ T cells pretreated with dexamethasone have increased levels of mRNA encoding IL-10 (Ref. 13). Similarly, during experimental endotoxemia or cardiopulmonary bypass, or in patients with multiple sclerosis (MS) having an acute relapse, treatment with glucocorticoids is associated with increased plasma IL-10 secretion[12,14,15]. This could be the result of a direct stimulatory effect of glucocorticoids on T-cell IL-10 production and/or a block on the restraining inputs of IL-12 and IFN-γ on monocyte/lymphocyte IL-10 production.

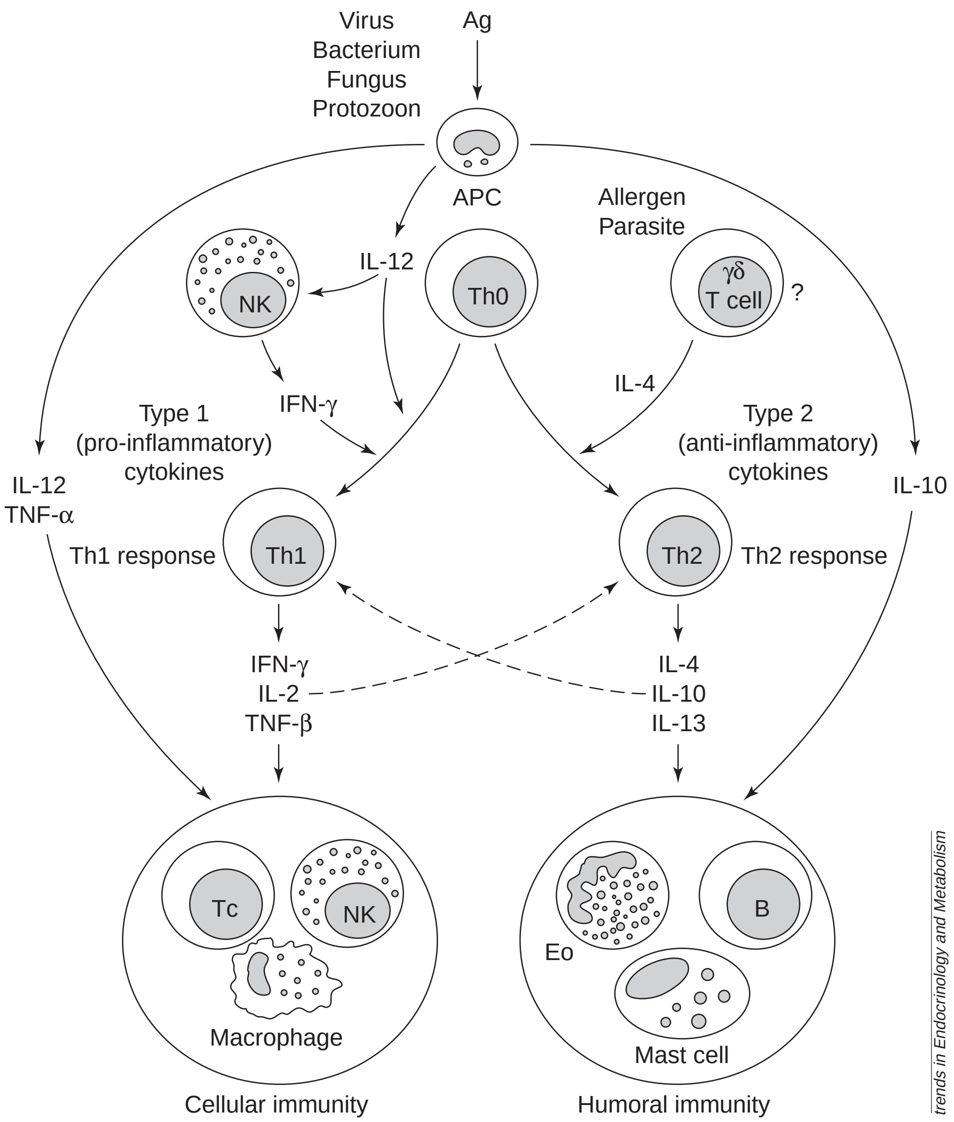

Figure 2. Role of Th1 and Th2 cells, and type 1 and type 2 cytokines, in the regulation of cellular and humoral immunity. Cellular immunity provides protection against intracellular bacteria, protozoa, fungi and several viruses, whereas humoral immunity provides protection against multicellular parasites, extracellular bacteria, some viruses, soluble toxins and allergens (see text). Solid lines represent stimulation, dashed lines inhibition. Abbreviations: Ag, antigen; APC, antigen-presenting cell; B, B cell; Eo, eosinophil; IFN-γ, interferon γ; IL, interleukin; NK, natural killer cell; Tc, T cytotoxic cell; Th, T helper cell, TNF-α, tumor necrosis factor α.

Effects of CAs

CAs drive a Th2 shift, both at the level of APCs and Th1 cells (Fig. 3). We demonstrated recently that NA and adrenaline potently inhibited or enhanced the production of IL-12 and IL-10, respectively, in human whole blood cultures stimulated with lipopolysaccharide (LPS) *ex vivo*[8]. These effects are mediated by stimulation of β-adrenoceptors (ARs), as they are completely prevented by propranolol, a β-AR antagonist. Our findings were subsequently extended by other laboratories showing that non-selective β-AR agonists and selective $β_2$-AR agonists inhibited the production of IL-12 *in vitro* and *in vivo*[16,17]. In conjunction with their ability to suppress IL-12 production, $β_2$-AR agonists inhibited the development of Th1-type cells, while promoting Th2 cell differentiation[16].

$?_?$-ARs are expressed on Th1 cells, but not on Th2 cells[18]. This might provide an additional mechanistic basis for a differential effect of CAs on Th1/Th2 functions. In fact, in both murine and human systems, $β_2$-AR agonists inhibit IFN-γ production by Th1 cells, but do not affect IL-4 production by Th2 cells[18,19]. Importantly, the differential effect of CAs on type 1/type 2 cytokine production also operates *in vivo*. Thus, increasing sympathetic outflow in mice by selective $α_2$-AR antagonists or application of β-AR agonists results in inhibition of LPS-induced TNF-α and IL-12 production[17,20,21]; in humans, the administration of the $β_2$-AR agonist salbutamol results in inhibition of IL-12 production *ex vivo*[16], and acute brain trauma that is followed by a massive release of CAs triggers secretion of substantial amounts of systemic IL-10 (Ref. 22).

CAs exert tonic inhibition on the production of pro-inflammatory cytokines *in vivo*. Application of propranolol,

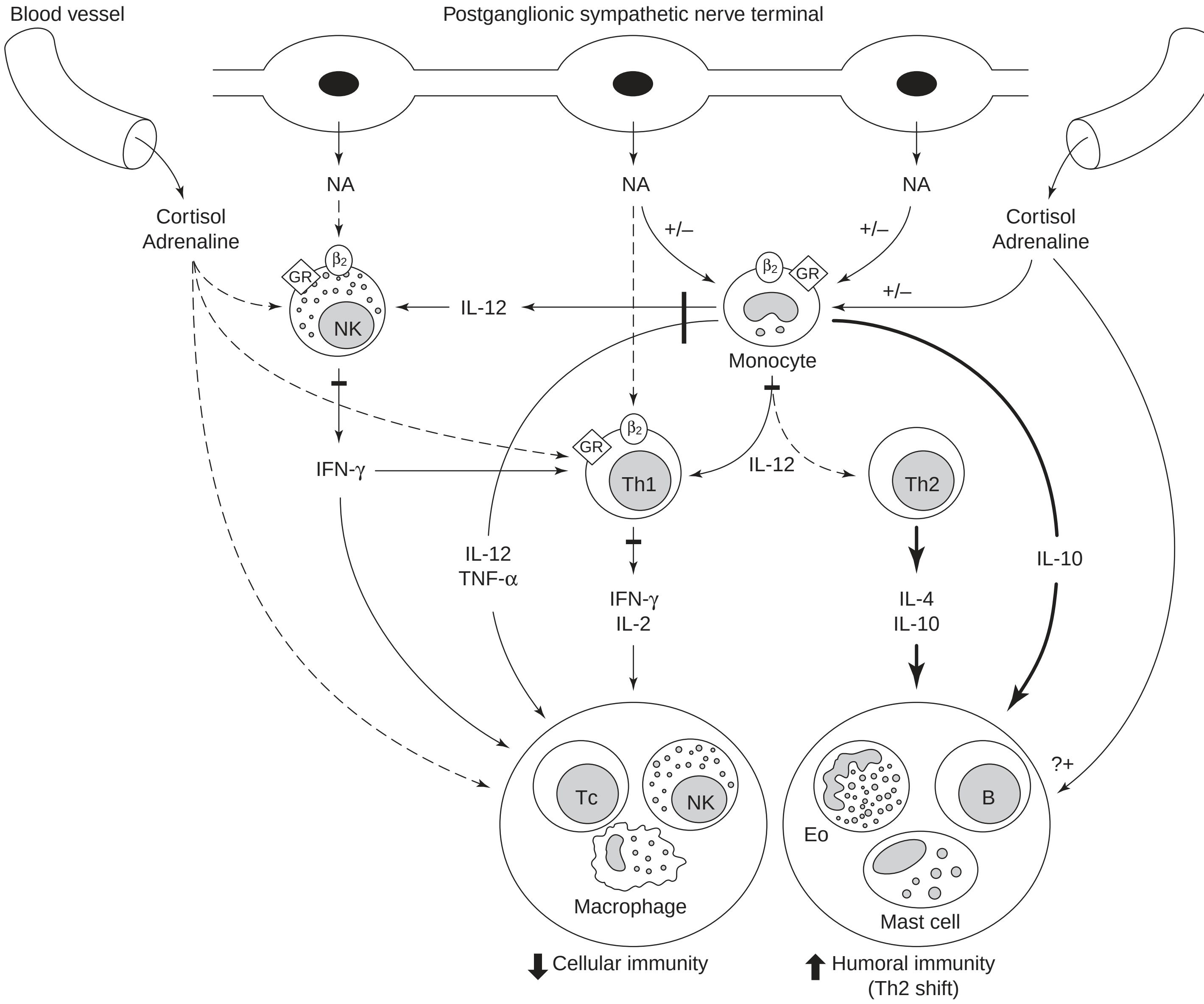

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Figure 3. Stress influences immunity by stimulating cortisol and adrenaline secretion from the adrenal cortex and medulla, respectively, and the release of noradrenaline from the postganglionic sympathetic nerve terminals in blood vessels and lymphoid organs. The systemic effects of glucocorticoids and catecholamines on the production of key regulatory type 1 and type 2 cytokines, Th1 and Th2 functions, and components of cellular and humoral immunity are shown. Solid lines represent stimulation, heavy solid lines represent increased stimulation and dashed lines represent inhibition. Abbreviations: β2, β-2-adrenoceptor; +/–, stimulation/inhibition; B, B cell; Eo, eosinophil; GR, glucocorticoid receptor; IFN-γ, interferon γ; IL, interleukin; NA, noradrenaline, NK, natural killer cell; Tc, T cytotoxic cell; Th, T helper cell; TNF-α, tumor necrosis factor α

which blocks the inhibitory effect of β-ARs on cytokine-producing cells, results in substantial increases of LPS-induced secretion of TNF-α and IL-12 in mice[17,21]. Thus, systemically, both glucocorticoids and CAs, through inhibition and stimulation of type 1 and type 2 cytokine secretion, respectively, cause selective suppression of cellular immunity and a shift towards Th2-mediated humoral immunity. This is substantiated by studies showing that stress hormones inhibit the effector function of cellular immunity components – the activity of NK cells, Tc cells and activated macrophages. For example, CAs are potent inhibitors of NK-cell activity, both directly, acting on ?-ARs expressed on these cells, or indirectly, though suppression of the production of IL-12 and IFN-γ, cytokines essential for NK-cell activity[8,23,24]. It appears that NK cells are the ones most 'sensitive' to the suppressive effect of stress; indeed, NK-cell activity has been used as an index of stress-induced immunosuppression in many studies (reviewed in Ref. 25).

The above general conclusion on the effects of stress hormones on Th1/Th2 balance might not pertain to certain conditions or local responses in specific compartments of the body. Thus, the synthesis of transforming growth factor β (TGF-β), another type 2 cytokine with potent anti-inflammatory activities, is differentially regulated by glucocorticoids: it is enhanced in human T cells but suppressed in glial cells[26]. In addition, NA, via stimulation of α_2-ARs, can augment LPS-stimulated production of TNF-α from mouse peritoneal macrophages[27], while hemorrhage, a condition associated with elevations of systemic CA concentrations, increases the production of TNF-? and IL-1 by lung mononuclear cells via stimulation?of α-AR (Ref. 28). Because the response to β-AR agonist stimulation wanes during the maturation of human monocytes into macrophages[29], it is possible that in certain compartments of the body the α-AR-mediated effect of CAs becomes transiently dominant. Through this mechanism, CAs might boost local cellular immune responses in a transitory fashion. This is substantiated by the finding that CAs potentiate the production of IL-8 from PBMCs and epithelial cells of the lung[30], which probably promotes the recruitment of polymorphonuclear leukocytes to this organ. Thus, in summary, although stress hormones suppress Th1 responses and pro-inflammatory cytokine secretion and boost Th2 responses systemically, they might differently affect certain local responses. Further studies are needed to address this question.

• Further Complexities: the CRH–Mast Cell–Histamine Axis

Central, hypothalamic CRH might influence the immune system indirectly, through activation of the end products of the peripheral stress response, such as glucocorticoids and CAs. CRH, however, is also secreted peripherally at inflammatory sites (peripheral or immune CRH) and influences the immune system directly, through local modulatory actions[1,31]. We identified immunoreactive CRH locally in: (1) experimental carrageenin-induced subcutaneous aseptic inflammation[31]; (2) streptococcal-cell-wall- and adjuvant-induced arthritis; (3) retinol-binding protein (RBP)-induced uveitis; and (4) human tissues from patients with various autoimmune /inflammatory diseases, including rheumatoid arthritis, autoimmune thyroid disease and ulcerative colitis (cf. Ref. 32). The demonstration of CRH-like immunoreactivity in the dorsal horn of the spinal cord, dorsal root ganglia and sympathetic ganglia support the hypothesis that most of the immune CRH in early inflammation is of peripheral nerve rather than immune cell origin (cf. Ref. 32).

Peripheral CRH has pro-inflammatory and vascular permeability-enhancing and vasodilatory actions. Thus, systemic administration of specific CRH antiserum blocks the inflammatory exudate volume and cell number in carrageenin-induced inflammation and RBP-induced uveitis, and inhibits stress-induced intracranial mast cell degranulation[31,33]. In addition, CRH administration to humans or nonhuman primates causes major peripheral vasodilation, which is manifested as flushing and increased blood flow and hypotension[34]; an intradermal CRH injection induces a marked increase of vascular permeability and mast cell degranulation[35]. Importantly, this effect is mediated through CRH type 1 receptors and is stronger than the effect of an equimolar concentration of C48/80, a potent mast cell secretagog[35]. Thus, it appears that the mast cell is a major target of immune CRH. This has an anatomic prerequisite: in blood vessels, periarterial sympathetic plexuses are closely associated with mast cells lining the perivascular regions, and plexuses of nerve fibers (noradrenergic and peptidergic) within lymphoid parenchyma are also closely associated with clusters of mast cells. Interestingly, recent evidence suggests that urocortin, a newly discovered member of the CRH family, which binds to the same receptors as CRH, is produced by human lymphocytes and Jurkat T lymphoma cells[36]. Thus, this peptide might also participate in the peripheral CRH-receptor-mediated inflammatory response.

Histamine, a major product of mast cell degranulation, is a well-recognized mediator of acute inflammation and allergic reactions. These actions are mainly mediated by activation of H1 histamine receptors and include vasodilation, increased permeability of the vessel wall, edema and, in the lungs, bronchoconstriction. Thus, it is conceivable that CRH activates mast cells via a CRH receptor type 1-dependent mechanism, leading to the release of histamine and other contents of the mast cell granules that subsequently cause vasodilation, increased vascular permeability and other manifestations of inflammation (Fig. 4).

The past 10–15 years have provided strong evidence that histamine might have important immunoregulatory functions via H2 receptors expressed on immune cells (reviewed in Ref. 37). We have found recently that histamine, via stimulation of H2 receptors on peripheral monocytes and subsequent elevation of cAMP, inhibits the secretion of human IL-12 and stimulates the production of IL-10 (Ref. 38). Our data are consistent with previous studies showing that histamine, via H2 receptors, also inhibits TNF-α production from monocytes and IFN-γ production by Th1-like cells, but has no effect on IL-4 production from Th2 clones[39]. Thus, histamine, similarly to CAs, appears to drive a Th2 shift at the level of both APCs and Th1 cells. Thus, the activation of the CRH–mast cell–histamine axis through stimulation of H1 receptors might induce acute inflammation and allergic reactions, whereas through activation of H2 receptors it might induce suppression of Th1 responses and a Th2 shift (Fig. 4).

Clinical Implications

Infections

A major factor governing the outcome of infectious diseases is the selection of Th1- versus Th2-predominant adaptive responses during and after the initial invasion of the host. Thus, stress, and the consequent stress-induced Th2 shift, might have a profound effect on the susceptibility of the organism to infection and/or might influence the course of an infection, the defense against which is primarily through cellular immune mechanisms (Table 1).

Cellular immunity, particularly IL-12 and IL-12-dependent IFN-γ secretion in humans, seems to be essential in the control of mycobacterial infections[40]. In the 1950s, Thomas Holmes (cf. Ref. 41) reported that individuals who had experienced stressful life events were more likely to develop tuberculosis and less likely to recover from it. Although it is

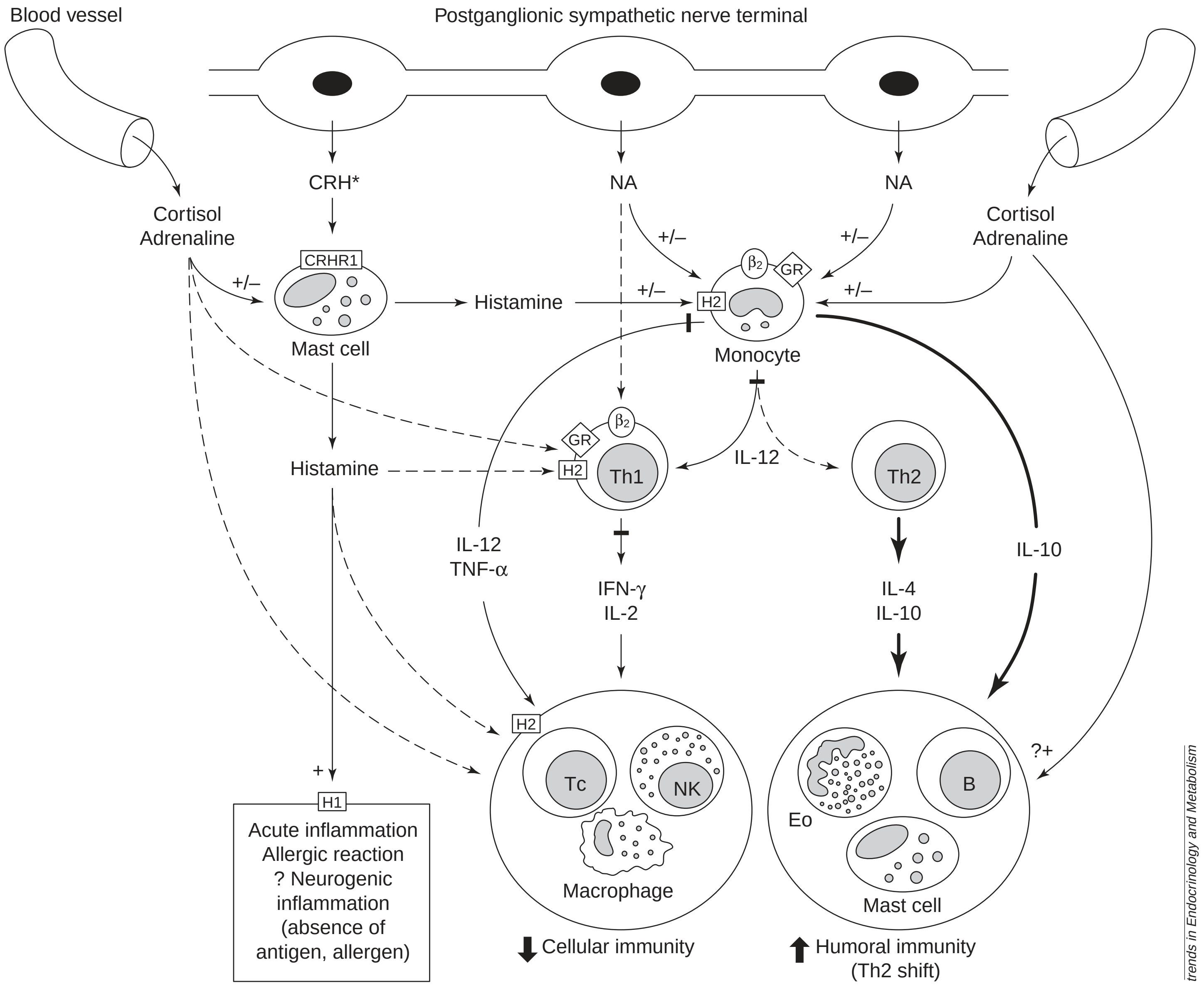

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Figure 4. Stress and CRH influence immune/inflammatory and allergic responses by stimulating glucocorticoid, catecholamines and peripheral (immune) CRH secretion and by altering the production of key regulatory cytokines and histamine (see text). *CRH is also released from sensory nerves upon their activation. Solid lines represent stimulation, heavy solid lines represent increased stimulation and dashed lines represent inhibition. Abbreviations: β2, β-2-adrenoceptor; +/–, stimulation/inhibition; B, B cell; CRH, peripheral (immune) corticotropin-releasing hormone; CRHR1, CRH receptor 1; Eo, eosinophil; GR, glucocorticoid receptor; H1/H2, histamine 1/2 receptors; IFN-

still a matter of some speculation, stress-hormone-induced inhibition of IL-12 and IFN-γ production, and the consequent suppression of cellular immunity, might explain the pathophysiological mechanisms of these observations.

Helicobacter pylori infection is the most common cause of chronic gastritis, which in some cases progresses to peptic ulcer disease. The role of stress in promoting peptic ulcers has been recognized for many years. Thus, increased systemic stress hormone levels, in concert with an increased local concentration of histamine, induced by inflammatory or stress-related mediators, might skew the local responses towards Th2-type responses and thus, might allow the onset or progression of a *H. pylori* infection.

Human immunodeficiency virus (HIV)-positive patients have IL-12 deficiency, while disease progression has been correlated with a Th2 shift. The innervation (primarily sympathetic/noradrenergic) of lymphoid tissue might be particularly relevant to HIV infection, as lymphoid organs represent the primary site of HIV pathogenesis. In fact, as recently shown, NA, the major sympathetic neurotransmitter released locally in lymphoid organs[42,43], is able to accelerate HIV-1 replication directly, by up to 11-fold in acutely infected human PBMCs (Ref. 44). The effect of NA on viral replication is transduced via the β-AR–adenylyl cyclase–cAMP–PKA (protein kinase A) signaling cascade[44]. In another recent study, Haraguchi *et al.* found that the induction of intracellular cAMP by a synthetic, immunosuppressive, retroviral envelope peptide caused a shift in the cytokine balance and led to suppression of cell-mediated immunity by inhibiting IL-12 and stimulating IL-10 production[45].

Progression of HIV infection is also characterized by increased cortisol secretion in both the early and late stages of the disease. Thus, increased glucocorticoid production, probably triggered by the chronic infection, was recently proposed to contribute to HIV progression[46]. In another recent study, Kino *et al*. found that one of the HIV-1 accessory proteins, Vpr, acts as a potent coactivator of the host glucocorticoid receptor, rendering lymphoid cells hyperresponsive to glucocorticoids[47]. Thus, on the one hand, stress hormones suppress cellular immunity and, hence, accelerate HIV replication, while, on the other hand, retroviruses might suppress cell-mediated immunity using the same pathways by which stress hormones, including CAs and glucocorticoids, alter the Th1/Th2 balance.

In a recent study, an association was shown between stress and the susceptibility to the common cold among 394 individuals who had been intentionally exposed to five different upper respiratory tract viruses. Psychological stress was found to be associated in a dose-dependent manner with an increased risk of acute infectious respiratory illness, and this risk was attributed to increased rates of infection rather than to an increased frequency of symptoms after infection[48]. Thus, stress hormones, through their selective inhibition of cellular immunity, might play important roles in the increased risk of an individual to acute respiratory infections caused by common cold viruses.

Major Injury

Major injury (serious traumatic injury and major burns) or major surgical procedures often lead to severe immunosuppression, which contributes to infectious complications, and in some cases to sepsis, the most common cause of late death after trauma. A strong stimulation of the SNS and the HPA axis correlates with the severity of both cerebral and extracerebral injury and an unfavorable prognosis (cf. Ref. 22). In patients with traumatic major injury, and in animal models of burn injury, the suppressed cellular immunity is associated with reduced production of IFN-γ and IL-12 and increased production of IL-10 (a Th2 shift)[49]. A recent study indicated that systemic release of IL-10 triggered by SNS activation might be a key mechanism of immunosuppression after injury. Thus, high levels of systemic IL-10 documented in patients with 'sympathetic storm', resulting from acute accidental or iatrogenic brain trauma, were associated with a high incidence of infection[22]. In a rat model, the increase of IL-10 was prevented by β-AR blockade[22], and cellular immunity was improved in burned mice after H2 histamine receptor blockade[37]. Therefore, stress hormones and histamine secretion triggered by major injury, via an induction of a Th2 shift, might contribute to the severe immunosuppression and infections seen in these conditions.

Autoimmunity

Several autoimmune diseases are characterized by common alterations of the Th1 versus Th2, and IL-12/TNF-α versus IL-10, balance (Table 1). In rheumatoid arthritis (RA), MS, type 1 diabetes mellitus, autoimmune thyroid disease (ATD) and Crohn's disease (CD) 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 are deficient. This appears to be a crucial factor that determines the proliferation and differentiation of Th1-related autoreactive cellular immune responses in such disorders[50]. On the other hand, systemic lupus erythematosus (SLE) is associated with a Th2 shift and an excessive production of IL-10, whereas IL-12 and TNF-α production appear to be deficient.

The effect of stress on autoimmunity is extremely complex; often, stress is related to both induction/exacerbation and amelioration of disease activity[51,52]. Animal studies and certain clinical observations suggest that a hyperactive or hypoactive stress system might be associated with decreased or increased vulnerability to different types of autoimmune diseases. Thus, Fischer rats, which have a hyperactive stress system, are extremely resistant to experimental induction of Th1-mediated autoimmune states, including arthritis, uveitis and experimental allergic encephalomyelitis (EAE)[52]. Similarly, women in the third trimester of pregnancy, who have increased levels of cortisol, experience remission of Th1-type-mediated autoimmune diseases, such as RA, MS, type 1 diabetes mellitus and ATD, possibly via suppression of pro-inflammatory (IL-12 and TNF-α) and potentiation of anti-inflammatory (IL-4 and IL-10) cytokine production[52,53]. Through a reciprocal mechanism, Th2-type-mediated autoimmune disorders mainly driven by IL-10, such as SLE, can flare up in high cortisol and CA output states, such as during stress or pregnancy[52,53]

Conversely, Lewis rats, which possess a hypoactive HPA axis, are extremely prone to develop experimentally induced Th1-mediated states, such as arthritis, uveitis or EAE (Ref. 52). Similarly, clinical situations associated with decreased stress system activity are associated with increased expression or susceptibility to Th1-type-mediated autoimune diseases such as RA, MS and ATD. These are the postpartum period and the period that follows cure of endogenous Cushing's syndrome or discontinuation of glucocorticoid therapy[1,8,52]. This might also include the period that follows cessation of chronic stress or a rebound effect upon relief from stressors.

Epidemiological studies suggest that severe stress, as reported by many patients, often precedes the development of certain Th1-mediated autoimmune states. Viral induction of autoimmunity is thought to occur either by bystander T-cell activation or molecular mimicry. Recent studies suggest that tissue-tropic coxsackie B4 virus is associated with the development of type 1 diabetes mellitus, as a result of bystander damage, whereas human parvoviruses might be causative agents for RA (Refs 54,55). If future studies confirm these hypotheses, severe stress, and hence severe suppression of cellular immunity, might prove to be a crucial factor that facilitates the establishment of pathogenic and tissue-tropic viral infection followed by autoimmune tissue damage. At a later stage, severe stress, by skewing the balance towards Th2 responses, might ameliorate disease activity, whereas acute stress and peripheral release of immune CRH, through its pro-inflammatory effects, might exacerbate disease activity in some cases.

Allergy/Atopy

Allergic reactions of type 1 hypersensitivity (atopy), such as asthma, eczema, hay fever, urticaria and food allergy, are characterized by dominant Th2 responses, overproduction of histamine and a shift to IgE production. As in autoimmunity, the effects of stress on atopic reactions are complex, at multiple levels, and can be in either direction. Stress hormones acting at the level of APCs and lymphocytes might induce a Th2 shift, and thus facilitate or sustain atopic reactions; however, this can be antagonized by their effects on the mast cell (Fig. 4). Glucocorticoids and CAs (through β_2-ARs) suppress the release of histamine by mast cells, thus abolishing its pro-inflammatory, allergic and bronchoconstrictor effects. Consequently, reduced levels of epinephrine and cortisol in the very early morning could contribute to nocturnal wheezing and have been linked to high circulating histamine levels in asthmatics[56]. This might also explain the beneficial effect of glucocorticoids and β_2-AR agonists in asthma. It is noteworthy that infusion of high doses of adrenaline, however, causes a rise in circulating histamine levels that might be the result of an α-adrenergic-mediated increase in mediator release (cf. Ref. 56). Thus, severe acute stress associated with high adrenaline 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 (Fig. 4).

Glucocorticoids alone or in combination with β_2-AR agonists are broadly used in the treatment of atopic reactions, particularly asthma. *In vivo*, *ex vivo* and *in vitro* exposure to glucocorticoids and β_2-AR agonists result in a reduction of IL-12 production, which persists for at least several days[8,10,16]. Thus, glucocorticoid and/or β_2-AR agonist therapy is likely to reduce the capacity of APCs to produce IL-12, to suppress greatly the synthesis of type 2 cytokines in activated but not resting T cells, and to abolish eosinophilia[10]. If, however, resting (cytokine-uncommitted) T cells are subsequently activated by APCs pre-exposed to glucocorticoids and/or β_2-AR agonists, enhanced IL-4 production, but limited IFN-γ synthesis, could be induced[10]. Thus, although in the short term the effect of glucocorticoids and β_2-AR agonists might be beneficial, their long-term effects might be to sustain the increased vulnerability of the patient to the allergic condition. This is substantiated by the observations that both glucocorticoids and β_2-AR agonists potentiate IgE production *in vitro* and *in vivo*[57,58].

Tumor Growth

The amount of IL-12 available at the tumor site appears to be crucial for tumor regression[59]. Thus, low levels of IL-12 have been associated with tumor growth, as opposed to the tumor regression observed with administration of IL-12 delivered *in situ* or systemically. On the other hand, local overproduction of IL-10 and TGF-β? by inhibiting the production of IL-12 and TNF-α, and the cytotoxicity of NK and Tc cells, seems to play an inappropriate immunosuppressive role, allowing increased malignant tumor growth, as seen for example in melanoma[60]. These and other studies suggest that Th1 function is locally downregulated during tumor growth.

Several lines of evidence suggest that stress can increase the susceptibility to tumors, tumor growth and metastases. In animals, β-AR stimulation suppresses NK-cell activity and compromises resistance to tumor metastases[61]; stress decreases the potential of spleen cells to turn into antitumor Tc cells against syngeneic B16 melanoma, and it significantly suppresses the ability of tumor-specific $CD4^{\leqslant}$ cells to produce IFN-γ and IL-2 (Ref. 62). In humans, the augmentation of the rate of tumor progression and cancer-related death has been associated with stress (cf. Ref. 62), whereas treatment with cimetidine, an H2 histamine antagonist, correlated with increased survival in patients with gastric and colorectal cancer[63]. In fact, high concentrations of histamine have been measured within colorectal and breast cancer tissues and large numbers of mast cells have been identified within certain tumor tissues (cf. Ref. 38). These data suggest that stress-hormone/histamine-induced suppression of cellular immunity might contribute to increased growth of certain tumors.

• Conclusions

Stress–immune system interactions are undoubtedly complex. Evidence accumulated over the past decade strongly suggests that stress hormones differentially regulate Th1/Th2 patterns and type 1/type 2 cytokine secretion. Although interest in the Th2 response was initially directed at its protective role in helminthic infections and its pathogenic role in allergy, this response might have important regulatory functions in countering the tissue-damaging effects of macrophages and Th1 cells[5]. Thus, an excessive immune response, through activation of the stress system, and hence through glucocorticoids and CAs, suppresses the Th1 response and causes a Th2 shift. This might protect the organism from 'overshooting' by type 1/pro-inflammatory cytokines and other products of activated macrophages with tissue-damaging potential.

Locally, as stated above, stress might exert pro- or anti-inflammatory effects. This might be influenced by several factors, such as the presence or absence of antigen, the nature of antigen and/or the presence and relative expression of particular receptor subtypes on the surface of immune cells (such as β_2- versus α_2-ARs or H1 versus H2 histamine receptors). In addition, recent evidence indicates that stress is not a uniform, nonspecific reaction[64]. Thus, different type of stressors with their own central neurochemical and peripheral neuroendocrine 'signatures' might have different effects on the immune response.

The immune system is often regarded as autonomous and there is still skepticism among some immunologists that the brain can regulate immune functions, despite the fact that the scientific evidence suggests that it can indeed do so. Only the combined efforts of immunologists, neurophysiologists, endocrinologists and molecular biologists will help unravel the complex interactions between the neuroendocrine and immune systems and will allow the susceptibility of an individual to certain common human diseases to be determined. Such knowledge will help the development of new therapeutic strategies. Thus, blocking the effect of stress by β_2-AR and/or H2 antagonists might result in boosting Th1 responses that could be useful in the management of certain infections or tumors, whereas the combined administration of β_2-AR agonists and glucocorticoids might help in the management of certain Th1-mediated autoimmune diseases. Finally, CRH antagonists might help prevent stress-induced Th1 suppression and triggering of stress-induced allergic or vasokinetic phenomena. Such antagonists are at hand and show promise in preclinical studies.

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