Cells communicate with each other through molecular messengers, the hormones. The simple definition of a hormone as an intercellular messenger is much more inclusive than the original one, which limited the hormones to substances produced by specialized multicellular organs—the glands—that circulated in blood and acted on distant target organs. This simplification allowed single cells to be considered glands or targets of hormones, or both, and eliminated blood circulation as a prerequisite. The concept of endocrine function thus was expanded to paracrine, autocrine, juxtacrine, and intracrine functions, whereas the classic endocrine system, which included the traditional endocrine axes, was expanded to every organ and cell in the body that produced and responded to hormones.

Other major conceptual changes have occurred in the past 2 decades. Many of the traditional hormones that had defined sites of origin, roles, and target organs also were found to be produced in nontraditional locations and to have apparently unrelated roles in nonconventional target tissues. Also, as the molecular mechanisms of action of hormones were elucidated, it became apparent that significant convergence between the actions of different hormones and between the endocrine axes took place at the level of the target cells or tissues.

Life exists through maintenance of a complex dynamic equilibrium, or homeostasis, that is constantly challenged by intrinsic or extrinsic adverse forces, or stressors. Thus, stress is defined as a state of threatened homeostasis that is re-established by a complex repertoire of physiologic and behavioral adaptive responses of the organism. Hormones have a crucial role in the coordination of both basal and threatened homeostasis. One can clearly see the “wisdom” of the endocrine system as it integrates its effects to readjust homeostasis and to improve the chances of the self and species for survival; this paradigm is used to illustrate this integration.

The present overview focuses on the neuroendocrine infrastructure of the adaptive response to stress and on its effects on the major endocrine axes in the body. Also discussed is the altered regulation or dysregulation of the adaptive response in various physiologic and pathophysiologic states, which may influence the growth and development of an individual and define the vulnerability of this individual to endocrine, psychiatric, or immunologic disease.

**HOMEOSTASIS: STRESS SYNDROME PHENOMENOLOGY**

The stress response is subserved by a complex system located in both the central nervous system (CNS) and the periphery.[1] This system receives and integrates a diversity of neurosensory
(visual, auditory, somatosensory, nociceptive, and visceral), blood-borne, and limbic signals, which arrive through distinct pathways. Activation of the stress system leads to behavioral and physical changes that are remarkably consistent in their qualitative presentation. These changes are normally adaptive and improve the chances of the individual for survival.

Behavioral adaptation includes increased arousal, alertness, and vigilance; improved cognition; focused attention; and euphoria or dysphoria. It also includes enhanced analgesia and elevations in core temperature, with concurrent inhibition of vegetative functions, such as appetite, feeding, and reproduction.

Concomitantly, physical adaptation occurs principally to promote an adaptive redirection of energy. Thus, oxygen and nutrients are shunted to the CNS and the stressed body site(s), where they are most needed. Increases in cardiovascular tone (e.g., heart rate, cardiac ejection fraction, and arterial blood pressure), respiratory rate, and intermediate metabolism (gluconeogenesis, lipolysis) work in concert to promote the availability of vital substrates. Detoxification functions are activated to rid the organism of unnecessary metabolic products from the stress-related changes in metabolism while digestive function and growth, reproduction, and immunity are inhibited.

During stress, the organism also activates restraining forces, which prevent an overresponse from both central and peripheral components of the stress system. These forces are essential for successful adaptation. If they fail to contain the various elements of the stress response in a timely manner, the “adaptive” changes may turn excessive, prolonged, and maladaptive and thus contribute to the development of pathologic processes.

Often, stress is of a magnitude and nature that allow the perception of control by the individual. As such, stress can be pleasant and rewarding. Seeking of novelty stress by an individual is related to such phenomena and is pivotal for emotional and intellectual growth and development.[2] It is of note that activation of the stress system occurs during both feeding and sexual activity, sine qua non functions for survival of self and species.

**HOMEOSTASIS: STRESS SYNDROME PHYSIOLOGY**

**Neuroendocrine Effectors of the Stress Response: “The Stress System”**

The central components of the stress system are located in the hypothalamus and the brain stem and include the parvocellular corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) neurons of the paraventricular nuclei (PVN) of the hypothalamus, the CRH neurons of the paragigantocellular and parabranchial nuclei of the medulla, and the locus ceruleus (LC) and other mostly noradrenergic (norepinephrine [NE]) cell groups of the medulla and the pons (the LC/NE-sympathetic system).[3–5] The peripheral limbs of the stress system are the hypothalamic-pituitary-adrenal (HPA) axis along with the efferent sympathetic-adrenomedullary system, and components of the parasympathetic system.

**CORTICOTROPIN-RELEASING HORMONE, ARGinine VAsopressin, AND CATECHOLAMINERGIC NEURONS**

Corticotropin-releasing hormone, a 41–amino acid peptide and the principal hypothalamic regulator of the pituitary-adrenal axis, was isolated and sequenced by Vale and colleagues in 1981.[6] The subsequent availability of synthetic CRH and CRH antagonists allowed giant steps to be taken in the investigation of stress. Thus, CRH and CRH receptors were found in many extrahypothalamic sites of the brain, including parts of the limbic system, the basal forebrain, and the LC/NE-sympathetic system in the brain stem and spinal cord.[7,8]
In addition, intracerebroventricular administration of CRH was shown to set into motion a coordinated series of behavioral and peripheral responses, which included characteristic stress behaviors and activation of the pituitary-adrenal axis and the sympathetic nervous system.\[9, 10\] Therefore, CRH had a broader role in coordinating the stress response than had been suspected previously.\[0, 1\]–5 This neuropeptide reproduced fully the phenomenology of the stress response.

The central neurochemical circuitry responsible for activation of the stress system has been studied extensively. There apparently are multiple sites of interaction among the various components of the stress system.

Reciprocal reverberatory neural connections exist between the CRH and noradrenergic neurons of the central stress system, with CRH and norepinephrine stimulating each other, the latter occurring primarily through a\(^1\)noradrenergic receptors.\[11–13\]

Autoregulatory ultrashort negative feedback loops are also present in both the PVN CRH and brain stem nor-adrenergic neurons,\[14,15\] with collateral fibers inhibiting CRH and catecholamine secretion, through presynaptic CRH and a\(^2\)-noradrenergic receptors, respectively.\[14–16\]

Both CRH and catecholaminergic neurons also receive stimulatory innervation from the serotonergic and cholinergic systems \[17,18\] and inhibitory input from the \(\gamma\)-aminobutyric acid/benzodiazepine and opioid peptide neuronal systems of the brain\[14,19,20\] as well as through the end product of the HPA axis, glucocorticoids.\[14,21\]

The secretion of CRH, a major anorexigenic peptide, is stimulated by neuropeptide Y (NPY), the most potent known orexigenic factor, which simultaneously inhibits the LC/NE-sympathetic system.\[21–25\] This may be of particular relevance to changes in stress system activity in states of dysregulation of food intake, including malnutrition, anorexia nervosa, and obesity. Interestingly, glucocorticoids stimulate hypothalamic NPY gene expression, whereas they inhibit both the PVN CRH and LC/NE-sympathetic systems.\[26\]

Substance P has actions reciprocal to those of NPY, because it inhibits the PVN CRH neuron \[27\] but activates the LC/NE-sympathetic system.\[28\] Presumably, the level of substance P is elevated centrally, when there is peripheral activation of somatic afferent fibers,\[29\] and thus may have relevance to changes in stress system activity in chronic inflammatory or painful states.

A subset of PVN parvocellular neurons synthesize and secrete both CRH and AVP, whereas another subset secretes AVP only.\[1,3–5\] The relative proportion of the subset that secretes both neuropeptides increases significantly during stress. The terminals of the parvocellular PVN CRH and AVP neurons project to different sites, including the noradrenergic neurons of the brain stem and the hypophysial portal system in the median eminence. PVN CRH and AVP neurons also send projections to and activate pro-opiomelanocortin (POMC)-containing neurons in the arcuate nucleus of the hypothalamus, which in turn project to the PVN CRH and AVP neurons, innervate LC/NE-sympathetic neurons of the central stress system in the brain stem, and terminate on pain control neurons of the hindbrain and the spinal cord.\[3–5, 30\]

**HYPOTHALAMIC-PITUITARY-ADRENAL AXIS**

Corticotropin-releasing hormone, released into the hypophysial portal system, is the principal regulator of anterior pituitary corticotroph adrenocorticotropic hormone (ACTH) secretion.\[6\] It is permissive for secretion of ACTH, whereas AVP, although a potent synergistic factor
of CRH, has very little ACTH secretagogue activity by itself.[31–33] Furthermore, it appears that there is a positive reciprocal interaction between CRH and AVP at the level of the hypothalamus, with each neuropeptide stimulating the secretion of the other.[34]

In nonstressful situations, both CRH and AVP are secreted in the portal system in a circadian and highly concordant pulsatile fashion.[35–40] The amplitude of the CRH and AVP pulses increases in the early morning, resulting eventually in increases in the amplitude and apparent frequency of ACTH and in cortisol secretory bursts in the general circulation. The circadian release of CRH, AVP, ACTH, and cortisol in their characteristic pulsatile manner appears to be controlled by one or more pacemakers, whose location in humans is not known. These diurnal variations are perturbed by changes in lighting, feeding schedules, and activity and are disrupted when a stressor is imposed.

During acute stress, the amplitude and the synchronization of the PVN CRH and AVP pulsations in the hypophysial portal system increase. Also, with strong physical stress, recruitment takes place of AVP of magnocellular neuron origin that is secreted into both the hypophysial portal system through collateral neuraxons and the systemic circulation.[40,41] Depending on the stressor, other factors, such as angiotensin II, various cytokines, and lipid mediators of inflammation, are secreted and act on hypothalamic, pituitary, or adrenal components of the HPA axis, mostly to potentiate its activity.

The adrenal cortex is the principal target organ of pituitary-derived circulating ACTH. The latter is the key regulator of glucocorticoid and adrenal androgen secretion by the zonae fasciculata and reticularis, respectively, and it also participates in the control of aldosterone secretion by the zona glomerulosa.[42,43] There is evidence that other hormones or cytokines, or both—either originating from the adrenal medulla or coming from the systemic circulation—or neuronal information from the autonomic nerves of the adrenal cortex may also participate in the regulation of cortisol secretion.[40,44–46]

Glucocorticoids are the final effectors of the HPA axis. These hormones are pleiotropic, and they exert their effects through their ubiquitously distributed intracellular receptors.[47,48]

The nonactivated glucocorticoid receptor resides in the cytosol in the form of a hetero-oligomer with heat-shock proteins and immunophilin.[49] On ligand binding, the glucocorticoid receptors dissociate from the rest of the hetero-oligomer and translocate into the nucleus, where they interact as homodimers with specific glucocorticoid-responsive elements within the DNA to transactivate appropriate hormone-responsive genes.[50] Through protein-protein interactions, the activated receptors also inhibit several transcription factors, such as c-jun/c-fos and NF-κB/Rel A, which are positive regulators of transcription of several genes involved in the activation of function and growth of nonimmune and immune cells.[51–53] They also change the stability of mRNAs and, therefore, the translation rates of several glucocorticoid-responsive proteins. Furthermore, glucocorticoids influence the secretion rates of specific proteins and alter the electrical potential of neuronal cells through mechanisms that have not yet been elucidated.

Glucocorticoids play a key regulatory role in the basal control of HPA axis activity and in the termination of the stress response by acting at extrahypothalamic regulatory centers, the hypothalamus, and the pituitary gland.[3,54] The inhibitory glucocorticoid feedback on the ACTH secretory response acts to limit the duration of the total tissue exposure to glucocorticoids, thus minimizing the catabolic, conditionally lipogenic, antireproductive, and immunosuppressive effects of these hormones.

Interestingly, a dual-receptor system exists for glucocorticoids in the CNS, including glucocorticoid receptor type I or mineralocorticoid receptor, which responds to low levels of...
glucocorticoids, and the classic glucocorticoid receptor (type II), which responds to both basal and stress levels. [54]

**LC/NE-SYMPATHETIC, ADRENOMEDULLARY, AND PARASYMPATHETIC SYSTEMS**

The autonomic nervous system responds rapidly to stressors and controls a wide range of functions. Cardiovascular, respiratory, gastrointestinal, renal, endocrine, and other systems are regulated by the sympathetic nervous system, the parasympathetic system, or both. [1,55] In general, the parasympathetic system can assist sympathetic functions by withdrawing and antagonizing them by increasing its activity.

Sympathetic innervation of peripheral organs is derived from the efferent preganglionic fibers, whose cell bodies lie in the intermediolateral column of the spinal cord. [55–57] These nerves synapse in the bilateral chain of sympathetic ganglia with postganglionic sympathetic neurons that innervate on a widespread basis the smooth muscle of the vasculature, the heart, the kidney, the gut, fat, and many other organs. The preganglionic neurons are primarily cholinergic, whereas the postganglionic neurons release mostly norepinephrine. The sympathetic system through the adrenal medulla also has a humoral contribution by providing all of the circulating epinephrine and some of the norepinephrine.

In addition to the “classic” neurotransmitters acetylcholine and norepinephrine, both sympathetic and para-sympathetic subdivisions of the autonomic nervous system contain several subpopulations of target-selective and neurochemically coded neurons that express a variety of neuropeptides and, in some cases, adenosine triphosphate, nitric oxide, or lipid mediators of inflammation. [56,57]

Thus, CRH, NPY, somatostatin, and galanin are colocalized in noradrenergic vasoconstrictive neurons, whereas vasoactive intestinal polypeptide and, to a lesser extent, substance P and calcitonin gene-related peptide are colocalized in cholinergic neurons. Transmission in sympathetic ganglia is also modulated by neuropeptides released from preganglionic fibers and short interneurons as well as by primary afferent nerve collaterals. [58]

**STRESS SYSTEM: INTERACTIONS WITH OTHER CENTRAL NERVOUS SYSTEM COMPONENTS**

In addition to setting the level of arousal and influencing the vital signs, the stress system interacts with three other major CNS elements: the mesocorticolimbic dopaminergic system, the amygdala-hippocampus complex, and the arcuate nucleus POMC neuronal system. [59–61] All three are activated during stress and, in turn, influence the activity of the stress system. In addition, the stress system interacts with thermoregulatory and appetite-satiety centers of the CNS.

**Mesocorticolimbic System**

Both the mesocortical and the mesolimbic components of the dopaminergic system are innervated by the LC/NE-sympathetic system and are activated by it during stress. [59,62] The mesocortical system, which includes dopaminergic neurons of the ventral tegmentum that send projections to the prefrontal cortex, is believed to be involved in anticipatory phenomena and cognitive functions. The mesolimbic system, which consists of dopaminergic neurons of the ventral tegmentum that innervate the nucleus accumbens, is believed to play a principal role in motivational/reinforcement/reward phenomena.
Euphoria or dysphoria is presumably mediated by the mesocorticolimbic system, which is also considered the target of several substances of abuse, such as cocaine.

**Amygdala/Hippocampus Complex**

The amygdala/hippocampus complex is activated during stress primarily by ascending catecholaminergic neurons originating in the brain stem or by inner emotional stressors, such as conditioned fear, possibly from cortical association areas.[60,63–65]

Activation of the amygdala is important for retrieval and emotional analysis of relevant information for any given stressor.

In response to emotional stressors, the amygdala can directly stimulate both central components of the stress system and the mesocorticolimbic dopaminergic system. Interestingly, there are CRH peptidergic neurons in the amygdala that respond positively to glucocorticoids and whose activation leads to anxiety. The hippocampus exerts an important inhibitory influence on the activity of the amygdala as well as of the PVN CRH and LC/NEsympathetic systems.

**Pro-opiomelanocortin Neuronal System: Analgesia**

The LC/NE-noradrenergic and the CRH/AVP-producing neurons reciprocally innervate and are innervated by opioid peptide (POMC-producing) neurons of the arcuate nucleus of the hypothalamus.[14,30,61] Activation of the stress system stimulates hypothalamic POMC-derived peptides, such as α-melanocyte–stimulating hormone and β-endorphin, which reciprocally inhibit the activity of both central components of the stress system and, through projections to the hindbrain and the spinal cord, produce analgesia.

**Temperature Regulation**

Activation of the LC/NE-noradrenergic and the PVN CRH systems elevates core temperature. Both norepinephrine and CRH administered intracerebroventricularly can cause temperature elevation, possibly through prostanoid-mediated actions on the septal and hypothalamic temperature-regulating center. CRH has also been shown to mediate partly the pyrogenic effects of the inflammatory cytokines tumor necrosis factor-α, interleukin-1 (IL-1), and interleukin-6 (IL-6), which are stimulated by lipopolysaccharide, an exogenous pyrogen.

**Appetite Regulation**

The appetite-satiety centers in the hypothalamus are influenced by stress. Acutely, CRH causes anorexia, whereas NPY, which is orexigenic, stimulates CRH secretion, probably to counterregulate its own actions.[22,23] Interestingly, at the same time, NPY inhibits the LC/NEsympathetic system and activates the parasympathetic system, actions that help with digestion and storage of nutrients.[24,25] Leptin, a satiety-stimulating polypeptide secreted by adipose tissue, is a potent inhibitor of hypothalamic NPY and stimulant of a subset of arcuate nucleus POMC neurons secreting α-melanocyte–stimulating hormone, another potent anorexiogen that exerts its effects through melanocortin receptor type 4.[66] Leptin has a circadian rhythm with a peak in the early part of the sleep period. [67] Ghrelin, is an appetite stimulating peptide, primarily secreted from the stomach. In a recent report it is suggested that ghrelin augments ACTH release in response to stress, but further investigation is needed to determine the function of ghrelin during stress. [68] Circulating concentrations of ghrelin peak exhibit a nocturnal maximum. [a] Another important system involved in energy homeostasis and sleep/wake regulation is the orexin (hypocretin) system. Centrally administered orexin activate PVN and CRH/vasopressin neurons, adrenocorticotropic hormone (ACTH) secretion and elevation of plasma concentration of corticosterone. Moreover, orexin administration is
associated with feeding stimulation, and stress due to restraint and cold in animals, has demonstrated an increase in the orexin m-RNA.[68]

**STRESS SYSTEM: INTERACTIONS WITH MAJOR ENDOCRINE AXES**

**Gonadal Axis**

The reproductive axis is inhibited at all levels by various components of the HPA axis. [66] Thus, either directly or through arcuate POMC neuron b-endorphin, CRH suppresses the gonadotropin-releasing hormone (GnRH) neuron of the arcuate nucleus.[69–70] Glucocorticoids, on the other hand, exert inhibitory effects at the levels of the GnRH neuron, the pituitary gonadotroph (influencing primarily the secretion of luteinizing hormone [LH]), and the gonads and render target tissues of sex steroids resistant to these hormones,[66,69–71] The inflammatory cytokines, levels of which are elevated during inflammatory stress, also suppress reproductive function at several levels. Thus, the pulsatile secretion of GnRH from the hypothalamus and ovarian or testicular steroidogenesis are concomitantly inhibited by these cytokines. These effects are exerted both directly and by activating hypothalamic neural circuits that secrete CRH and POMC-derived peptides as well as by peripheral elevations of glucocorticoids. Leptin plays a major permissive and activational role in the activity of the gonadal axis, and low levels have been implicated in the gonadal suppression observed in starvation and anorexia nervosa.[66] The elevation of leptin levels that takes place around the onset of puberty has been suggested as the peripheral signal that notifies the hypothalamus of the adequacy of caloric resources for development of effective reproductive function.

Suppression of gonadal function caused by chronic HPA activation has been demonstrated in highly trained runners of either sex and in ballet dancers.[72–74] These subjects have increased evening plasma cortisol and ACTH levels, increased urinary free cortisol excretion, and blunted ACTH responses to exogenous CRH; males have low LH and testosterone levels, and females have amenorrhea. Characteristically, obligate athletes go through withdrawal symptoms and signs if they discontinue their exercise routine. This syndrome may be the result of withdrawal from the daily exercise-induced elevation of opioid peptides and from the similarly induced stimulation of the mesocorticolimbic system.[1]

The interaction between CRH and the gonadal axis appears to be bidirectional. The presence of estrogenresponsive elements in the promoter area of the CRH gene and direct stimulatory estrogen effects on CRH gene expression were recently shown.[75] This finding implicates the CRH gene and, therefore, the HPA axis as potentially important targets of gonadal steroids and potential mediators of sex-related differences in stress-response/HPA-axis activity.[70]

**Growth Axis**

The growth axis is also inhibited at many levels during stress. Prolonged activation of the HPA axis leads to suppression of growth hormone (GH) secretion and inhibition of somatomedin C and other growth factor effects on target tissues by glucocorticoids.[76–81] the latter presumably occurring through inhibition of the c-jun/c-fos heterodimer by the ligand-bound glucocorticoid receptor. Acute elevations of GH concentration in plasma may occur at the onset of the stress response, however, or after acute administration of glucocorticoids, presumably through stimulation of the GH gene by glucocorticoids through glucocorticoid-responsive elements in its promoter region.[82] In addition to the direct effects of glucocorticoids, which are pivotal in the suppression of growth observed in prolonged stress, increases in somatostatin secretion caused by CRH, with resultant inhibition of GH secretion, have been implicated as a potential mechanism of stress-related suppression of GH secretion.[83]

In several stress system–related mood disorders with a hyperactive HPA axis, such as anxiety or melancholic depression, levels of GH or insulin-like growth factor-1 (IGF-1), or both, are

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significantly decreased. Nervous pointer dogs, an animal model of anxiety with mixed panic and phobic features, have low IGF-1 levels and decreased body growth compared with nonaffected animals.[84]

Compared with healthy control subjects, patients with panic disorder have blunted GH responses to intravenously administered clonidine, and children with anxiety disorders might have short stature.[85,86] The HPA axis–induced tissue resistance to GH, IGF-1, or both is restored after hypophysectomy or adrenalectomy in a stressed animal model, underscoring the importance of glucocorticoids in this phenomenon.[87] In melancholic depression, not only is GH secretion decreased but also the dexamethasone-induced GH increase is blunted.[88]

**Thyroid Axis**

A corollary phenomenon to growth axis suppression is the stress-related inhibition of thyroid axis function. Activation of the HPA axis is associated with decreased production of thyroid-stimulating hormone and inhibition of conversion of the relatively inactive thyroxine to the more biologically active triiodothyronine in peripheral tissues (the “euthyroid sick” syndrome). [89–90] Although the exact mechanism for these phenomena is not known, both phenomena may be caused by the increased levels of glucocorticoids and may serve to conserve energy during stress. Inhibition of thyroid-stimulating hormone secretion by CRH-stimulated increases in somatostatin might also participate in the central component of thyroid axis suppression during stress. During inflammatory stress, inhibition of thyroid-stimulating hormone secretion and enhancement of somatostatin production may occur in part through the direct action of inflammatory cytokines on the hypothalamus, the pituitary, or both.

Also, peripheral 59-deiodinase may be directly inhibited by the same cytokines.

**Metabolic Axis**

Glucocorticoids not only have profound inhibitory effects on GH and sex steroid production but also antagonize the actions of these hormones on fat tissue catabolism (lipolysis) and muscle and bone anabolism. Thus, chronic activation of the stress system would be expected to increase visceral adiposity, decrease lean body (bone and muscle) mass, and suppress osteoblastic activity. Interestingly, the phenotype of central obesity, decreased lean body mass, osteoporosis, or all three is shared by patients with Cushing syndrome, some patients with melancholic depression (pseudo-Cushing syndrome), and patients with (dys)metabolic syndrome X (visceral obesity, hyperlipidemia, hypertension), many of whom are characterized by increased activity of the HPA axis and a similar somatic and biochemical phenotype.[91–95]

Because increased gluconeogenesis is a characteristic feature of the stress response1,2 and glucocorticoids induce insulin resistance,[96] activation of the HPA axis may contribute to the poor control of diabetic patients with emotional stress or concurrent inflammatory and other disease. Indeed, mild, chronic activation of the HPA axis was recently demonstrated in patients with type 1 diabetes under moderate or poor glycemic control [97] and in patients with type 2 disease who had developed diabetic neuropathy.[98]

Glucocorticoid-induced progressively increasing visceral adiposity directly causes further insulin resistance and deterioration of glycemic control of diabetes mellitus. Thus, chronic activation of the stress system in this disorder participates in a vicious cycle of increasing hyperglycemia, hypercholesterolemia, and insulin need.

Adiponectin, is an adipokine exclusively secreted from the adipose tissue. Glucocorticoids inhibit adiponectin release in vitro, and elevated cortisol levels in stress may lower adiponectin. Moreover, adiponectin concentrations are decreased in obesity, diabetes type 2 and insulin
resistance, and increase with weight reduction. Furthermore, there are recent indications that adiponectin is inversely associated with markers of inflammation, and endothelial dysfunction and is a significant inverse predictor of cardiovascular disease and cancer.[99]

**STRESS SYSTEM AND GASTROINTESTINAL FUNCTION**

An increasing body of evidence suggests that CRH is involved in the central mechanisms by which stress influences gastrointestinal function. Thus, PVN CRH induces inhibition of gastric acid secretion and emptying while stimulating colonic motor function, independent of the associated stimulation of the HPA.[100–101] This is by inhibition of the vagus nerve (with ensuing selective inhibition of gastric motility) and by stimulation, through the LC/NE-sympathetic system, of the sacral parasympathetic system (with ensuing selective stimulation of colonic motility). Thus, CRH may be implicated in mediating the gastric stasis that results from the stress of surgery or from high levels of central IL-1.[102] CRH may also be implicated in the stress-induced colonic hypermotility in patients with irritable bowel syndrome. Colonic contraction and pain in these patients may activate LC/NE-sympathetic neurons, thus forming a vicious cycle, which may help explain the chronicity of the condition.

**STRESS SYSTEM: IMMUNE SYSTEM INTERACTIONS**

**Effects of the Immune Inflammatory Reaction on the HPA Axis and the LC/NE-Sympathetic System**

The immune system exerts its surveillance defense function constantly, mostly on an unconscious level for the individual.[103,104] It has been known for several decades that immune inflammatory insults in the form of an infectious disease, an active autoimmune inflammatory process, or accidental or surgical trauma are associated with concurrent activation of the HPA axis. More recently, it became apparent that immune cytokines and other humoral mediators of inflammation are potent activators of central stress-responsive neurotransmitter systems, constituting the afferent limb of the feedback loop through which the immune inflammatory system and the CNS communicate. In this way, the peripheral immunologic apparatus signals the brain to participate in maintaining immunologic homeostasis.

The three “inflammatory cytokines,” tumor necrosis factor-a, IL-1, and IL-6, all produced at inflammatory sites and elsewhere in a cascade-like fashion, can cause stimulation of the HPA axis in vivo, alone, or in synergy with each other.[105,106] This can be blocked significantly with CRH-neutralizing antibodies, prostanoid synthesis inhibitors, and glucocorticoids. In addition, all three cytokines directly stimulate hypothalamic CRH secretion in vitro, an action that is also suppressed by glucocorticoids and prostanoid synthesis inhibitors.[107–109]

There is evidence to suggest that IL-6, the main endocrine cytokine, plays the primary role in the immune stimulation of the human HPA axis. Thus, in humans, IL-6 is an extremely potent activator of the axis and lacks the vascular leak–promoting and hypotensive side effects of the other two inflammatory cytokines.[110,111] The elevations in ACTH and cortisol levels attained by IL-6 are well above those observed with maximal stimulatory doses of CRH, suggesting that parvocellular AVP and other ACTH secretagogues are also recruited by this cytokine. At high doses, IL-6 also stimulates peripheral elevations of AVP, presumably as a result of a stimulatory effect on magnocellular AVP-secreting neurons.[111] This suggests that IL-6 may be involved in the genesis of the syndrome of inappropriate antidiuretic hormone secretion, which is observed during the course of infectious or inflammatory disease or during trauma.
The route of access of the inflammatory cytokines to the central CRH- and AVP-secreting neurons is not clear, given that the cellular bodies of both are protected by the blood-brain barrier.[103]

It has been suggested that they may act on nerve terminals of these neurons at the median eminence through the fenestrated endothelia of this circumventricular organ. Other possibilities include stimulation of intermediate neurons located in the organum vasculosum of the lamina terminalis, another circumventricular organ, and crossing of the blood-brain barrier with the help of a specific transport system. Also, it is quite likely that each of these cytokines might initiate a cascade of paracrine and autocrine events with sequential secretion of local mediators of inflammation by nonfenestrated endothelial cells, glial cells, cytokinergic neurons, or all three, resulting in activation of CRH- and AVP-secreting neurons.[112–113]

Some of the activating effects of inflammation on the HPA axis may be exerted indirectly through stimulation of the central noradrenergic pathways by the inflammatory cytokines and other humoral mediators of inflammation. Also, activation of peripheral nociceptive, somatosensory, and visceral afferent fibers would lead to stimulation of both the catecholaminergic and the CRH neuronal systems via ascending spinal pathways. Interestingly, in chronic inflammatory states, in which chronic central elevations of substance P may take place, an impairment of HPA axis responsiveness to stimuli or stress is observed, probably because of the suppressive effect of substance P on the CRH neuron.[27–29] Such an impairment has been observed in African trypanosomiasis, the acquired immunodeficiency syndrome, and extensive burns in humans and in chronic animal models of inflammation. [29,103,114–117]

Inflammatory mediators other than the three inflammatory cytokines may also participate in activation of the HPA axis. Thus, several eicosanoids, platelet-activating factor, and epidermal growth factor have strong CRH-releasing abilities.[112,113,118] It is not clear, however, which of the effects are endocrine and which are paracrine. Direct effects, albeit delayed, of most of these cytokines and mediators of inflammation on pituitary ACTH and adrenocortical glucocorticoid secretion have also been shown.[119–122]

**Effects of the HPA Axis and LC/NE-Sympathetic System on the Immune Inflammatory Reaction**

Activation of the HPA axis has profound inhibitory effects on the immune inflammatory response, because virtually all the components of the immune response are inhibited by cortisol. [47,103,104,123] At the cellular level, alterations in leukocyte traffic and function, decreases in production of cytokines and mediators of inflammation, and inhibition of the effects by the latter on target tissues are among the main anti-inflammatory and immunosuppressive effects of glucocorticoids. These effects are exerted both at the resting basal state and during inflammatory stress, when the circulating concentrations of glucocorticoids are elevated. Thus, circadian activity of several immune functions has been demonstrated in reverse-phase synchrony with that of plasma glucocorticoid levels.

A large infrastructure of anatomic, chemical, and molecular connections allows communication not only within but also between the neuroendocrine and immune systems. The efferent sympathetic-adrenomedullary system apparently has a major role in the interactions between the HPA axis and immune inflammatory stress by being reciprocally connected with the CRH system, by transmitting humoral and nervous signals to both primary and secondary lymphoid organs, and by reaching all sites of inflammation through the postganglionic sympathetic neuron.[124,125] Thus, immune and immune accessory cells contain receptors for and respond to neurotransmitters, neuropeptides, and neurohormones secreted by postganglionic sympathetic neurons. Of particular relevance is the mast cell, which

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is activated by products of these neurons, such as the neuropeptide CRH. This may explain the induction by stress of allergic diseases, such as asthma and eczema, or of functional vascular diseases, such as migraine headache.

When activated during stress, the autonomic nervous system exerts systemic effects on immune organs humorally by inducing secretion of IL-6 in the systemic circulation. Despite its inherent inflammatory activity, IL-6, by causing glucocorticoid secretion and by directly suppressing the secretion of tumor necrosis factor-a and IL-1, plays a major role in the overall control of inflammation.

The combined effect of glucocorticoid on the monocyte-stimulating macrophage is to inhibit innate immunity and T helper-1 cytokines, such as IL-12, and to stimulate T helper-2–related cytokines, such as IL-10. This suggests that stress-related immunosuppression refers mostly to innate and cellular immunity, facilitating diseases (e.g., the common cold, tuberculosis, and certain tumors) related to deficiency of such type of immune responses, against which they are recruited.

**STRESS SYSTEM: PATHOPHYSIOLOGY**

**Chronic Hyperactivation States**

In theory, the dose-response relation between the responsiveness of the stress system and the potency of a stressor is represented by a sigmoidal curve, which would be expected to differ from individual to individual, with two major pathologic groups located at the two extremes. Thus, one individual’s dose-response curve might be shifted to the left of that of a normally reactive individual, whereas another individual’s might be shifted to the right. The former denotes an excessive reaction; the latter, a defective one. Similarly, the dose-response relation between an individual’s sense of well-being or performance ability and the activity of the stress system is represented by an inverted U-shaped curve that covers the range of the activity of the latter. Shifts to either the left or the right of this range would result, respectively, in hypoarousal or hyperarousal (anxiety) and a suboptimal sense of well-being or diminished performance.

Several of the multiple factors that determine the stress responses of individuals are inherited, as quantitative genetics of human complex behaviors indicate. It has been estimated that approximately two thirds of reliable variance in measured personality traits are due to genetic influences. Thus, genetic polymorphisms—clinically significant alterations of the expression of genes involved in the regulation of the stress system such as those of CRH, AVP, and their receptors and regulators—are expected to account for the observed variability in the function of the stress system. A significant variance of the stress responses of individuals is environmental, however. The intrauterine period, infancy, childhood, and adolescence are times of increased plasticity for the stress system. Excessive or sustained activation during these critical periods may have profound effects on its later function, especially as it relates to pathophysiology (see later).

In general, the stress response with the resultant activation of the HPA axis is meant to be short term or at least of a limited duration. The time-limited nature of this process renders its accompanying antigrowth, antireproductive, catabolic, and immunosuppressive effects temporarily beneficial and of no adverse consequences. Chronicity of stress system activation, on the other hand, would lead to the syndromal state that Selye described in 1936. Because CRH coordinates behavioral, neuroendocrine, autonomic, and immunologic adaptation during stressful situations, increased and prolonged production of CRH could explain the pathogenesis and all the manifestations of the syndrome, including its psychiatric, circulatory, metabolic, and immune components.
The syndrome of adult melancholic depression represents a prototypical example of dysregulation of the generalized stress response, leading to dysphoric hyperarousal, chronic activation of the HPA axis and the sympathetic nervous system, and relative immunosuppression.[132–133] Cortisol excretion is increased, and plasma ACTH response to exogenous CRH is decreased.[91] Also, cerebrospinal fluid levels of CRH are elevated in these patients. These findings suggest that in depression, there is hypersecretion of CRH, which may participate in the initiation or perpetuation, or both, of a vicious cycle. Depressed patients were found at autopsy to have markedly increased numbers of PVN CRH neurons.[134] Whether this is genetically determined, environmentally induced, or both is unclear.

In addition to melancholic depression, a spectrum of other conditions may be associated with increased and prolonged activation of the HPA axis; these include anorexia nervosa and malnutrition,[135–137] obsessive-compulsive disorder,[138] panic anxiety,[139] excessive exercise,[72] chronic active alcoholism,[140] alcohol and narcotic withdrawal,[141,142] diabetes mellitus types 1 and 2,[97,98] central (visceral) obesity,[92–94] childhood sexual abuse,[143] and, perhaps, hyperthyroidism[144] and the premenstrual tension syndrome.[145]

It is of interest that anorexia nervosa and malnutrition are characterized by increased levels of cerebrospinal fluid NPY, which, together with the markedly decreased leptin levels, could provide an explanation why the HPA axis in these subjects is activated while the LC/NE-sympathetic system shows clear evidence of profound hypoactivity.[22–25,66] Glucocorticoids, on the other hand, by stimulating NPY and by inhibiting the PVN CRH and the LC/NE-sympathetic systems,5 would produce the hyperphagia and obesity observed in Cushing syndrome and many rodent models of obesity, such as the Zucker rat.[1,26]

The association between chronic, experimentally induced psychosocial stress and a hypercortisolism or metabolic syndrome–like state, with increased incidence of atherosclerosis, has been reported in cynomolgus monkeys.[146] In these animals, chronic, stress-induced activation of the HPA axis, and therefore hypercortisolism, apparently leads to visceral obesity, insulin resistance, and suppression of GH secretion, all converging to result in the development of varying degrees of the physical and biochemical phenotype of the metabolic syndrome X90–92.

One area of recent interest relates to the association of chronic stress and gastrointestinal illness. In a study of selectively referred patients with chronic gastrointestinal pain, a high incidence of physically and sexually abused women was reported.[147] Sexually abused girls suffer chronic activation of the HPA axis, like patients with melancholic depression.[143] Thus, CRH hypersecretion could be the hidden link between the symptoms of chronic gastrointestinal pain and a history of abuse.[148] Chronic activation of the HPA axis, the LC/NE-sympathetic system, or both by depletion or tachyphylaxis of the opioid-peptide system responsible for stress-induced analgesia may also explain the observed lower pain thresholds for visceral sensation in patients with functional gastrointestinal disorders.[147]

Psychosocial dwarfism is a term describing severe childhood or adolescent short stature, delayed puberty, or both caused by emotional deprivation or psychologic harassment.[149] Decreased GH secretion that is reversible after separation of the child from the responsible environment is a characteristic finding in this condition,[150] which is also associated with a variety of behavioral abnormalities, such as depression and bizarre eating behaviors.[151]

Psychosocial dwarfism was first studied in infants housed in foundling homes or orphanages who had decreased growth and high mortality rates. It was hypothesized that this failure to thrive resulted from lack of attention and stimulation, deficient nutrition, or both. Later, it was shown that weight gain was independent of food intake, whereas with a caring and attentive...
environment, growth advanced and the psychological profile improved. In addition to low GH secretion, these patients had a dysfunctional thyroid axis, resembling the euthyroid sick syndrome.

Interestingly, very little is known about the HPA axis in children with this condition; however, it is suspected to be chronically activated, and this would explain the other endocrine abnormalities in these children.

Infantile malnutrition is characterized by hypercortisolism, decreased responsiveness to CRH, incomplete dexamethasone suppression, and thyroid function test changes reminiscent of the euthyroid sick syndrome, abnormalities that are restored after nutritional rehabilitation. [1, 137] It is noteworthy that in this condition, increases rather than decreases in GH secretion are present, resulting apparently from starvation-induced hyposecretion of IGF-1, a potent negative feedback regulator of GH secretion.

Premature infants are especially at risk of delayed growth, development, or both, especially after a prolonged hospitalization in the intensive care nursery. The condition is similar to psychosocial dwarfism but is known as reactive attachment disorder of infancy. Interestingly, activation of the fetal HPA axis is also associated with fetal growth retardation. [131] The major influence of infant care on growth and development has been shown in a species of nonhuman primates that are socially organized in extended families. [152]

The third trimester of pregnancy is also characterized by hypercortisolism of a degree similar to that observed in severe depression, anorexia nervosa, and mild Cushing syndrome and is the only known physiologic state in humans in which CRH circulates in plasma at levels high enough to cause activation of the HPA axis. [66,153,154] Although circulating CRH, which is placental in origin, is bound with high affinity to CRH-binding protein, [155,156] it appears that the circulating free fraction is sufficient to explain the observed escalating hypercortisolism when the CRH binding concentration starts to decrease gradually in plasma after the 35th week of pregnancy. [157]

**Chronic Hypoactivation States**

Hypoactivation of the stress system, rather than sustained activation in which chronically reduced secretion of CRH may result in pathologic hypoarousal, characterizes another group of states. Patients with atypical and seasonal depression and the chronic fatigue syndrome are in this category. [158,159] In the depressive (winter) state of the former and in the period of fatigue in the latter, there is chronically decreased activity of the HPA axis. Similarly, patients with fibromyalgia have decreased urinary free cortisol excretion and frequently complain of fatigue. [160] Hypothyroid patients also have clear evidence of CRH hyposecretion. [144] Interestingly, one of the major manifestations of hypothryoidism is depression of the “atypical” type. Withdrawal from smoking has also been associated with decreased cortisol and catecholamine secretion. [161,162] Decreased CRH secretion in the early period of nicotine abstinence could explain the hyperphagia, hypometabolism, and weight gain frequently observed in these patients. It is interesting that in Cushing syndrome, the clinical picture of atypical depression, hyperphagia, weight gain, fatigue, and anergia is consistent with the suppression of the CRH neuron by the associated hypercortisolism. [163] The period after cure of hypercortisolism, the postpartum period, and periods after cessation of chronic stress are also associated with suppressed PVN CRH secretion and decreased HPA axis activity. [1–4, 66,164,165]

Theoretically, an excessive HPA axis response to inflammatory stimuli would mimic the stress or hypercortisolemic state and would lead to increased susceptibility of the individual to certain infectious agents or tumors but enhanced resistance to autoimmune inflammatory disease; in
contrast, a defective HPA axis response to such stimuli would reproduce the glucocorticoid-deficient state and would lead to relative resistance to infections and neoplastic disease but increased susceptibility to autoimmune inflammatory disease.[103,104] Such properties were unraveled in an interesting pair of near-histocompatible, highly inbred rat strains, the Fischer and Lewis rats, both of which were genetically selected out of Sprague-Dawley rats, for their resistance or susceptibility, respectively, to inflammatory disease.[166,167] There is an increasing body of evidence that patients with rheumatoid arthritis have a mild form of central hypocortisolism, because they have reduced 24-hour cortisol excretion, a blunted diurnal rhythm of cortisol secretion, and blunted adrenal responses to surgical stress.[168,169] Thus, dysfunction of the HPA axis may play a role in development, perpetuation, or both of the T helper-1 type of autoimmune disease rather than being an epiphenomenon. The same rationale may explain the high incidence of autoimmune disease in the period after cure of hypercortisolism and the postpartum period as well as in unreplaced or underreplaced adrenal insufficiency.[104]

CONCLUSION

The concept of a hormone as a chemical messenger that allows local, regional, or distant cellular communication challenges formerly narrow definitions. These newer concepts merge the views of separate signaling mechanisms by means of classic hormones and neurochemical networks into an integrated pattern from which can emerge a clearer understanding of homeostasis and its disturbances, at the extremes of which we recognize disease. Through this view of integration and organization, there also emerge mutually interdependent linkages between neurobehavioral psychoemotional states and “classic” disease states of malignancy, autoimmunity, inflammation, reproductive disturbances, and disturbances in growth. Although the view presented now is initially largely inferential, it is increasingly supported by solid experimental and epidemiologic evidence. Establishing an even more solid scientific basis for the views presented in this chapter is an ongoing challenge.

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2. Reproduction

Beta-endorphin

LHRH → CRH

LH, FSH

Testosterone, Estradiol

ACTH → Glucocorticoids

Target tissues
3.

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4. 

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5.
6. 

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