

Stress System Activity, Innate and T Helper Cytokines, and Susceptibility to Immune-Related Diseases

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ABSTRACT: Associations between stress and health outcomes have now been carefully documented, but the mechanisms by which stress specifically influences disease susceptibility and outcome remain poorly understood. Recent evidence indicates that glucocorticoids (GCs) and catecholamines (CAs), the major stress hormones, inhibit systemically IL-12, TNF- α , and INF- γ , but upregulate IL-10, IL-4, and TGF- β production. Thus, during an immune and inflammatory response, the activation of the stress system, through induction of a Th2 shift may protect the organism from systemic “overshooting” with T helper lymphocyte 1 (Th1)/proinflammatory cytokines. In certain local responses and under certain conditions, however, 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 corticotropin-releasing hormone (CRH)/substance P(SP)-histamine axis. Autoimmunity, chronic infections, major depression, and atherosclerosis are characterized by a dysregulation of the pro/anti-inflammatory and Th1/Th2 cytokine balance. Thus, hyperactive or hypoactive stress system, and a dysfunctional neuroendocrine-immune interface associated with abnormalities of the “systemic anti-inflammatory feedback” and/or “hyperactivity” of the local proinflammatory factors may contribute to the pathogenesis of these diseases. Conditions that are associated with significant changes in stress system activity, such as acute or chronic stress, cessation of chronic stress, pregnancy and the postpartum period, or rheumatoid arthritis (RA) through modulation of the systemic or local pro/anti-inflammatory and Th1/Th2 cytokine balance, may suppress or potentiate disease activity and/or progression. Thus, stress hormones-induced inhibition or upregulation of innate and Th cytokine production may represent an important mechanism by which stress affects disease susceptibility, activity, and outcome of various immune-related diseases.

KEYWORDS: stress; cytokines; innate immunity; T helper 1 and T helper 2 cells; autoimmunity

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INTRODUCTION

Cytokines, the “immune hormones” mediate and control immune and inflammatory responses. Complex interactions exist between cytokines, inflammation, and the adaptive responses in maintaining homeostasis. During an immune and inflammatory reaction, the release of cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), IL-6, and IL-12 results in the activation of the stress system. Two major pathway systems are involved in this regulation: the hypothalamic-pituitary-adrenal (HPA) axis and the systemic/adrenomedullary sympathetic nervous system (SNS). Several studies during the 1970s and 1980s revealed that stress hormones inhibit lymphocyte proliferation, cytotoxicity, and the secretion of certain cytokines, such as IL-2 and interferon- γ (INF- γ). These observations lead to the conclusion that stress was, in general, immunosuppressive. Recent evidence, however, indicates that stress hormones influence the immune response in a less monochromatic way—they selectively inhibit the T helper lymphocyte 1 (Th1)/proinflammatory but potentiate Th2/anti-inflammatory cytokine production, systemically, while locally, in certain conditions they may exert proinflammatory effects. Through this mechanism, stress, that is, hyperactive or hypoactive stress system, may influence the onset and/or course of various common human immune-related diseases. This new concept that has emerged and developed in the last decade is briefly outlined below.

SYSTEMIC EFFECTS OF STRESS HORMONES ON INNATE AND TH CYTOKINE PRODUCTION

Glucocorticoids (GCs) and catecholamines (CAs) systemically mediate a Th2 shift by suppressing antigen-presenting cells (APCs) and Th1 and upregulating Th2-cytokine production.¹ Thus, GCs and the two major CAs, norepinephrine (NE) and epinephrine (EPI), through stimulation of classic cytoplasmic/nuclear GR and β 2-ARs, respectively, suppress the production by APCs of IL-12, the main inducer of Th1 responses.²⁻⁵ 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.⁵⁻⁷ GCs also have a direct effect on Th2 cells by upregulating their IL-4, IL-10, and IL-13 production.^{5,8} GCs do not affect the production of IL-10 by monocytes,^{2,9} yet, lymphocyte-derived IL-10 production is upregulated by GCs.⁸ 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.^{10–14} Since β 2-ARs are expressed on Th1 cells, but not on Th2 cells,¹⁵ CAs do not affect directly the cytokine production by Th2 cells—in 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.^{15,16} However, CAs through stimulation of β 2-AR upregulate the production of the anti-inflammatory cytokine IL-10 and IL-6 by APCs.^{2,17–19}

LOCAL EFFECTS OF STRESS HORMONES

The above systemic effects of stress 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.²⁰ The number of IL-4⁺ cells in the bronchial and nasal mucosa is also reduced by GC treatment.^{21,22} Furthermore, the synthesis of transforming growth factor- β (TGF- β), another cytokine with potent anti-inflammatory activities, is enhanced by GCs in human T cells but suppressed in glial cells,²³ and low doses of GCs can indeed activate alveolar macrophages, leading to increased lipopolysaccharide (LPS)-induced IL-1 β production.²⁴ In addition, NE, via stimulation of α 2-ARs can augment LPS-stimulated production of TNF- α from mouse peritoneal macrophages,²⁵ while hemorrhage, a condition associated with elevations of systemic CA concentrations, increases the expression of TNF- α and IL-1 by lung mononuclear cells via stimulation of α -ARs.²⁶ Because the response to β -AR agonist stimulation wanes during maturation of human monocytes into macrophages,²⁷ it is possible that in certain compartments of the body, the α -AR-mediated effect of CAs becomes transiently dominant. 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.^{28–31} Furthermore, CAs through β 2/ β 3-ARs upregulate IL-6 production by human adipocytes.^{32,33} IL-6 is the major inducer of C-reactive protein (CRP) production by the liver and both GCs and CAs enhance this induction to a greater or lesser extent.³⁴ Interestingly, chronic β -AR stimulation induces myocardial, but not systemic, elaboration of TNF- α , IL-1 β , and IL-6.³⁵

CRH/SP-Mast Cell-Histamine Axis

Peripherally produced corticotropin-releasing hormone (CRH) acts as a local auto/paracrine proinflammatory agent (*peripheral* or *immune* CRH).

Immunoreactive CRH is identified locally in experimental carrageenin-induced subcutaneous aseptic inflammation, streptococcal cell wall- and adjuvant-induced arthritis, and in human tissues from patients with rheumatoid arthritis (RA), autoimmune thyroid disease (ATD), and ulcerative colitis. CRH may be produced locally by immune cells but also delivered to inflamed tissues by peripheral nerves.^{36,37} Urocortin, a recently identified 40 amino acid peptide that shares 45% sequence homology with CRH is also overexpressed in synovial tissues of RA patients, and both CRH and urocortin stimulate the production of the proinflammatory cytokines IL-1 β and IL-6 by human peripheral mononuclear cells.³⁸ Most of the proinflammatory actions of CRH and urocortin are mediated by CRH-R1 rather than CRH-R2.

Peripheral CRH has vascular permeability enhancing and vasodilatory actions. CRH administration causes major peripheral vasodilatation manifested as flushing and increased blood flow and hypotension.³⁹ An intradermal CRH injection induces a marked increase of vascular permeability and mast cell degranulation, mediated through CRH-R1.⁴⁰ It appears that the mast cell is a major target of immune CRH. Substance P (SP) and peripheral CRH, which are released from sensory peptidergic neurons, are two of the most potent mast cell secretagogues.⁴⁰⁻⁴³ Thus, peripheral CRH and SP activates 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 subsequently may cause vasodilatation, increased vascular permeability, and other manifestations of inflammation.

INTRACELLULAR 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 by the pathogen. Stress-induced Th2 shift may, therefore, have a profound effect on the susceptibility of the host to infections and/or may influence the course of infections, and particularly the intracellular ones, the defense against which is primarily through cellular immunity mechanisms. In the 1950s, Thomas Holmes reported that individuals who had experienced stressful life events were more likely to develop tuberculosis and less likely to recover from it.^{cf.44} Although it is 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 pathophysiologic mechanisms of these observations.²

The *Helicobacter pylori* intracellular 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.⁴⁵ Thus, increased systemic stress hormone levels, in concert with an increased local concentration of histamine, induced by inflammatory or stress-related

mediators, may skew the local responses toward Th2 and thus might allow the onset or progression of a *H. pylori* infection.

The innervation (primarily sympathetic/noradrenergic) of lymphoid tissue may be particularly relevant to HIV infection, since lymphoid organs represent the primary site of HIV pathogenesis. In fact, as recently shown, NE, the major sympathetic neurotransmitter released locally in lymphoid organs,^{46,47} is able to directly accelerate HIV-1 replication by up to 11-fold in acutely infected human peripheral blood mononuclear cells (PBMCs).⁴⁸ The effect of NE on viral replication is transduced via the β -AR-adenylyl cyclase-cAMP-PKA signaling cascade.⁴⁸ Progression of HIV infection is also characterized by increased cortisol secretion in both the early and late stages of the disease. Increased GC production, triggered by the chronic infection, was recently proposed to contribute to HIV progression.⁴⁹ Kino *et al.* found that one of the HIV-1 accessory proteins, Vpr, acts as a potent co-activator of the host GC receptor rendering lymphoid cells hyperresponsive to GCs.⁵⁰

TH1-RELATED AUTOIMMUNITY

Several autoimmune diseases are characterized by common alterations of the Th1 versus Th2 and IL-12/TNF- α versus IL-10, balance. In RA, multiple sclerosis (MS), type 1 diabetes mellitus, ATD, and Crohn's disease (CD), the balance is skewed toward 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 critical factor that determines the proliferation and differentiation of Th1-related autoreactive cellular immune responses in these disorders.⁵¹ Taking into consideration the Th2-driving effects of stress hormones systemically, one could postulate that a hypoactive stress system may facilitate or sustain the Th1 shift in MS or RA (FIG. 1). Animal studies and certain clinical observations support this hypothesis.

Recent studies suggest that suboptimal production of cortisol is involved in the onset and/or progression of RA.⁵²⁻⁵⁴ Most patients with RA have relatively "inappropriately normal" plasma cortisol levels in the setting of severe, chronic inflammation, characterized by increased production of TNF- α , IL-1, and IL-6. Since these cytokines are powerful stimulants to the HPA axis and cortisol production, we would have expected significantly elevated plasma cortisol levels in RA patients. The available data suggest that the HPA axis response is blunted in these patients. Whether this abnormality is primary or secondary has not been established.⁵³

Several lines of evidence indicate that the sympathetic-immune interface is defective in MS and its experimental model, the experimental allergic encephalomyelitis (EAE). Thus, sympathetic skin responses are decreased and lymphocyte β -ARs are increased in progressive MS.⁵⁵ The density of β -ARs on CD8⁺ T cells are increased from two- to threefold, compared with age-matched controls.^{56,57} Furthermore, isoproterenol and terbutaline,

β -AR- and β_2 -AR-agonists, respectively, were reported to suppress chronic/relapsing EAE in Lewis (LEW) rats.^{58,59}

Several recent data suggest a “protective” role of the SNS in experimental models of RA in animals. Thus, in the arthritis-prone LEW rats sympathectomy with 6-OHDA enhanced the severity of adjuvant induced-arthritis.^{60,61} The “protective” role of SNS is further substantiated by the recent study of Malfait *et al.*⁶² demonstrating that the β_2 -AR agonist, salbutamol, is a potent suppressor of established collagen-induced arthritis in mice. Recent studies in humans also suggest a defective SNS in RA. In patients with RA, diminished autonomic responses were observed after cognitive discrimination and the Stroop color–word interference tests.⁶³ Miller *et al.*,⁶⁴ demonstrated that patients with long-term RA had a highly significant reduction of sympathetic nerve fibers in synovial tissues, which was dependent on the degree of inflammation. 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 SNS. Interestingly, in RA synovial tissues it appears there is preponderance of about 10:1 for primary sensory, SP-positive fibers as compared with sympathetic fibers.⁶⁴ Since SP is powerful proinflammatory agent, via release of histamine and TNF- α and IL-12, such preponderance may lead to an unfavorable proinflammatory state, supporting the disease process of RA (FIG. 1).

The Lewis/Fischer Paradigm

LEW rats are highly susceptible to type II collagen-induced arthritis, adjuvant-induced arthritis, EAE, and experimental autoimmune uveitis (EAU), whereas Fischer (*F344*) rats are highly resistant to these diseases.^{52,65} These experimentally induced diseases are mediated by Th1-dominant immune responses. In ocular tissues of EAU, LEW express type 1/proinflammatory cytokines (IL-12p40, IFN- α and TNF- α), coincident with the peak of the response, whereas *F344* express high basal IL-10 levels mRNA in the eyes.⁶⁶ Recently, Sakamoto *et al.*,⁶⁷ have also demonstrated that lymph node cells from LEW rats express high levels of IL-12 p40 and there is upregulation of the expression of IL-12 receptor β_1 and β_2 . These data suggest that LEW mounts a more polarized Th1 response that makes them more susceptible to Th1-mediated diseases, whereas *F344* overproduces IL-10 that may contribute to a higher resistance to induction of these diseases. LEW have globally blunted stress system responses and fail, in response to a wide variety of stressors, to activate the hypothalamic CRH neuron appropriately.⁵² Since *F344* are known to have hyperresponsiveness stress responses and high corticosteroid production, but LEW rats have blunted stress responses with subnormal corticosteroid production, it is postulated that corticosteroids contribute to the differences in the development of pathogenic T cells in these two strains.⁵²

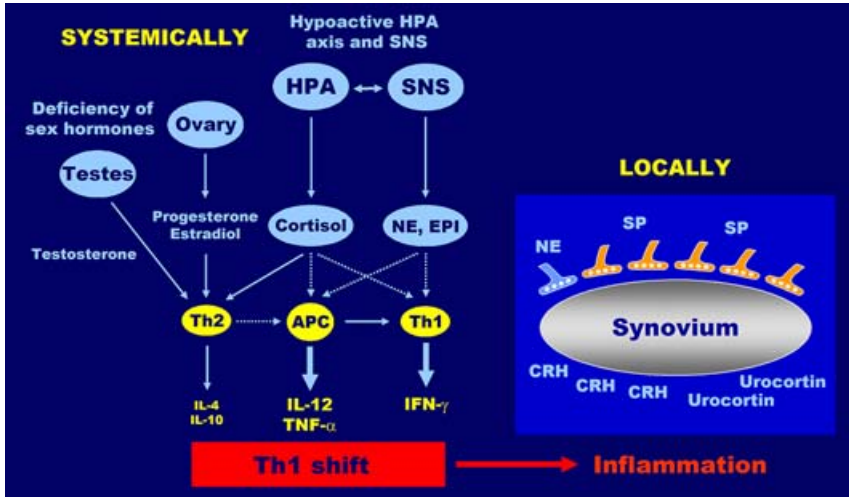


FIGURE 1. Role of systemic and local neuroendocrine factors in the pathogenesis of RA. The hypoactive stress system results in less inhibition of the Th1 responses by GCs and CAs, systemically. In aging men and postmenopausal women, the gonadal deficiency (i.e., less stimulation of the Th2 responses) will further intensify the Th1 shift. These neuroendocrine abnormalities may sustain and facilitate the Th1 shift observed in RA and further promote the local inflammation. Locally, the preponderance of primary sensory, SP-positive fibers as compared with sympathetic fibers and the overexpression of CRH and urocortin results in a dominance of the autocrine and paracrine proinflammatory factors in the synovium of RA patients. Solid lines represent stimulation, while dashed lines inhibition. APC, antigen-presenting cell; CRH, corticotropin-releasing hormone (peripheral); EPI, epinephrine; HPA, hypothalamic-pituitary-adrenal axis; IL, interleukin; NE, norepinephrine; SNS, sympathetic nervous system; SP, substance P; Th, T helper lymphocyte; TNF, tumor necrosis factor.

Pregnancy/Postpartum and Autoimmune Diseases Activity

Some autoimmune diseases like RA and MS often remit during pregnancy, particularly the third trimester but have an exacerbation or their initial onset during the postpartum period.^{52,68-71} The risk of developing new onset RA during pregnancy, compared to nonpregnancy, is decreased by about 70%. In contrast, the risk of developing RA is markedly increased in the postpartum period, particularly the first 3 months (odds ratio of 5.6 overall and 10.8 after first pregnancy). In women with MS, the rate of relapses declines during pregnancy, especially in the third trimester, increases during the first 3 months of the post partum, and then returns to the prepregnancy rate.⁷⁰

A decrease in the production of IL-2 and IFN- γ by antigen- and mitogen-stimulated PBMCs, accompanied by an increase in the production of IL-4 and IL-10, is observed in normal pregnancy. The lowest quantities of IL-2 and IFN- γ and the highest quantities of IL-4 and IL-10 are present in the third

trimester of pregnancy.⁷² Placental tissues from mothers at term express high levels of IL-10,⁷³ while IL-10 is present in the amniotic fluid of the majority of pregnancies, with higher concentrations found at term compared with the second trimester.⁷⁴ We have recently found that during the third trimester of pregnancy, *ex vivo* monocytic IL-12 production was about threefold and TNF- α production approximately 40% lower than postpartum values.⁷⁵ These studies suggest that type 1/proinflammatory cytokine production and cellular immunity are suppressed, and there is a Th2 shift during normal pregnancy, particularly, the third trimester. The third trimester of pregnancy and the early postpartum is also known to be associated with abrupt changes in several hormones. Thus, during the third trimester of pregnancy urinary cortisol and NE excretion, and serum levels of 1,25-dihydroxyvitamin D3 are about two- to threefold higher than postpartum values.⁷⁵ This is accompanied by the well-known marked elevations of estradiol and progesterone serum concentrations. The data reviewed here are consistent with the view that the increased levels of cortisol, NE, 1,25-dihydroxyvitamin D3, estrogens, and progesterone in the third trimester of pregnancy might orchestrate the improvement in autoimmune diseases, such as RA and MS via suppression of type 1/proinflammatory (IL-12, IFN- γ , and TNF- α) and potentiation of type 2/anti-inflammatory (IL-4 and IL-10) cytokine production. Conversely, this particular type of hormonal control of pro/anti-inflammatory cytokine balance might contribute to the flare up of systemic lupus erythematosus (SLE) observed during pregnancy. Post partum, the hormonal state abruptly shifts. The deficit in hormones that inhibit Th1-type cytokines and cell-mediated immunity might permit autoimmune diseases, such as RA and MS to first develop or established disease to flare up.^{52,75,76}

MAJOR DEPRESSION AND ATHEROSCLEROSIS

Recent evidence indicates that proinflammatory 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. 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 proinflammatory cytokines, such as IL-6, in subjects with depressive symptoms and syndromes. Fourth, the involvement of proinflammatory cytokines and specifically IL-6 is further substantiated by reports showing increased plasma levels of acute-phase proteins, such as haptoglobin and CRP in major depression.⁷⁷⁻⁷⁹

Patients with melancholic depression have significantly higher cerebrospinal fluid (CSF) NE and plasma cortisol levels with inappropriately high plasma

TABLE 1. Stress hormones-induced cytokine dysfunction in common human immune-related diseases

Disease group	Disease or condition	Cytokines and Th profiles	Comments	Role of stress hormones
Intracellular infections*	<i>Mycobacterium tuberculosis</i> <i>H. pylori</i> HIV	Suppressed cellular immunity, deficit of IL-12 and INF- γ , Th2 shift with progression of infection	HIV infection at some stages can express mixed Th1 and Th2 responses	Stress-induced Th2 shift might contribute to increase susceptibility to, or progression of these infections.
Th1-related autoimmunity	RA, MS, ATD, diabetes type 1, CD	Overproduction of IL-12, TNF- α , IFN- γ , deficit of 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)
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 upregulate IL-6 production, and thus increase its systemic levels
Atherosclerosis	Myocardial infarction, unstable angina, and stroke	Local overproduction of IFN- γ , TNF- α , IL-1 β , IL-8, IL-12, and IL-18; Systemic elevation of IL-6, IL-8, IL-1 β , and CRP	The effect of stress hormones on adipose tissue and lipid metabolism may facilitate their local proinflammatory effects	Stress hormones and histamine may induce the production of proinflammatory cytokines by myocardium, endothelium, and adipose tissues

*Modified from Elenkov and Chrousos, 1999 (See Ref. 1).

adrenocorticotrophic hormone (ACTH) 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 each are driven and sustained by hypercortisolism.⁸⁰ On the other hand, atypical depression might be associated with concomitant hypofunctioning of the CRH and locus ceruleus (LC)–NE systems.^{81,82} There is a strong association 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 of plasma IL-1 and IL-6.⁷⁸ Alternatively, since CAs upregulate IL-6 production, the chronic hypernoradrenergic state may drive the increase in systemic IL-6 levels (TABLE 1).

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. 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 proinflammatory mediators. Locally produced proinflammatory mediators with atherogenic activity include IFN- γ , TNF- α , IL-1 β , IL-8, IL-12, IL-18, and monocyte chemoattractant protein-1 (MCP-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-6.⁸³ Although a complete discussion is beyond the scope of this article, through a mechanism similar to that in depression, chronic stress-related abnormalities and hyperactivity of the local proinflammatory factors, and particularly the CRH/SP-histamine axis, and the induction of IL-6, IL-8, and CRP, secretion may play a role in the pathogenesis of atherosclerosis (TABLE 1).

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