REVIEW ARTICLE

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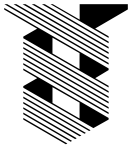

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THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS AND IMMUNE-MEDIATED INFLAMMATION

GEORGE P. CHROUSOS, M.D.

CELSUS described four of the five cardinal signs of inflammation 2000 years ago, and Eustachio discovered the adrenal glands almost 500 years ago, but not until 1936 did Selye note that in rats exposed to stressors, the adrenal glands were enlarged, and the thymus and lymph nodes shrunken.[1-3] Cortisone, the active principle of the adrenal glands, was isolated by Kendall and Reichstein in the late 1940s and shown to suppress immune organs. These scientists, along with Hench, received the Nobel Prize in Physiology and Medicine, after Hench and colleagues showed that cortisone could ameliorate rheumatoid arthritis.[4,5]

In recent years, our understanding of the interactions between the hypothalamic–pituitary–adrenal (HPA) axis and immune-mediated inflammatory reactions has expanded enormously. This review outlines the influences that the HPA axis and immune-mediated inflammatory reactions exert on each other and discusses the implications of these interactions for human disease.

THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

The HPA axis and the systemic sympathetic and adrenomedullary (sympathetic) system are the peripheral limbs of the stress system, whose main function is to maintain basal and stress-related homeostasis.[6,7] The central components of this system are located in the hypothalamus and the brain stem (Fig. 1). The stress system is active when the body is at rest, responding to many distinct circadian, neurosensory, blood-borne, and limbic signals. These signals include cytokines produced by immune-mediated inflammatory reactions, such as tumor necrosis factor α, interleukin-1, and interleukin-6.[6-8]

Activation of the stress system heightens arousal, accelerates motor reflexes, improves attention and cognitive function, decreases appetite and sexual arousal, and increases the tolerance of pain.[6,7] The activated system also changes cardiovascular function and intermediary metabolism and inhibits immune-mediated inflammation.

Corticotropin-releasing hormone (CRH) and noradrenergic neurons of the central stress system innervate and stimulate each other.[6-9] Thus, CRH stimulates the secretion of norepinephrine through specific receptors, and norepinephrine stimulates the secretion of CRH primarily through α_1-noradrenergic receptors.[6,7,9] By means of autoregulatory, ultrashort negative-feedback loops, CRH and norepinephrine collateral fibers inhibit presynaptic CRH and α_2-noradrenergic receptors, respectively. CRH, arginine vasopressin (AVP), and noradrenergic neurons are stimulated by the serotonergic and cholinergic systems and inhibited by the γ-aminobutyric acid–benzodiazepine and opioid-peptide systems of the brain. Centrally secreted substance P inhibits hypothalamic CRH neurons but not AVP neurons and stimulates the central noradrenergic system.[10-12]

Each of the paraventricular nuclei has three parvicellular divisions: a medial group that mostly produces CRH and secretes it into the hypophysial portal system; an intermediate group that secretes AVP into the hypophysial portal system; and a lateral group that primarily produces CRH and innervates noradrenergic and other neurons of the stress system in the brain stem (Fig. 2).[6,7,9] Some parvicellular neurons contain and secrete both CRH and AVP.[13,14] Other paraventricular CRH neurons project to and innervate proopiomelanocortin-containing neurons of the central stress system in the arcuate nucleus of the hypothalamus, as well as neurons in pain-control areas of the hind brain and spinal cord (Fig. 1 and 2). Activation of the stress system causes CRH-induced secretion of proopiomelanocortin-derived and other opioid peptides,[15,16] which enhance analgesia.[6,7] These peptides simultaneously inhibit the stress system by suppressing the secretion of CRH and norepinephrine.[6,7]

CRH also stimulates the secretion of corticotropin through the corticotrophs of the anterior pituitary.[17-19] When CRH is absent, very little corticotropin is secreted. AVP alone has little effect on corticotropin secretion but acts synergistically with CRH.

Every hour, the parvicellular neurons secrete two or three mostly synchronous pulses of CRH and AVP into the hypophysial portal system.[20-24] Early in the morning, when these pulses are at their peak, they increase the magnitude of corticotropin and cortisol pulses. The amplitude of these pulses also increases during acute stress, but under these conditions, the stress system recruits additional secretagogues of CRH, AVP, or corti-

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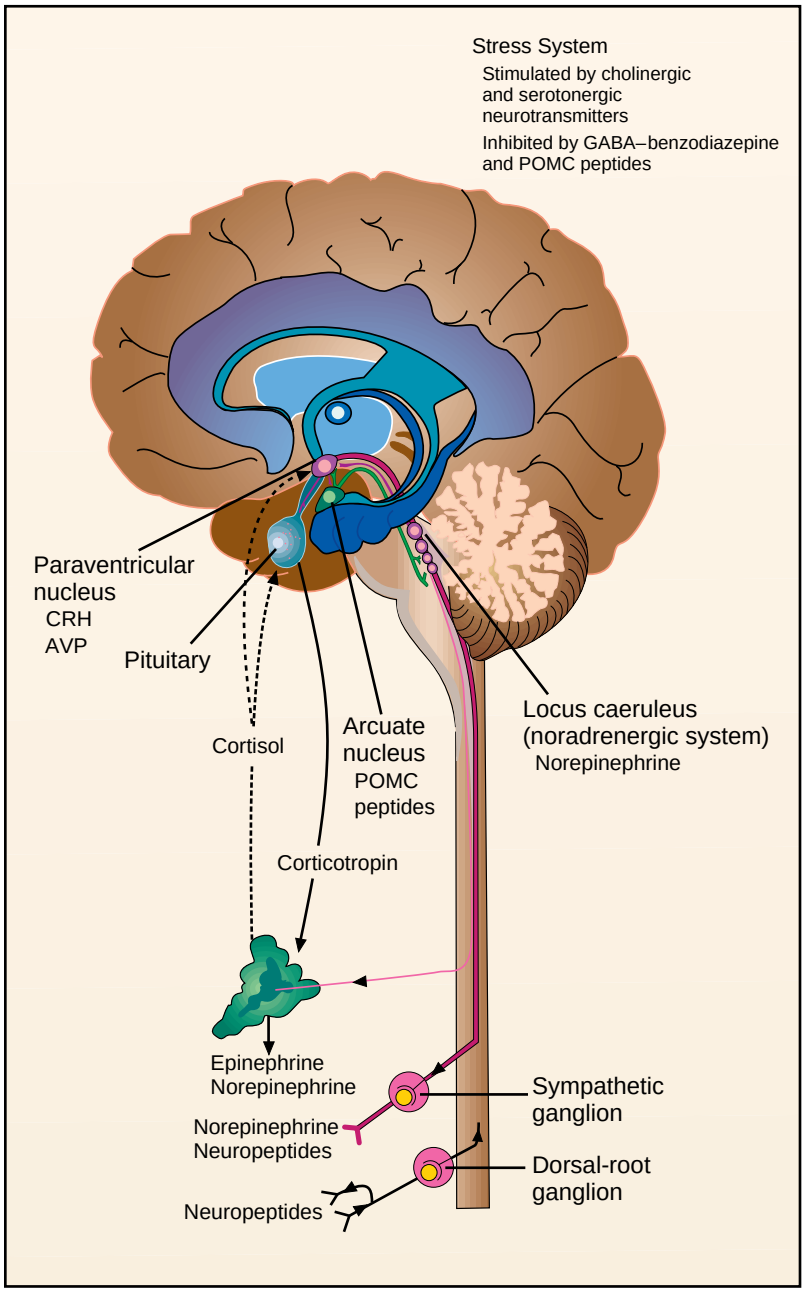

Figure 1. Major Components of the Central and Peripheral Stress Systems.

The paraventricular nucleus and the locus caeruleus (noradrenergic system) are shown along with their peripheral components, the pituitary–adrenal axis, and the adrenomedullary and systemic sympathetic systems. Hypothalamic corticotropin-releasing hormone (CRH) and central nervous system noradrenergic neurons innervate and activate each other, whereas they exert presynaptic autoinhibition through collateral fibers. Arginine vasopressin (AVP) from the paraventricular nucleus acts synergistically with CRH in stimulating corticotropin secretion. Both components of the central stress system are stimulated by cholinergic and serotonergic neurotransmitters and inhibited by γ-aminobutyric acid (GABA)–benzodiazepine and arcuate nucleus pro-opiomelanocortin (POMC) peptides. These peptides are directly activated by the stress system and are important in the enhancement of analgesia that takes place during stress. Corticotropin (solid arrow) stimulates the adrenal cortex to produce cortisol. Cortisol (broken arrow) inhibits the production of CRH, AVP, and corticotropin.

cotropin, such as magnicellular AVP and angiotensin II.[6,7,25,26] Corticotropin is the key regulator of glucocorticoid secretion by the adrenal gland. Other hormones, including those from the adrenal medulla, and autonomic neural input to the adrenal cortex can also regulate cortisol secretion.[24,27-30]

The Immune-Mediated Inflammatory Reaction

The immune system constantly and silently destroys, dilutes, or walls off injurious agents and injured tissue.[31] Locally, microvessels dilate and become more permeable, thereby increasing blood flow and exudation of plasma and allowing leukocytes to accumulate in the inflammatory focus (Fig. 3). The cells in the inflammatory reaction arrive from the blood (e.g., monocytes, neutrophils, basophils and eosinophils, and lymphocytes) or originate locally (e.g., endothelial cells, mast cells, tissue fibroblasts, and resident macrophages). Locally, immune and immune accessory cells are activated, and cytokines, lipid mediators of inflammation, and neuropeptides are generated.[31,32] Usually, these events are clinically silent, but inflammation occasionally causes activation of the stress system and systemic symptoms and signs.

Afferent sensory fibers and postganglionic sympathetic neurons of the peripheral nervous system influence inflammation (Fig. 3).[33-37] The sensory fibers not only signal the central nervous system but also secrete proinflammatory or antiinflammatory neuropeptides, such as substance P or somatostatin, into the site of inflammation. The postganglionic sympathetic neurons, which are peripheral extensions of the central stress system, also secrete proinflammatory and antiinflammatory substances locally.

Effects of the HPA Axis on the Immune-Mediated Inflammatory Reaction

Adrenocortical Hormones

The antiinflammatory and immunosuppressive properties of glucocorticoids make them invaluable thera-

peutic agents in numerous diseases.[38] The glucocorticoid receptor is a 777–amino acid cytoplasmic protein with three major functional domains and several subdomains. The carboxyterminal region binds glucocorticoid, and the midregion binds to specific sequences of DNA in the regulatory regions of glucocorticoid-responsive genes (glucocorticoid-responsive elements).[38,39]

Glucocorticoids influence the traffic of circulating leukocytes and inhibit many functions of leukocytes and immune accessory cells.[6,7,38,39] They suppress the immune activation of these cells, inhibit the production of cytokines and other mediators of inflammation, and cause resistance to cytokines. Glucocorticoids preferentially affect certain subgroups of T lymphocytes; they suppress the function of type 1 helper T lymphocytes and stimulate apoptosis of eosinophils and certain groups of T cells. They also inhibit the expression of adhesion molecules and their corresponding receptors[40] and potentiate the acute-phase reaction.[41] All these effects depend on alterations of the transcription rates of glucocorticoid-responsive genes or changes in the stability of messenger RNA of several inflammatory proteins.[42-44] For instance, glucocorticoids suppress the production of interleukin-6 and interleukin-1β by decreasing the transcription rates of the genes for these interleukins and the stability of their messenger RNA. Suppression of the phospholipase A_2, cyclooxygenase 2, and nitric oxide synthase 2 genes[38,45-49] by glucocorticoids decreases the production of prostanoids, platelet-activating factor, and nitric oxide — three key molecules in the inflammatory response. Activated glucocorticoid receptors also inhibit the proinflammatory activity of many growth factors and cytokines by blocking transcription factors required for the expression or cellular action of these substances.[38,39] In a reciprocal fashion, elevated intracellular concentrations of these factors prevent the activated glucocorticoid receptor from affecting the genome.

Several circadian immune functions cause disease-associated diurnal changes that correspond to the diurnal variations in plasma glucocorticoid concentrations.[50,51] For example, the delayed hypersensitivity reaction, which is particularly responsive to glucocorticoids, is most pronounced in the evening, when glucocorticoid secretion is low, and least pronounced in the morning, when secretion is high.[50]

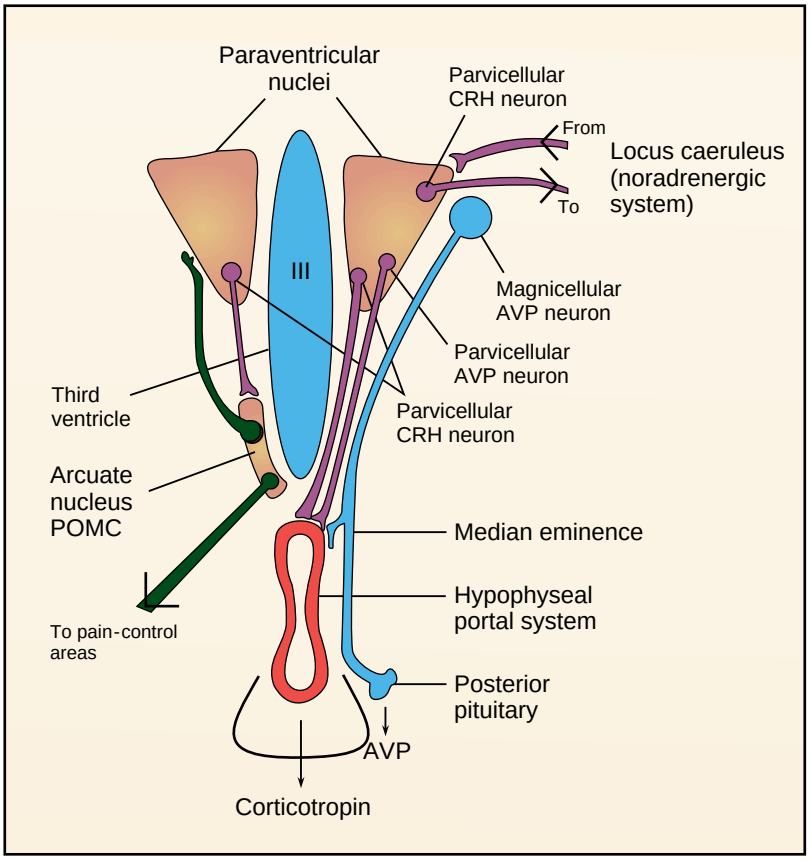

Figure 2. Close-up View of the Paraventricular Nuclei of the Hypothalamus.
Parvicellular neurons secreting corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) project to and secrete into the hypophysial portal system. Parvicellular CRH neurons also project to the brain stem to innervate neurons of the locus caeruleus (noradrenergic system). Magnicellular AVP-secreting neurons terminate in the posterior pituitary and secrete into the systemic circulation; they also have collateral terminals in the portal system. CRH permits and stimulates pituitary corticotropin secretion, and AVP has a synergistic role with CRH in the secretion of corticotropin. The arcuate nucleus proopiomelanocortin (POMC) is shown, along with the mutual innervation between CRH and POMC peptide–secreting neurons.

Adrenal androgens with the Δ^5 configuration in the A ring may modulate immune function.[52-56] An orphan receptor of the steroid–thyroid-receptor superfamily specific for Δ^5-adrenal androgens has been detected in T lymphocytes; it presumably allows these androgens to enhance cellular immunity.[56] The secretion of adrenal androgens, which follows the circadian pattern of corticotropin secretion, has a distinct developmental pattern, with the highest levels in utero and during puberty and early adulthood.[52]

Pituitary Hormones

The pituitary hormones of the HPA axis, corticotropin and β-endorphin,[57,58] have immunopotentiating and proinflammatory properties; β-endorphin produced at inflammatory sites is a potent local analgesic.[59] The relative contributions of circulating and locally

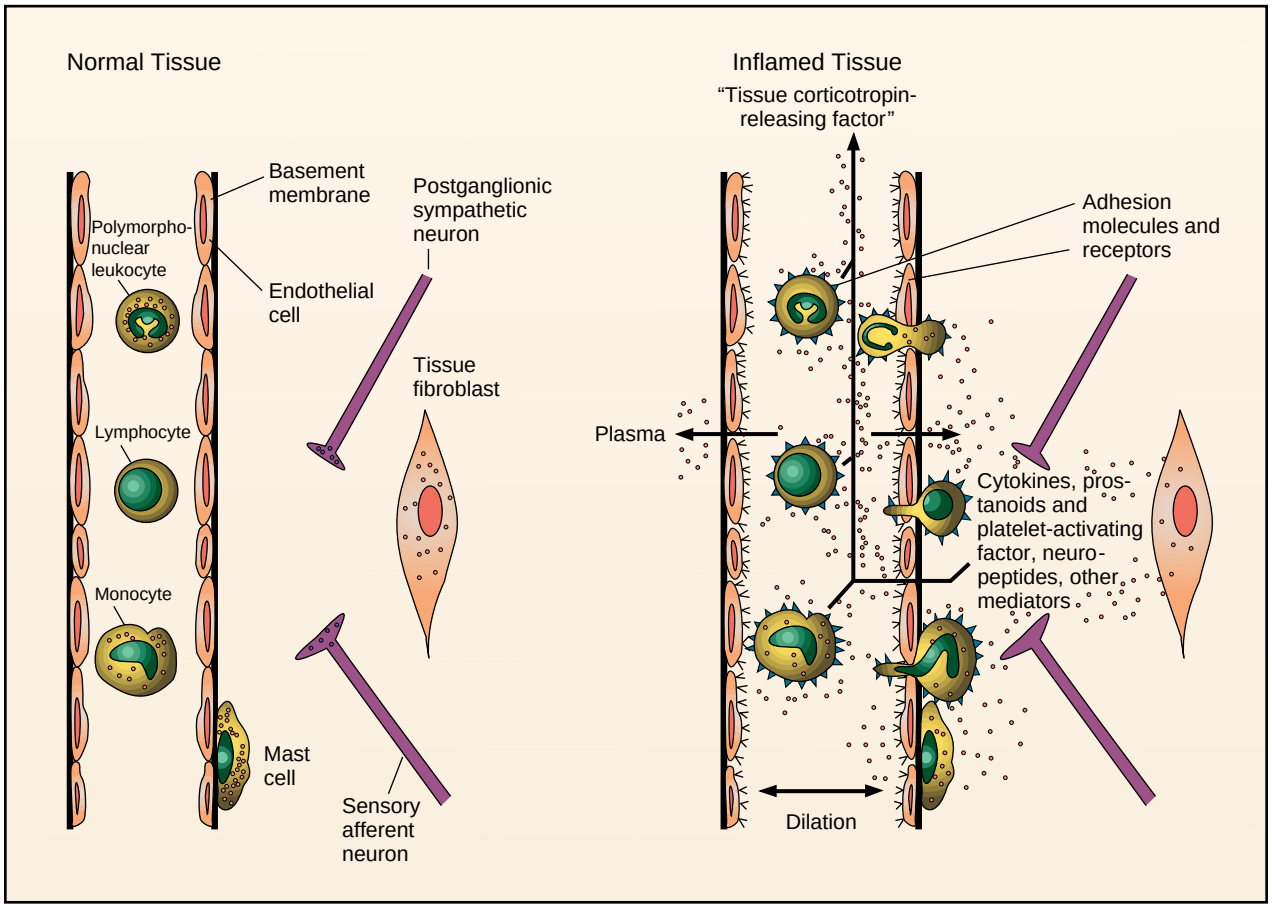

Figure 3. Components and Events of Inflammation.

Quiescent circulating leukocytes, local immune accessory cells, and the terminals of peripheral postganglionic sympathetic and sensory afferent neurons are shown in normal tissue (left-hand panel). In inflamed tissue (right-hand panel), there is vasodilation, increased permeability of the vessel, and exudation of plasma. Activated leukocytes and endothelial cells express adhesion molecules and adhesion-molecule receptors. Cells attach to the vessel wall and diapedesis takes place, with chemotaxis toward a chemokine gradient at the focus of inflammation. Activated circulating cells, migrant cells, local immune accessory cells, and peripheral nerves secrete cytokines, prostanoids, platelet-activating factor, neuropeptides, and other mediators of inflammation. Some of these substances, such as interleukin-6, leukotrienes, complement component 5α, corticotropin-releasing hormone, and transforming growth factor β, have chemokinetic activity. Some substances, such as the inflammatory cytokines tumor necrosis factor α, interleukin-1, and interleukin-6, escape into the systemic circulation, causing systemic symptoms and activating the hypothalamic–pituitary–adrenal axis. Because of such effects, these substances have been called "tissue corticotropin-releasing factor."

produced corticotropin and β-endorphin to inflammation, as well as the local sources of these neuropeptides, are unknown.

Hypothalamic Hormones

The principal hypothalamic regulators of the HPA axis, CRH and perhaps AVP, have proinflammatory effects in vitro and in vivo.[60-67] Sites of inflammation contain large amounts of immunoreactive CRH, mostly within immune accessory cells and the inflammatory exudate. CRH, as well as its oxidized and proteolytic products, has been found in synovial fluid from patients with rheumatoid arthritis and in the thyroid glands in patients with Hashimoto's thyroiditis.[62,63] CRH, its messenger RNA, or both are also present in circulating white cells and in cells of the thymus and spleen.[65-67] Neutralizing antibodies against CRH diminish inflammation as effectively as immunoneutralization of tumor necrosis factor α, a well-defined proinflammatory cytokine.[60] The concentrations of CRH in inflammatory sites are as high as those in the hypophysial portal system, but in plasma samples obtained concurrently the hormone is undetectable.[60] Rapid catabolism, uptake, or binding may prevent the entrance of the peptide into the systemic circulation.[60,68]

Effects of Immune-Mediated Inflammatory Reactions on the HPA Axis

Several circulating mediators have a major role in activating the HPA axis during the stress of inflammation. Initially designated "tissue corticotropin-releasing factor,"[69] these mediators are actually distinct from immune CRH, which normally does not diffuse into the general circulation.[60] Instead, they are a mixture of cy-

tokines and other major participants in the immune and inflammatory reaction.

Three cytokines — tumor necrosis factor α, interleukin-1, and interleukin-6 — account for most of the HPA-axis–stimulating activity in plasma. Tumor necrosis factor α usually appears first, followed by secretion of interleukin-1 and interleukin-6 (Fig. 4).[70-72] All three cytokines stimulate their own secretion from the cells that produce them. Tumor necrosis factor α and interleukin-1 also stimulate the secretion of interleukin-6, whereas interleukin-6 inhibits the secretion of tumor necrosis factor α and interleukin-1. Interleukin-6 acts synergistically with glucocorticoids in stimulating the production of acute-phase reactants.[38,41] Systemic interleukin-6 concentrations also increase during stress unrelated to inflammation, presumably stimulated by catecholamines acting through β_2-adrenergic receptors.[73,74]

The three inflammatory cytokines activate the HPA axis independently; in combination, their effects are synergistic.[75-80] CRH-neutralizing antibodies, glucocorticoids, and prostanoid-synthesis inhibitors block activation of the axis; in vitro, all three cytokines stimulate CRH secretion in rat hypothalamic explants, an effect that glucocorticoids and prostanoid-synthesis inhibitors block. The three inflammatory cytokines also mediate the stimulation of the HPA axis through bacterial lipopolysaccharide. Antibodies against interleukin-6 almost completely inhibit this effect.[80]

In humans, interleukin-6 elevates plasma concentrations of corticotropin and cortisol well above the concentrations achieved with maximal stimulating doses of CRH. Thus, interleukin-6 may also stimulate parvicellular AVP and other corticotropin secretagogues.[81,82] Plasma corticotropin concentrations are already maximal with doses of interleukin-6 that do not increase peripheral plasma AVP concentrations. At higher doses, however, interleukin-6 causes elevations of plasma AVP, indicating that this cytokine can also activate magnicellular AVP-secreting neurons. This effect suggests that interleukin-6 has a role in the inappropriate secretion of antidiuretic hormone that can occur in patients with infectious or inflammatory diseases or trauma.[82]

How inflammatory cytokines reach the hypothalamic CRH and AVP neurons is unclear, given that the blood–brain barrier protects the cell bodies of both kinds of neurons (Fig. 2).[75,83,84] The cytokines may cause endothelial and glial cells to secrete interleukin-6 and other mediators of inflammation, which reach the CRH and AVP neurons in a cascade-like fashion.[80,85] Alternatively, there may be a special transport system for inflammatory cytokines, or they may directly activate the terminals of the CRH and AVP neurons in the median eminence, which is outside the blood–brain barrier.

Inflammation may also activate the HPA axis indirectly. This could occur through the stimulation of the central noradrenergic stress system by cytokines and other mediators that act first on stress-system neurons outside the blood–brain barrier (the area postrema) or on neurons inside the barrier, through the endothelial–glial–neuronal cascade mentioned above. In addition, inflammatory sites contain nociceptive, visceral, and somatosensory afferent neurons, which stimulate the noradrenergic and CRH stress systems through an ascending spinal or cerebral nerve route.[86,87]

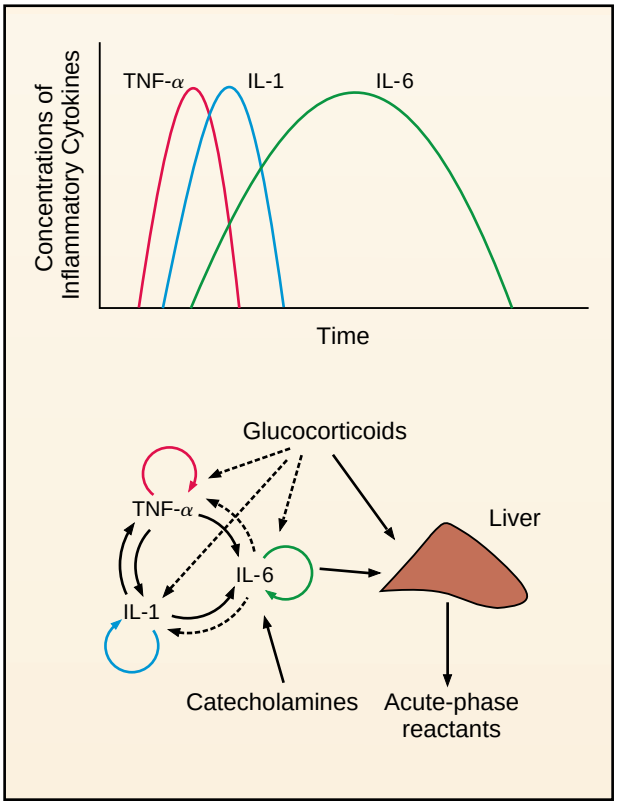

Figure 4. Interactions among the Inflammatory Cytokines and the Effects of Glucocorticoids and Catecholamines.

The upper panel shows the sequence of events at an inflammatory site. Tumor necrosis factor α (TNF-α) is secreted first, interleukin-1 (IL-1) second, and interleukin-6 (IL-6) last. Each of the inflammatory cytokines stimulates its own production (lower panel). Tumor necrosis factor α and interleukin-1 stimulate each other, and both stimulate interleukin-6. Interleukin-6 inhibits the secretion of both tumor necrosis factor α and interleukin-1. Glucocorticoids, the end products of the hypothalamic–pituitary–adrenal axis, inhibit the production of all three inflammatory cytokines and also inhibit their effects on target tissues, except for the effect of interleukin-6 on the production of acute-phase reactants by the liver, which is potentiated by glucocorticoids. Catecholamines, the other end products of the stress system, have a major role in the control of inflammation through the stimulation of interleukin-6, which inhibits the other two cytokines, stimulates glucocorticoids, and induces the acute-phase response. The solid lines denote stimulation, and the broken lines inhibition.

In addition to their short-term effects on the hypothalamus, the inflammatory cytokines can apparently stimulate pituitary corticotropin and adrenal cortisol secretion directly at high concentrations or if given adequate time for interaction with these tissues.[75,76,81,88-92] Normally, the anterior pituitary and adrenal glands produce interleukin-1 and interleukin-6, which may in-

fluence local hormone production.[75,93,94] However, these cytokines may not always stimulate the pituitary gland or the adrenal cortex. Interleukin-6, tumor necrosis factor α, and interferon γ inhibit the stimulatory effect of CRH on anterior pituitary-cell cultures,[95,96] whereas tumor necrosis factor α is a potent inhibitor of corticotropin-induced secretion of cortisol by cultured adrenocortical cells.[97]

Other inflammatory mediators, including interferon α and interferon γ, interleukin-2, epidermal growth factor, transforming growth factor β, and platelet-activating factor, may also participate in the regulation of the HPA axis (Table 1). The interferons and interleukin-2 may do so indirectly, by causing the secretion of inflammatory cytokines. Prostanoids and platelet-activating factor, however, are autacoid amplifiers of hypothalamic CRH and AVP secretion. Receptors for these substances are present in the paraventricular nuclei, and CRH and AVP neurons respond to them.[6,75,83]

Certain cytokines or combinations of cytokines can cause resistance to glucocorticoids.[98,99] Interleukin-2 and interleukin-4 together induce glucocorticoid resistance in T cells by markedly decreasing the affinity of the glucocorticoid receptor for its ligand.[99] In addition, the conversion of cortisol into less active or inactive metabolites alters the sensitivity of cells of the immune system to glucocorticoids.[100]

Interactions between the HPA Axis and Immune-Mediated Inflammation

Short- and Long-Term Adaptations

Chronic activation of the HPA axis or chronic inflammation results in reciprocally protective adaptations. For instance, immune suppression in patients with endogenous Cushing's syndrome is mild, suggesting the development of tolerance to glucocorticoids. Indeed, even though neutrophilia and eosinopenia persist, the lymphocyte phenotypes and function in such patients are equivalent to those in age- and sex-matched normal subjects. Animals with chronic inflammatory disease, on the other hand, have mild rather than severe hypercortisolism, which is associated with surprisingly low CRH and high AVP messenger-RNA expression and peptide secretion in the hypothalamus.[101-103]

Hypothalamic elevation of substance P, an inhibitor of CRH secretion, may be the mechanism underlying the suppression of CRH neurons in inflammation.[10-12] In addition, elevated levels of inflammatory cytokines and interferon γ may restrain the HPA axis by blocking the stimulatory effects of CRH and corticotropin on the pituitary and adrenal cortex, respectively.[95-97] This process occurs in some patients with septic shock or the acquired immunodeficiency syndrome (AIDS) and in most patients with African trypanosomiasis, who have impaired adrenal responses to stress or exogenous CRH and corticotropin.[104-107]

Chronic activation of the HPA axis may also cause a relative decrease in the production by the adrenals of Δ^5-adrenal androgens.[108] This process, in turn, may alter the helper-T-cell phenotype in chronically affected patients, resulting in a predominance of type 2 helper T cells.[52-55]

Table 1. Cytokines and Other Mediators of Inflammation That Influence the Hypothalamic–Pituitary–Adrenal Axis.

Inflammatory cytokines
Tumor necrosis factor α
Interleukin-1α and interleukin-1β
Interleukin-6
Other cytokines
Interferon α
Interferon γ
Interleukin-2
Growth factors
Epidermal growth factor
Transforming growth factor β
Lipid mediators
Prostanoids
Platelet-activating factor

Influences of Reproductive Hormones

In general, autoimmune diseases affect females more often than males. In animals, androgens usually suppress the immune response, whereas estrogens stimulate it.[109,110] The mechanisms of these effects are unknown, although estrogens can stimulate adhesion molecules and their receptors in immune cells and immune accessory cells.[111] In addition, the CRH gene and, hence, immune CRH expression are responsive to estrogen.[112] Prolactin potentiates immune-mediated inflammation in vitro and in animals.[113] Inhibition of prolactin secretion in patients with autoimmune diseases has not been effective therapeutically, perhaps because local, autacoid prolactin production may not respond to dopaminergic inhibition.[114]

Disturbances in the Interaction between the HPA Axis and Immune-Mediated Inflammation

Defects of the HPA Axis

Figure 5 shows disturbances of the interaction between the HPA axis and immune-mediated inflammation. An excessive HPA response to inflammation can mimic the state of stress or hypercortisolemia and thus increase susceptibility to infectious agents and tumors but enhance resistance to autoimmune or inflammatory disease. Conversely, a defective HPA-axis response can mimic the glucocorticoid-deficient state and thus cause resistance to infections and neoplasms but increased susceptibility to autoimmune or inflammatory disease. Indeed, such properties were identified in Fischer and Lewis rats, two highly inbred strains selected for their resistance (Fischer rats) or susceptibility (Lewis rats) to inflammatory disease.[115,116] The responsiveness of the HPA axis to inflammatory stimuli is decreased in Lewis rats but increased in Fischer rats.

Lewis rats are susceptible to a host of experimentally induced inflammatory diseases, whereas Fischer rats are resistant to these diseases. In Lewis rats hypothalamic CRH neurons respond poorly to all stimulatory neurotransmitters,[117] and the overall HPA-axis response to stress is decreased. These animals have chronic elevations of vasopressin and behavior reminis-

cent of atypical depression in humans, a state characterized by low levels of hypothalamic CRH secretion.[6,7,118,119]

Do the abnormalities in Lewis rats have parallels in humans? A subgroup of patients with active rheumatoid arthritis have low or normal circadian plasma concentrations of corticotropin and cortisol, despite elevated plasma concentrations of interleukin-1β and interleukin-6.[120,121] Such patients have a poor response to the stress associated with major surgery, such as replacement of a large joint, despite dramatic postoperative elevations of plasma interleukin-1β and interleukin-6.[121] Like Lewis rats, these patients also have consistently elevated plasma AVP concentrations. The inflamed joints of patients with active rheumatoid arthritis, like the joints of Lewis rats with arthritis induced by streptococcal-cell-wall peptidoglycan, have markedly elevated concentrations of immunoreactive CRH.[61,62] None of these abnormalities of the HPA axis occur in patients with osteomyelitis (inflammatory disease) or degenerative osteoarthritis.

Is the hyporesponsiveness of the HPA axis in patients with rheumatoid arthritis caused by a genetic abnormality, a particular type of chronic inflammation, or both? The data point to a genetic disturbance,[122] but prospective studies of susceptible families or studies of identical twins, one of whom is affected, have not been performed.

Table 2 lists other possible examples of a defective HPA axis that increases the susceptibility to autoimmune disease or causes increased immune reactivity.[6,7,123,124] Given the many behavioral effects of CRH, it is not surprising that fatigue, dysthymia, irritability, and even frank depression are frequent in many of these low-CRH states.[6,7]

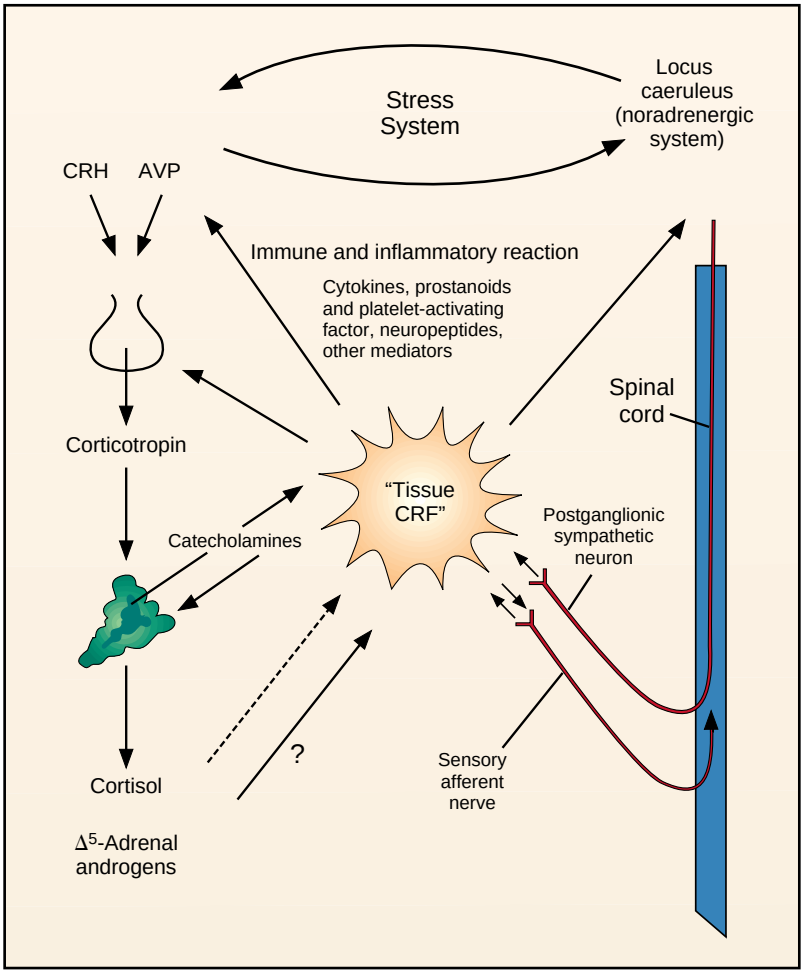

Figure 5. Interactions between the Stress System and Immune-Mediated Inflammation.

Tumor necrosis factor α, interleukin-1, interleukin-6, and perhaps other mediators of inflammation collectively called "tissue corticotropin-releasing factor" stimulate the secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from hypothalamic CRH and AVP neurons; at high concentrations or over a prolonged period, they stimulate the secretion of corticotropin from the pituitary corticotroph and glucocorticoids from the adrenal cortex. All these effects are augmented by local prostanoids and platelet-activating factor at each level. The same mediators may stimulate the central noradrenergic system (locus caeruleus) humorally or through the peripheral afferent sensory and autonomic nervous system and may alter the sensitivity of immune target tissues to glucocorticoids.

Glucocorticoids directly inhibit immune target tissues, whereas CRH, AVP, corticotropin, and β-endorphin have primarily immunopotentiating or proinflammatory roles. Neuropeptides are produced locally by sensory afferent fibers, sympathetic postganglionic nerves, and immune cells or immune accessory cells and act as autacoids. The autonomic system influences immune-mediated inflammatory reactions through specific sympathetic postganglionic neurons, by local secretion of proinflammatory and antiinflammatory substances, and humorally, through circulating catecholamines, which suppress natural-killer-cell activity and stimulate interleukin-6 secretion. Excessive responses of the stress system to inflammation are associated with resistance to autoimmune and inflammatory diseases. Inadequate responses of the stress system to inflammation are associated with increased susceptibility to autoimmune and inflammatory diseases. The solid lines denote stimulation, and the broken lines inhibition.

Defects of the Glucocorticoid Target Tissues

Excessive immune-mediated inflammation may also arise from glucocorticoid resistance in target tissues[39,125-130] (Table 2). Four diseases illustrate this mechanism. In rheumatoid arthritis, the concentration of glucocorticoid receptors in circulating leukocytes is reduced by approximately 50 percent.[125,126] This phenomenon cannot be attributed to hypercortisolism. Leukocyte resistance to glucocorticoids also occurs in steroid-resistant asthma.[127,128] Most patients with this disorder have marked but reversible decreases in the affinity of glucocorticoid receptors in T lymphocytes. In a

Table 2. States Potentially Associated with Suppression or Activation of Immune-Mediated Inflammation through Defects in the Hypothalamic–Pituitary–Adrenal (HPA) Axis or Its Target Tissues.

Suppression of Immune-Mediated Inflammatory Reaction	Activation of Immune-Mediated Inflammatory Reaction
Increased HPA-axis activity	**Decreased HPA-axis activity**
Cushing's syndrome	Adrenal insufficiency
Melancholic depression	Rheumatoid arthritis
Chronic alcoholism	Atypical or seasonal depression
Chronic stress	Chronic fatigue or fibromyalgia
Long-term excessive exercise	Hypothyroidism
Pregnancy (last trimester)	Post-traumatic stress disorder
Fischer-rat model	Nicotine withdrawal
	After successful treatment for Cushing's syndrome
	After glucocorticoid therapy
	Postpartum period
	After chronic stress
	Lewis-rat model
	Obese-chicken model of autoimmune thyroiditis
	Resistance to glucocorticoids
	Rheumatoid arthritis
	Steroid-resistant asthma
	AIDS
	Degenerative osteoarthritis
	Systemic lupus erythematosus*

*Due to increased catabolism of cortisol in target tissues.[101]

small subgroup of patients, however, glucocorticoid-receptor concentrations in all leukocyte subtypes are irreversibly decreased, suggesting a congenital syndrome.[128] In some patients with AIDS, leukocytes also have a marked decrease in the affinity of glucocorticoid receptors for cortisol.[129] In these patients, the glucocorticoid resistance may be generalized, since there are signs of glucocorticoid deficiency, including postural hypotension and hyponatremia, despite elevated levels of corticotropin and cortisol. A fourth disease in which the reduced expression of glucocorticoid receptors and glucocorticoid resistance may have a role is degenerative osteoarthritis.[130] Osteoarthritic chondrocytes contain approximately half the number of glucocorticoid receptors in normal chondrocytes and resist dexamethasone-induced suppression of metalloprotease synthesis. Metalloprotease participates in the limited inflammatory destruction of the cartilage in the joints of patients with osteoarthritis.

Therapeutic Perspectives

Glucocorticoids and agents that potentiate their actions are options for the treatment of patients with autoimmune inflammatory diseases.[38] By potentiating the effects of hypothalamic CRH, the CRH secretagogues, CRH agonists, or CRH-binding protein antagonists that cross the blood–brain barrier may prevent inflammatory disease in susceptible persons with a hypofunctional HPA axis. At the same time, these agents may correct central nervous system symptoms of CRH deficiency.[6,7] Antagonists of substance P that can cross the blood–brain barrier would be expected to reverse the CRH suppression that occurs in chronic inflammatory states and at the same time act as local anti-inflammatory agents.

Antagonists of proinflammatory peptides may control inflammatory diseases or processes in which these peptides have a primary pathogenic role. Depending on their ability to cross the blood–brain barrier and the location of the therapeutic target, these antagonists could be used systemically or in a compartmentalized fashion.

Tumor necrosis factor α and interleukin-1 are involved in the pathogenesis of septic shock. It might be possible to exploit the natural ability of interleukin-6 to inhibit the secretion of tumor necrosis factor α and interleukin-1 by using this cytokine either alone or together with glucocorticoids to control septic shock.[131] Recombinant interleukin-6 or agents that stimulate its secretion, such as β-mimetic agents or α_2-noradrenergic antagonists, may also be useful in this context.

Elucidation of the mechanisms of congenital or acquired glucocorticoid resistance in rheumatoid arthritis, steroid-resistant asthma, AIDS, and other diseases may lead to therapy that sensitizes the affected tissues or the immune cells within these tissues to glucocorticoids.

Finally, the immunopotentiating effects of Δ^5-adrenal androgens on type 1 helper T cells may be useful in the treatment of patients with systemic lupus erythematosus and those in the final stages of AIDS. A prospective, placebo-controlled study showed marked clinical improvement and minimal adverse effects in patients with lupus who were treated with dehydroepiandrosterone.[132] This therapy may also be beneficial in patients with other such diseases.

Discussion

DR. FRANKLIN EPSTEIN: Is the peripheral production of CRH ever sufficient, in your opinion, to elevate the circulating concentrations enough to influence the production of corticotropin?

DR. CHROUSOS: No. I do not think so, with the exception of CRH production during the third trimester of pregnancy and in the rare paraneoplastic syndromes of ectopic CRH production. What we used to call "tissue CRH" is in fact the inflammatory cytokines and other mediators of inflammation, which separately or collectively activate the HPA axis when their plasma concentrations are elevated.

DR. EPSTEIN: Do other cells besides those of the immune system, such as liver or kidney cells, produce CRH?

DR. CHROUSOS: Yes. Chromaffin cells of the gut produce CRH, as well as theca and stromal cells of the ovary and Leydig cells of the testes. CRH autoregulates Leydig cells by inhibiting testosterone biosynthesis.

DR. ROGER SMITH: Would you comment on the effect of peripheral CRH production on corticotropin and the associated changes in immune function during pregnancy?

DR. CHROUSOS: During pregnancy, the placenta secretes CRH. As a result, plasma CRH concentrations

are quite elevated in the last trimester and are probably high enough to stimulate corticotropin secretion, causing the mild hypercortisolism that occurs at this time. Generally, there is immune suppression during pregnancy, presumably with the prevalence of type 2 over type 1 helper T lymphocytes, whereas after delivery, when the hypercortisolism subsides, there is a return to the prevalence of the type 1 phenotype. The onset or reactivation of certain autoimmune diseases, such as chronic thyroiditis and rheumatoid arthritis, in which hyperfunction of type 1 helper T cells has been postulated, can occur during the postpartum period.

DR. JEFFREY FLIER: Do families with cortisol resistance and genetic defects in glucocorticoid receptors have any immune defect or predisposition to autoimmune disease?

DR. CHROUSOS: Such families have generalized resistance, which means that they compensate for the low levels of glucocorticoid receptors by hypersecretion of cortisol.[39] Generally, members of these families do not have functional hypercortisolism or hypocortisolism but instead have problems that stem from the excessive production of adrenal androgens and mineralocorticoids. In such patients, the immune system appears to function normally.

DR. FLIER: Would you comment on the possible connection between the chronic fatigue syndrome and low CRH production?

DR. CHROUSOS: Patients with the chronic fatigue syndrome have subtle hypothalamic or suprahypothalamic adrenal insufficiency and immune hyperfunction.[6,7] Urinary cortisol excretion is decreased by 20 to 30 percent, and plasma cortisol responses to corticotropin are diminished. It has been postulated that in this syndrome a viral illness causes HPA-axis hypoactivity, which is reversed with recovery. A CRH-agonist analogue that crosses the blood–brain barrier or agents that stimulate hypothalamic CRH secretion may correct the CRH deficiency, which is presumably responsible for suboptimal arousal and debilitating fatigue in patients with the syndrome.

DR. FLIER: Was a connection found between inflammation and mood in these studies? Is there evidence that interleukin-1 stimulates the central CRH system?

DR. CHROUSOS: During acute inflammation, CRH and catecholamines are indeed stimulated; paradoxically, however, patients become somnolent and tired. These symptoms may be caused by interleukin-1 and other cytokines with hypnagogic effects. As inflammatory stress becomes chronic, things change. Apparently, the CRH neurons are mildly suppressed, whereas the vasopressin neurons are activated. When the inflammatory stress subsides, vasopressin secretion returns to normal, but the HPA may become transiently hypofunctional as a result of continued suppression of CRH neurons. During this period, patients may feel suboptimally aroused and fatigued, and the immune system may be hyperactive.

DR. SEYMOUR REICHLIN: Are the chronic fatigue syndrome and atypical depression manifestations of the same disease?

DR. CHROUSOS: They have many common characteristics, such as low central nervous system CRH secretion, fatigue, decreased arousal, or dysthymia, but appear to be different entities.[6,7] The chronic fatigue syndrome is presumably an acquired state with no seasonal variation, whereas atypical depression may have a genetic basis and be seasonal. Many diseases or states result from the convergence of two or more acquired or genetic factors, and this may be the case with the chronic fatigue syndrome and atypical depression, which have in common low CRH secretion and its sequelae.

DR. SPYROS PAVLOU: Can you differentiate between the effects of CRH and glucocorticoid on mood expression?

DR. CHROUSOS: In animals these effects have been separated. For example, in animals that have been pretreated with dexamethasone, the administration of CRH in the central nervous system results in all the characteristic behavioral effects of this neuropeptide. Generally, glucocorticoids have mixed effects. In the short term, they cause arousal and euphoria, possibly by stimulating the production of CRH by the central nucleus of the amygdala and the production of dopamine by neurons of the mesocorticolimbic system, even though they suppress the stress system at the same time. Over a longer period, glucocorticoids cause the atypical type of depression one sees in patients with Cushing's syndrome, presumably because of the suppression of hypothalamic CRH, which is reflected in low CRH concentrations in the cerebrospinal fluid. Approximately 50 to 60 percent of CRH in the cerebrospinal fluid comes from the paraventricular-nuclei CRH system. The rest, which comes from other areas of the brain and spinal cord, cannot be suppressed with glucocorticoids. It is therefore fair to say that prolonged hypersecretion or administration of glucocorticoids leads to the overall suppression of CRH secretion within the central nervous system.

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