Annu. Rev. Physiol. 2005. 67:259–84
doi: 10.1146/annurev.physiol.67.040403.120816

ENDOCRINOLOGY OF THE STRESS RESPONSE[1]

Evangelia Charmandari, Constantine Tsigos, and George Chrousos
Pediatric and Reproductive Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892, and Hellenic National Diabetes Center, Athens, 10675, Greece;
email: charmane@mail.nih.gov; chrousosG@aol.com

Key Words stress system, endocrinology of stress, stress-related disorders

■ **Abstract** The stress response is subserved by the stress system, which is located both in the central nervous system and the periphery. The principal effectors of the stress system include corticotropin-releasing hormone (CRH); arginine vasopressin; the proopiomelanocortin-derived peptides α-melanocyte-stimulating hormone and β-endorphin, the glucocorticoids; and the catecholamines norepinephrine and epinephrine. Appropriate responsiveness of the stress system to stressors is a crucial prerequisite for a sense of well-being, adequate performance of tasks, and positive social interactions. By contrast, inappropriate responsiveness of the stress system may impair growth and development and may account for a number of endocrine, metabolic, autoimmune, and psychiatric disorders. The development and severity of these conditions primarily depend on the genetic vulnerability of the individual, the exposure to adverse environmental factors, and the timing of the stressful events, given that prenatal life, infancy, childhood, and adolescence are critical periods characterized by increased vulnerability to stressors.

INTRODUCTION

Life exists through maintenance of a complex dynamic equilibrium, termed homeostasis, that is constantly challenged by intrinsic or extrinsic, real or perceived, adverse forces, the stressors (1, 2). Stress is defined as a state of threatened or perceived as threatened homeostasis. The human body and mind react to stress by activating a complex repertoire of physiologic and behavioral central nervous system and peripheral adaptive responses, which, if inadequate or excessive and/or prolonged, may affect personality development and behavior, and may have adverse consequences on physiologic functions, such as growth, metabolism, circulation, reproduction, and the inflammatory/immune response (1, 2). The state of chronic

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dyshomeostasis due to inadequate or excessive/prolonged adaptive responses, in which the individual survives but suffers adverse consequences, has been called allostasis.

The present review focuses on the neuroendocrinology of the stress response and the effects of stress on the major endocrine axes. It also provides a brief overview of the altered regulation of the adaptive response in various physiologic and pathologic states that may influence the growth and development of an individual and may define vulnerability of the individual to endocrine, psychiatric, cardiovascular, neoplastic, or immunologic disorders.

ENDOCRINOLOGY OF THE STRESS RESPONSE

Neuroendocrine Effectors of the Stress Response

The stress response is subserved by the stress system, which has both central nervous system (CNS) and peripheral components (1–3). The central components of the stress system are located in the hypothalamus and the brainstem, and include (*a*) the parvocellular neurons of corticotropin-releasing hormone (CRH); (*b*) the arginine vasopressin (AVP) neurons of the paraventricular nuclei (PVN) of the hypothalamus; (*c*) the CRH neurons of the paragigantocellular and parabranchial nuclei of the medulla and the locus ceruleus (LC); and (*d*) other mostly noradrenergic (NE) cell groups in the medulla and pons (LC/NE system). The peripheral components of the stress system include (*a*) the peripheral limbs of the hypothalamic-pituitary-adrenal (HPA) axis; (*b*) the efferent sympathetic-adrenomedullary system; and (*c*) components of the parasympathetic system (1–3) (Figure 1).

The central neurochemical circuitry responsible for activation of the stress system has been studied extensively. There 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 primarily through CRH type 1 and α_1-noradrenergic receptors, respectively (4–6). Autoregulatory negative feedback loops are also present in both the PVN CRH and brainstem noradrenergic neurons (7, 8), with collateral fibers inhibiting CRH and catecholamine secretion via presynaptic CRH and α_2-noradrenergic receptors, respectively (7–9). Both the CRH and the noradrenergic neurons also receive stimulatory innervation from the serotoninergic and cholinergic systems (10, 11), and inhibitory input from the γ-aminobutyric acid (GABA)-benzodiazepine (BZD) and opioid peptide neuronal systems of the brain (7, 12, 13), as well as from the end-product of the HPA axis, the glucocorticoids (7, 14).

Corticotropin-Releasing Hormone, Arginine Vasopressin, and Catecholaminergic Neurons

CRH, a 41-amino acid peptide, is the principal hypothalamic regulator of the pituitary-adrenal axis. CRH and CRH receptors have been detected in many

TABLE 1 Behavioral and physical adaptation during acute stress

Behavioral adaptation: adaptive redirection of behavior	**Physical adaptation: adaptive redirection of energy**
Increased arousal and alertness	Oxygen and nutrients directed to the CNS and stressed body site(s)
Increased cognition, vigilance, and focused attention	Altered cardiovascular tone, increased blood pressure and heart rate
Euphoria (or dysphoria)	Increased respiratory rate
Heightened analgesia	Increased gluconeogenesis and lipolysis
Increased temperature	Detoxification from toxic products
Suppression of appetite and feeding behavior	Inhibition of growth and reproduction
Suppression of reproductive axis	Inhibition of digestion-stimulation of colonic motility
Containment of the stress response	Containment of the inflammatory/immune response

Adapted from Chrousos & Gold (2).

extrahypothalamic sites of the brain, including parts of the limbic system, the basal forebrain, and the LC-NE sympathetic system in the brainstem and spinal cord. Intracerebroventricular administration of CRH results in a series of behavioral and peripheral responses, as well as activation of the pituitary-adrenal axis and the sympathetic nervous system (SNS), indicating that CRH has a much broader role in coordinating the stress response than initially recognized (1–3) (Table 1).

Since CRH was first characterized, a growing family of ligands and receptors has evolved. The mammalian family members include CRH, urocortinI (UcnI), UcnII, and UcnIII, along with two receptors, CRHR1 and CRHR2, and a CRH-binding protein. These family members differ in their tissue distribution and pharmacology and play an important role in the regulation of the endocrine and behavioral responses to stress. Although CRH appears to play a stimulatory role in stress responsivity through activation of CRHR1, specific actions of UcnII and UcnIII on CRHR2 may be important for dampening stress sensitivity. UcnI is the only ligand with high affinity for both receptors and its role may be promiscuous (15).

CRH receptors belong to the class B subtype of G protein–coupled receptors (GPCR). CRHR1 and CRHR2 are produced from distinct genes and have several splice variants expressed in various central and peripheral tissues (15). The CRH-R1 subtype is widely distributed in the brain, mainly in the anterior pituitary, the neocortex, and the cerebellum, as well as in the adrenal gland, skin, ovary, and testis. CRH-R2 receptors are expressed mostly in the peripheral vasculature, the skeletal muscles, the gastrointestinal tract, and the heart, but also in subcortical structures of the brain, such as the lateral septum, amygdala, hypothalamus, and brain stem. The diversity in CRH receptor subtype and isoform expression is thought to play a key role in modifying the stress response by implicating locally

the actions of different ligands (CRH and CRH-related peptides) and different intracellular second messengers (15).

CRH is a major anorexiogenic peptide, whose secretion is stimulated by neuropeptide Y (NPY). NPY is the most potent known orexiogenic factor, which inhibits the LC-NE sympathetic system simultaneously (16–18). The latter may be of particular relevance to alterations in the activity of the stress system in states of dysregulation of food intake, such as malnutrition, anorexia nervosa, and obesity. Glucocorticoids enhance the expression of hypothalamic NPY, whereas they directly inhibit both the PVN CRH and LC-NE sympathetic systems. Substance P (SP) has actions reciprocal to those of NPY, given that it inhibits the PVN CRH neuron while it activates the LC-NE sympathetic system. SP release is likely to be increased centrally secondary to peripheral activation of somatic afferent fibers and may, therefore, have relevance to changes in the stress system activity induced by chronic inflammatory or painful states (19).

A subset of PVN parvocellular neurons synthesize and secrete both CRH and AVP, while another subset secretes AVP only (2, 20, 21). During stress, the relative proportion of the subset of neurons that secrete both CRH and AVP increases significantly. The terminals of the parvocellular PVN CRH and AVP neurons project to different sites, including the noradrenergic neurons of the brainstem and the hypophyseal portal system in the median eminence. PVN CRH and AVP neurons also send projections to and activate proopiomelanocortin (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 brainstem, and terminate on pain control neurons of the hind brain and spinal cord (2, 20, 21). Thus, activation of the stress system via CRH and catecholamines stimulates the secretion of hypothalamic β-endorphin and other POMC-derived peptides, which reciprocally inhibit the activity of the stress system and result in stress- induced analgesia.

The Hypothalamic-Pituitary-Adrenal Axis

CRH is the principal hypothalamic regulator of the pituitary-adrenal axis, which stimulates the secretion of adrenocorticotropin hormone (ACTH) from the anterior pituitary. AVP, although a potent synergistic factor of CRH, has very little ACTH secretagogue activity on its own (22, 23). A positive reciprocal interaction between CRH and AVP also exists at the level of hypothalamus, with each neuropeptide stimulating the secretion of the other. In nonstressful situations, both CRH and AVP are secreted in the portal system in a circadian, pulsatile, and highly concordant fashion (24–27). The amplitude of the CRH and AVP pulses increases early in the morning, resulting in increases primarily in the amplitude of the pulsatile ACTH and cortisol secretion. Diurnal variations in the pulsatile secretion of ACTH and cortisol are often perturbed by changes in lighting, feeding schedules, and activity, as well as following stress.

During acute stress, there is an increase in the amplitude and synchronization of the PVN CRH and AVP pulsatile release into the hypophyseal portal system. AVP

of magnocellular neuron origin is also secreted into the hypophyseal portal system via collateral fibers and the systemic circulation via the posterior pituitary (27, 28). In addition, depending on the stressor, other factors, such as angiotensin II, various cytokines, and lipid mediators of inflammation are secreted and act on the hypothalamic, pituitary, and/or adrenal components of the HPA axis and potentiate its activity.

The adrenal cortex is the main target of ACTH, which regulates glucocorticoid and adrenal androgen secretion by the zona fasciculata and reticularis, respectively, and participates in the control of aldosterone secretion by the zona glomerulosa. Other hormones, cytokines, and neuronal information from the autonomic nerves of the adrenal cortex may also participate in the regulation of cortisol secretion (27, 29–31).

Glucocorticoids are the final effectors of the HPA axis. These hormones are pleiotropic, and exert their effects through their ubiquitously distributed intracellular receptors (32–34). In the absence of ligand, the nonactivated glucocorticoid receptor (GR) resides primarily in the cytoplasm of cells as part of a large multiprotein complex consisting of the receptor polypeptide, two molecules of hsp90, and several other proteins (34). Upon hormone binding, the receptor dissociates from hsp90 and other proteins and translocates into the nucleus, where it binds as homodimer to glucocorticoid-response elements (GREs) located in the promoter region of target genes, and regulates the expression of glucocorticoid-responsive genes positively or negatively, depending on the GRE sequence and promoter context. The receptor can also modulate gene expression independently of GRE-binding, by physically interacting with other transcription factors, such as activating protein-1 (AP-1) and nuclear factor-κB (NF-κB) (34).

Glucocorticoids play an important role in the regulation of basal activity of the HPA axis, as well as in the termination of the stress response by acting at extrahypothalamic centers, the hypothalamus, and the pituitary gland. The negative feedback of glucocorticoids on the secretion of CRH and ACTH serves to limit the duration of the total tissue exposure of the organism to glucocorticoids, thus minimizing the catabolic, lipogenic, antireproductive, and immunosuppressive effects of these hormones. A dual-receptor system exists for glucocorticoids in the CNS, which includes the glucocorticoid receptor type I or mineralocorticoid receptor that responds to low concentrations of glucocorticoids, and the classic glucocorticoid receptor type II that responds to both basal and stress concentrations of glucocorticoids. The negative feedback control of the CRH and ACTH secretion is mediated through type II glucocorticoid receptors (1–3).

The LC-NE, Sympathetic, Adrenomedullary, and Parasympathetic Systems

The autonomic nervous system (ANS) responds rapidly to stressors and controls a wide range of functions. Cardiovascular, respiratory, gastrointestinal, renal, endocrine, and other systems are regulated by the SNS and/or the parasympathetic

system. In general, the parasympathetic system can both assist and antagonize sympathetic functions by withdrawing or increasing its activity, respectively (3).

Sympathetic innervation of peripheral organs is derived from the efferent preganglionic fibers, whose cell bodies lie in the intermediolateral column of the spinal cord. These nerves synapse in the bilateral chain of sympathetic ganglia with postganglionic sympathetic neurons, which innervate widely the smooth muscle of the vasculature, the heart, skeletal muscles, kidney, gut, fat, and many other organs. The preganglionic neurons are primarily cholinergic, whereas the postganglionic neurons are mostly noradrenergic. The sympathetic system of the adrenal medulla also provides all of circulating epinephrine and some of the norepinephrine.

In addition to the classic neurotransmitters acetylcholine and norepinephrine, both sympathetic and parasympathetic subdivisions of the autonomic nervous system include several subpopulations of target-selective and neurochemically coded neurons that express a variety of neuropeptides and, in some cases, adenosine triphosphate (ATP), nitric oxide, or lipid mediators of inflammation (3). Thus CRH, NPY, somatostatin, and galanin are found in postganglionic noradrenergic vasoconstrictive neurons, whereas vasoactive intestinal peptide (VIP), SP, and calcitonin gene-related peptide are found in cholinergic neurons. Transmission in sympathetic ganglia is also modulated by neuropeptides released from preganglionic fibers and short interneurons, and by primary afferent nerve collaterals.

Adaptive Responses to Stress

The stress system receives and integrates a diversity of cognitive, emotional, neurosensory, and peripheral somatic signals that arrive through distinct pathways. Activation of the stress system leads to behavioral and physical changes that are remarkably consistent in their qualitative presentation and are collectively defined as the stress syndrome (Table 1). These changes are normally adaptive and time limited and improve the chances of the individual for survival.

Behavioral adaptation includes increased arousal, alertness, and vigilance; improved cognition; focused attention; euphoria; enhanced analgesia; elevations in core temperature; and inhibition of vegetative functions, such as appetite, feeding, and reproduction. A concomitant physical adaptation also occurs mainly to promote an adaptive redirection of energy. Oxygen and nutrients are shunted to the CNS and the stressed body sites, where they are most needed. Increases in cardiovascular tone, respiratory rate, and intermediate metabolism (gluconeogenesis, lipolysis) work in concert with the above alterations to promote availability of vital substrates. Detoxification functions are activated to rid the organism of unnecessary metabolic products from the stress-related changes in metabolism, whereas digestive function, growth, reproduction, and immunity are inhibited (3, 35).

During stress, the organism also activates restraining forces that prevent an overresponse from both the central and peripheral components of the stress system.

These forces are essential for successful adaptation. If they are excessive or fail to contain the various elements of the stress response in a timely manner, the adaptive changes may become chronically deficient or excessive, respectively, and may contribute to the development of pathology. Thus the restraining forces may participate in the development of allostasis. Stress is often of a magnitude and nature that allow the subjective perception of control by the individual. In such cases, stress can be pleasant and rewarding, or at least not damaging. On the other hand, stress of a nature, magnitude, or duration that is beyond the adaptive resources of an individual may be associated with a perception of loss of control, dysphoria, and chronic adverse behavioral and physical consequences (1, 3, 35). Frequently allostasis and sense of loss of control go hand-in-hand, with the latter serving as a useful index of the former.

Stress System Interactions with Other CNS Components

In addition to setting the level of arousal and influencing the vital signs, the stress system interacts with three other major CNS components: the mesocorticolimbic dopaminergic or reward system, the amygdala-hippocampus complex, and the hypothalamic arcuate nucleus POMC neuronal system. All three CNS components 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, as well as the growth, thyroid, and reproductive axes and the immune system (1, 3).

MESOCORTICOLIMBIC SYSTEM Both the mesocortical and mesolimbic components of the dopaminergic system are innervated by PVN CRH neurons and the LC-NE system and are activated during stress (36, 37). The mesocortical system consists of dopaminergic neurons of the ventral tegmentum, which send projections to the prefrontal cortex, and is involved in anticipatory phenomena and cognitive functions. The mesolimbic system also consists of dopaminergic neurons of the ventral tegmentum, which innervate the nucleus accumbens, and plays a principal role in motivational/reinforcement/reward phenomena and in the formation of the central dopaminergic reward system. Therefore, euphoria or dysphoria is likely to be mediated by the mesocorticolimbic system, which is also considered to be the target of several substances of abuse, such as cocaine. Interestingly, activation of the prefrontal cortex, which is part of the mesocortical dopaminergic system, is associated with inhibition of the stress system (38).

AMYGDALA-HIPPOCAMPUS COMPLEX The amygdala-hippocampus complex is activated during stress primarily by ascending catecholaminergic neurons originating in the brainstem, and by the end-product of the HPA axis, glucocorticoids, but also by inner emotional stressors, such as fear, which is generated in the amygdala (39). Activation of the amygdala is important for retrieval and emotional analysis of relevant information for any given stressor. The amygdala can directly

stimulate both central components of the stress system and the mesocorticolimbic dopaminergic system in response to emotional stressors. The hippocampus exerts tonic and stimulated inhibitory effects on the activity of the amygdala, PVN CRH, and LC-NE-sympathetic system.

POMC NEURONAL SYSTEM 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 (7, 40). Activation of the stress system stimulates hypothalamic POMC-derived peptides, such as α-melanocyte-stimulating hormone (α-MSH) and β-endorphin, which reciprocally inhibit the activity of both of the central components of the stress system, produce analgesia through projections to the hind brain and spinal cord, where they inhibit ascending pain stimuli.

TEMPERATURE REGULATION Activation of the LC-NE and PVN/CRH systems increases the core temperature. Intracerebroventricular administration of norepinephrine and CRH results in elevations in core temperature, probably through prostanoid-mediated actions on the septal and hypothalamic temperature-regulating centers (41, 42). CRH has also been shown to partly mediate the pyrogenic effects of the inflammatory cytokines, tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6 (3).

APPETITE REGULATION Stress is also involved in the regulation of appetite by influencing the appetite-satiety centers in the hypothalamus. Acute elevations in CRH concentrations cause anorexia. On the other hand, fasting-stimulated increases in NPY enhance CRH secretion (43), while they concomitantly inhibit the LC-NE-sympathetic system and activate the parasympathetic system, thereby facilitating digestion and storage of nutrients (44). Leptin, a satiety-stimulating polypeptide secreted by the white adipose tissue, is a potent inhibitor of hypothalamic NPY and a stimulant of a subset of arcuate nucleus POMC neurons that secrete α-MSH, another potent anorexiogen that exerts its effects primarily through specific melanocortin receptors type 4 (45, 46).

EFFECTS OF CHRONIC HYPERACTIVATION OF THE STRESS SYSTEM

In general, the stress response is meant to be of short or limited duration. The time-limited nature of this process renders its accompanying antigrowth, antireproductive, catabolic, and immunosuppressive effects temporarily beneficial and/or of no adverse consequences to the individual. However, chronic activation of the stress system may lead to a number of disorders that are the result of increased and/or prolonged secretion of CRH and/or glucocorticoids (Table 2).

TABLE 2 States associated with altered hypothalamic-pituitary-adrenal (HPA) axis activity and altered regulation or dysregulation of behavioral and/or peripheral adaptation

Increased HPA axis activity	Decreased HPA axis activity
Chronic stress	Adrenal insufficiency
Melancholic depression	Atypical/seasonal depression
Anorexia nervosa	Chronic fatigue syndrome
Malnutrition	Fibromyalgia
Obsessive-compulsive disorder	Hypothyroidism
Panic disorder	Nicotine withdrawal
Excessive exercise (obligate athleticism)	Discontinuation of glucocorticoid therapy
Chronic active alcoholism	After Cushing syndrome cure
Alcohol and narcotic withdrawal	Premenstrual tension syndrome
Diabetes mellitus	Postpartum period
Truncal obesity (Metabolic syndrome X)	After chronic stress
Childhood sexual abuse	Rheumatoid arthritis
Psychosocial short stature	Menopause
Attachment disorder of infancy	
'Functional' gastrointestinal disease	
Hyperthyroidism	
Cushing syndrome	
Pregnancy (last trimester)	

Adapted from Chrousos & Gold (2).

Growth and Development

During stress, the growth axis is inhibited at many levels (Figure 2*a*). Prolonged activation of the HPA axis leads to suppression of growth hormone (GH) secretion and glucocorticoid-induced inhibition of the effects of insulin-like growth factor I (IGF-I) and other growth factors on target tissues (47–49). Children with Cushing's syndrome have delayed or arrested growth and achieve a final adult height that is on average 7.5–8.0 cm below their predicted height (49). The molecular mechanisms by which glucocorticoids suppress growth are complex and involve both transcriptional and translational mechanisms that ultimately influence GH action (50, 51).

In addition to the direct effects of glucocorticoids, CRH-induced increases in somatostatin secretion, and therefore inhibition of GH secretion, have been implicated as a potential mechanism of chronic stress-related suppression of GH secretion. However, acute elevations of serum GH concentrations may occur at the onset of the stress response or following acute administration of glucocorticoids, most likely due to stimulation of the GH gene by glucocorticoids through GREs in the promoter region of the gene (52).

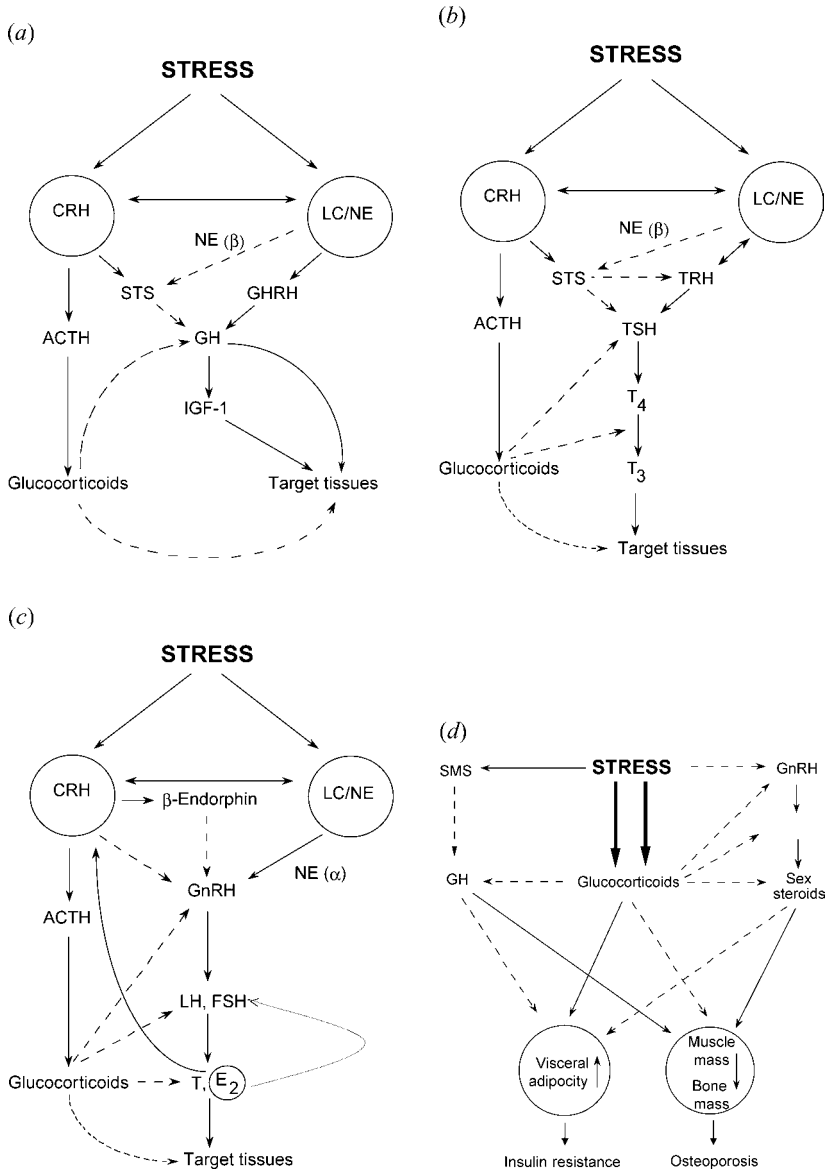

Figure 2 Schematic representation of the interactions between the stress system and (*a*) the GH/IGF-I axis, (*b*) the thyroid axis, (*c*) the hypothalamic-pituitary-gonadal axis, and (*d*) metabolic functions. Adapted from Chrousos & Gold (2).

In several stress-related mood disorders with a hyperactive HPA axis, such as anxiety or melancholic depression, GH and/or IGF-I concentrations are significantly decreased, and the GH response to intravenously administered glucocorticoids is blunted. Compared with healthy control subjects, patients with panic disorder have diminished GH response to intravenously administered clonidine, whereas children with anxiety disorders may have short stature (53, 54). Furthermore, nervous pointer dogs, an animal model of anxiety with both panic and phobic components, have low IGF-I concentrations and deceleration in growth velocity compared with normal animals. The tissue resistance to GH and/or IGF-I of chronically stressed animals can be restored following hypophysectomy or adrenalectomy, a fact that further underlines the importance of glucocorticoids in chronic stress-induced growth suppression (55).

Psychosocial short stature is characterized by severely compromised height in children owing to emotional deprivation and/or physical/psychologic abuse and represents another example of the detrimental effects of a chronically hyperactive stress system on growth. These children display a significant decrease in GH secretion, which is fully restored within a few days following separation of the child from the adverse environment (56, 57). In addition to low GH secretion, they have impaired thyroid function, biochemical findings reminiscent of those of the euthyroid sick syndrome, and a variety of emotional, behavioral and/or psychiatric manifestations.

The inhibited child syndrome usually involves a hyperactive or hyperreactive amygdala, which generates excessive and prolonged fear and anxiety, an activated stress system, which results in the corresponding peripheral physiologic responses, a tachyphylactic or labile mesocorticolimbic dopaminergic system, which generates dysphoria, and/or a hypoactive hippocampus unable to inhibit/limit the activity of the stress system and amygdala (58) (Figure 3). These alterations in the interrelation of the above systems increase the vulnerability of the individual to conditions characterized by a chronically hyperactive or hyperreactive stress, such as chronic anxiety, melancholic depression, eating disorders, substance and alcohol abuse, personality and conduct disorders, as well as psychosomatic conditions, such as chronic fatigue syndrome. Other consequences of hyperactive stress system include delayed growth and puberty, manifestations of the metabolic syndrome, such as visceral obesity, insulin resistance, hypertension, dyslipidemia, cardiovascular disease, and osteoporosis.

Thyroid Function

Thyroid function is also inhibited during stress (Figure 2*b*). Activation of the HPA axis is associated with decreased production of thyroid-stimulating hormone (TSH), as well as inhibition of peripheral conversion of the relatively inactive thyroxine to the biologically active triiodothyronine (59). These alterations may be due to the increased concentrations of CRH-induced somatostatin and glucocorticoids. Somatostatin suppresses both TRH and TSH, whereas glucocorticoids inhibit the

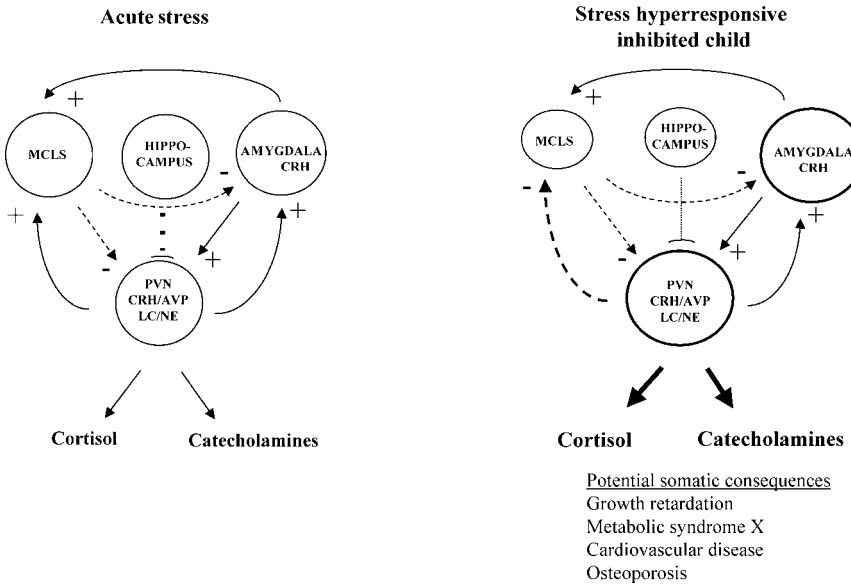

Figure 3 Central neurocircuitry in the stress-hyperresponsive/inhibited child leading to a hyperactive stress system compared with the central neurocircuitry of the normal stress response. The hyperfunctioning amygdala, hypofunctioning hippocampus, and/or hypofunctioning mesocorticolimbic dopaminergic system could predispose an individual to anxiety, melancholic depression, and their somatic consequences. Solid lines represent activation; dashed lines indicate inhibition. Adapted from Chrousos & Gold (58).

activity of the enzyme 5-deiodinase, which converts thyroxine to triiodothyronine. During inflammatory stress, the inflammatory cytokines, such as TNF-α, IL-1, and IL-6, also activate CRH secretion and inhibit 5-deiodinase activity (3, 35).

Reproduction

The reproductive axis is inhibited at all levels by various components of the HPA axis (Figure 2*c*). CRH suppresses the secretion of gonadotropin-releasing hormone (GnRH) either directly or indirectly, by stimulating the arcuate POMC peptide-secreting neurons (60, 61). Glucocorticoids also exert an inhibitory effect on the GnRH neuron, the pituitary gonadotroph, and the gonads, and render target tissues of gonadal steroids resistant to these hormones (60–63). During inflammatory stress, the elevated concentrations of cytokines also result in suppression of reproductive function via inhibition of both GnRH pulsatile secretion from the hypothalamus and ovarian/testicular steroidogenesis. These effects are exerted both directly and indirectly, by activating hypothalamic neural circuits that secrete CRH and POMC-derived peptides and by increasing the circulating concentrations of glucocorticoids (64).

Suppression of gonadal function secondary to chronic activation of the HPA axis has been demonstrated in highly trained runners of both sexes and ballet dancers (65, 66). These subjects display elevated concentrations of serum cortisol and plasma ACTH in the evening, increased 24-hour urinary-free cortisol excretion, and diminished ACTH responses to exogenous CRH administration. Males have low LH and testosterone concentrations and females have amenorrhea. Interestingly, obligate athletes develop withdrawal symptoms and signs following discontinuation of their exercise routine, which may reflect withdrawal from the daily exercise-induced elevation of opioid peptides and stimulation of the mesocorticolimbic system.

The interaction between CRH and the hypothalamic-pituitary-gonadal axis is bidirectional, given that estrogen increases CRH gene expression via estrogen-response elements in the promoter region of the CRH gene (67). Therefore, the CRH gene is an important target of gonadal steroids and a potential mediator of sex-related differences in the stress-response and the activity of the HPA axis.

Metabolism

In addition to their direct catabolic effects, glucocorticoids also antagonize the actions of GH and sex steroids on fat tissue catabolism (lipolysis) and muscle and bone anabolism (Figure 2*d*) (3). Chronic activation of the stress system is associated with increased visceral adiposity, decreased lean body (bone and muscle) mass, and suppressed osteoblastic activity, a phenotype observed in patients with Cushing's syndrome, some patients with melancholic depression, and patients with the metabolic syndrome (visceral obesity, insulin resistance, dyslipidemia, hypertension, hypercoagulation, atherosclerotic cardiovascular disease, sleep apnea), many of whom display increased HPA axis activity and demonstrate similar clinical and biochemical manifestations (68–72). The association between chronic stress, hypercortisolism and metabolic syndrome-related manifestations has also been reported in cynomolgus monkeys (70, 71).

Because increased gluconeogenesis is a cardinal feature of the stress response and glucocorticoids induce insulin resistance, activation of the HPA axis may also contribute to the poor control of diabetic patients with emotional stress or concurrent inflammatory or other diseases. Mild, chronic activation of the HPA axis has been demonstrated in type I diabetic patients under moderate or poor glycemic control, and in type II diabetic patients who had developed diabetic neuropathy (71, 73). Over time, progressive glucocorticoid-induced visceral adiposity causes further insulin resistance and deterioration of the glycemic control. Therefore, chronic activation of the stress system in patients with diabetes mellitus may result in a vicious cycle of hyperglycemia, hyperlipidemia, and progressively increasing insulin resistance and insulin requirements.

Low turnover osteoporosis is almost invariably seen in association with hypercortisolism and GH deficiency, and represents another example of the adverse effects of elevated cortisol concentrations and decreased GH/IGF-I concentrations

on osteoblastic activity. The stress-induced hypogonadism and the reduced concentrations of sex steroids may further contribute to the development of osteoporosis. Increased prevalence of osteoporosis has been demonstrated in young women with depression or a previous history of depression (74).

Gastrointestinal Function

PVN CRH induces inhibition of gastric acid secretion and emptying, whereas it stimulates colonic motor function (75, 76). These effects are mediated by inhibition of the vagus nerve, which leads to selective inhibition of gastric motility, and by stimulation of the LC-NE-regulated sacral parasympathetic system, which results in selective stimulation of colonic motility. Therefore, CRH may be implicated in mediating the gastric stasis observed following surgery or during an inflammatory process, when central IL-1 concentrations are elevated (77). CRH may also play a role in the stress-induced colonic hypermotility of patients with the irritable bowel syndrome. Colonic contraction and pain in these patients may activate LC-NE-sympathetic neurons, forming a vicious cycle that may account for the chronicity of the condition.

CRH hypersecretion may also be a link between chronic gastrointestinal pain and a history of abuse. A high incidence of physically and sexually abused women has been reported in patients with chronic gastrointestinal pain. Sexually abused women may suffer from chronic activation of the HPA axis (78), and increased CRH secretion may produce colonic pain via activation of the sacral parasympathetic system (79).

Immune Function

Activation of the HPA axis has profound inhibitory effects on the immune/inflammatory response, given that virtually all the components of the immune response are inhibited by glucocorticoids (80, 81). At the cellular level, the main anti-inflammatory and immunosuppressive effects of glucocorticoids include alterations in leukocyte traffic and function, decreases in production of cytokines and mediators of inflammation, and inhibition of their action on target tissues by the latter. These effects are exerted both at the resting, basal state and during inflammatory stress, when the circulating concentrations of glucocorticoids are elevated. A circadian activity of several immune factors has been demonstrated in reverse-phase synchrony with that of plasma glucocorticoid concentrations (82).

During stress, the activated ANS also exerts systemic effects on immune organs by inducing the secretion of IL-6 in the systemic circulation (83). Despite its inherent inflammatory activity, IL-6 plays a major role in the overall control of inflammation by stimulating glucocorticoid secretion (84, 85) and by suppressing the secretion of TNF-α and IL-1. Furthermore, catecholamines inhibit IL-12 and stimulate IL-10 secretion via β-adrenergic receptors, thereby causing suppression of innate and cellular immunity, and stimulation of humoral immunity (86).

The combined effects of glucocorticoids and catecholamines on the monocyte/macrophage and dendritic cells are to inhibit innate immunity and T helper-1-related cytokines, such as interferon-γ and IL-12, and to stimulate T helper-2-related cytokines, such as IL-10 (87). This suggests that stress-related immunosuppression refers mostly to innate and cellular immunity, facilitating diseases related to deficiency of these immune responses, such as common cold, tuberculosis, and certain tumors (87).

Psychiatric Disorders

The syndrome of adult melancholic depression represents a typical example of dysregulation of the generalized stress response, leading to chronic dysphoric hyperarousal, activation of the HPA axis and the LC-NE/SNS, and relative immunosuppression (88, 89). Patients suffering from the condition have hypersecretion of CRH, as evidenced by the elevated 24-hour urinary cortisol excretion, the decreased ACTH responses to exogenous CRH administration, and the elevated concentrations of CRH in the cerebrospinal fluid (CSF). They also have elevated concentrations of norepinephrine in the CSF, which remain elevated even during sleep (90), and a marked increase in the number of PVN CRH neurons on autopsy.

Childhood sexual abuse is associated with an increased incidence of adult psychopathology, as well as abnormalities in the HPA function. Sexually abused girls have a greater incidence of suicidal ideation, suicide attempts, and dysthymia compared with controls (91). In addition, they excrete significantly higher amounts of catecholamines and their metabolites, and display lower basal and CRH-stimulated ACTH concentrations compared with controls. However, the total and free basal and CRH-stimulated serum cortisol concentrations and 24-h urinary-free cortisol concentrations in these subjects are similar to those in controls. These findings reflect pituitary hyporesponsiveness to CRH, which may be corrected for by the presence of intact glucocorticoid feedback regulatory mechanisms (91, 92).

A spectrum of other conditions may also be associated with increased and prolonged activation of the HPA axis. These include anorexia nervosa (93), malnutrition (94), obsessive-compulsive disorder, panic anxiety (95), excessive exercise (65, 66), chronic active alcoholism (96), alcohol and narcotic withdrawal (97), diabetes mellitus types I and II (71, 73), visceral obesity (70), and perhaps, hyperthyroidism.

Both anorexia nervosa and malnutrition are characterized by a marked decrease in circulating leptin concentration and an increase in CSF NPY concentration, which could provide an explanation as to why the HPA axis in these subjects is activated in the presence of a profoundly hypoactive LC-NE-sympathetic system (43–46). Glucocorticoids, on the other hand, may produce the hyperphagia and obesity observed in patients with Cushing's syndrome and many rodent models of obesity, such as the Zucker rat, by stimulating NPY and by inhibiting the PVN CRH and the LC-NE sympathetic systems. Glucocorticoids have also been associated with leptin resistance (98). Zucker rats are leptin receptor–deficient with concurrent hypercorticosteronism and decreased LC-NE-sympathetic system activity (99).

EFFECTS OF CHRONIC HYPOACTIVATION OF THE STRESS SYSTEM

Hypoactivation of the stress system is characterized by chronically reduced secretion of CRH and norepinephrine, and may result in hypoarousal states (Table 2). For example, patients with atypical or seasonal depression and the chronic fatigue syndrome demonstrate chronic hypoactivity of the HPA axis in the depressive (winter) state of the former, and in the period of fatigue of the latter (100). Similarly, patients with fibromyalgia often complain about fatigue and have been shown to have decreased 24-h urinary-free cortisol excretion (101). Hypothyroid patients have clear evidence of CRH hyposecretion, and they often present with depression of the atypical type. Withdrawal from smoking has also been associated with time-limited decreased cortisol and catecholamine secretion, which is associated with fatigue, irritability, and weight gain (102). Decreased CRH secretion in the early period of nicotine abstinence could explain the hyperphagia, decreased metabolic rate, and weight gain frequently observed in these patients. In Cushing's syndrome, the clinical manifestations of atypical depression, hyperphagia, weight gain, fatigue, and anergia are consistent with the suppression of CRH by the elevated cortisol concentrations. 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 (1–3, 62, 103). Chronic hypoactivation of the HPA axis and/or the LC-NE-sympathetic system owing to decreases in the activity of the opioid-peptide system responsible for stress-induced analgesia may also account for the lower pain threshold for visceral sensation reported in patients with functional gastrointestinal disorders.

Hyper- or Hypoactivation of the Stress System and Immune Function

In theory, an exaggerated HPA axis response to inflammatory stimuli would be expected to mimic the stress or hypercortisolemic state and lead to increased susceptibility of the individual to certain infectious agents or tumors but enhanced resistance to autoimmune inflammatory disease. By contrast, a suboptimal HPA axis response to inflammatory stimuli would be expected to reproduce the glucocorticoid-deficient state and lead to relative resistance to infections and neoplastic diseases but increased susceptibility to autoimmune inflammatory disease (80, 87). These findings have been observed 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 (104).

Patients with depression or anxiety have been shown to be more vulnerable to tuberculosis, both in terms of prevalence and severity of the disease (105). Similarly, stress has been associated with increased vulnerability to the common cold

virus. A compromised innate and T helper-1 driven immunity may predispose an individual to these conditions. Furthermore, patients with rheumatoid arthritis, a T-helper-1 driven inflammatory disease, have a mild form of central hypocortisolism, as indicated by the normal 24-h cortisol excretion despite the major inflammatory stress, and diminished HPA axis responses to surgical stress (106). Therefore, dysregulation of the HPA axis may play a critical role in the development and/or perpetuation of T helper-1-type of autoimmune disease. The same theoretical concept may explain the high incidence of T helper-1 autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, observed following cure of hypercortisolism, in the postpartum period and in patients with adrenal insufficiency, who do not receive adequate replacement therapy (87, 107, 108).

GENETICS, DEVELOPMENT, ENVIRONMENT, AND THE STRESS RESPONSE

Appropriate responsiveness of the stress system to stressors is a crucial prerequisite for a sense of well-being, adequate performance of tasks, and positive social interactions. Improper responsiveness has been associated with inadequacies in these functions and increased vulnerability to one or more of the stress-related states. Vulnerability may be the result of genetic, developmental, and environmental factors, and may be considered as the endpoint of converging influences. Depending on the genetic background of the individual and his/her exposure to adverse stimuli in prenatal and/or postnatal life (developmental influences), one might fail to cope with life stressors and may develop any of the above-described states in any combination and any degree of severity (58).

The stress response of an individual is determined by multiple factors, many of which are inherited (1, 3, 109, 110). Genetic polymorphisms, such as those of CRH, AVP, and their receptors and/or regulators, are expected to account for the observed variability in the function of the stress system. This genetic vulnerability is polygenic and allows expression of the clinical phenotype in the presence of environmental triggers. There is a complex genetic background continuum in our population that ranges from extreme resilience to extreme vulnerability to these stress-related comorbid states. Stressors of gradually decreasing intensity may be sufficient to result in the development of these conditions in an individual, whose genetic vulnerability places him on the vulnerable side of the continuum (Figure 4*a*).

The dose-response relation between the potency of a stressor and the responsiveness of the stress system is represented by a sigmoidal curve, which is expected to differ from individual to individual. One individual's dose-response curve might be shifted to the left of that of an average reactive individual, whereas another individual's dose-response curve might be shifted to the right. The former denotes an excessive reaction, whereas the latter a defective one. Similarly, the dose-response relation between an individual's sense of well-being or performance

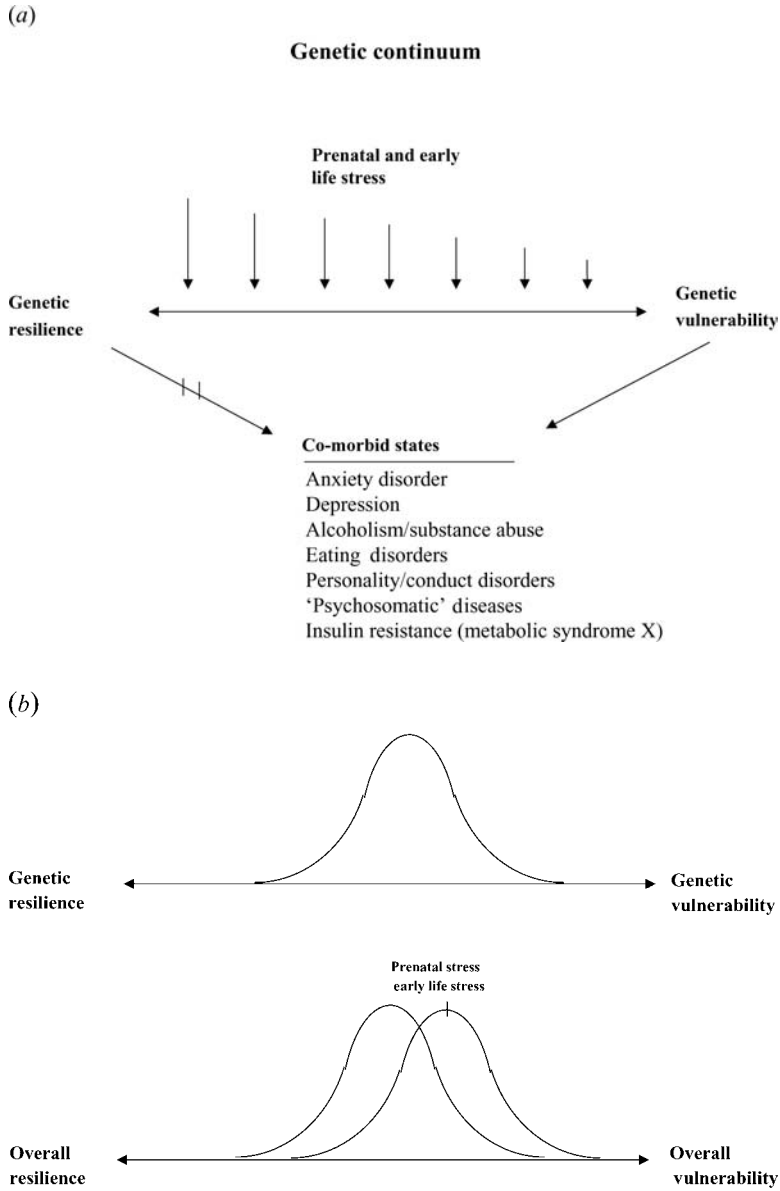

Figure 4 (*a*) Schematic representation of the genetic continuum that defines an individual's genetically determined vulnerability/resilience to stressors. The vertical arrows indicate the magnitude of environmental stressors necessary to result in disease. (*b*) Early environmental stressors may have a permanent effect on the ability of the individual to respond to stress effectively, thus altering the constitutional vulnerability/resilience of an individual to stressors. Adapted from Chrousos (58a).

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 in hypoarousal or hyperarousal, respectively, and a suboptimal sense of well-being or diminished performance (58). Developmental influences, when propitious, may shift an individual toward a more resilient response to stress, whereas, when negative, may have the opposite effect (Figure 4*b*). Therefore, a supportive or an adverse environment may alter the course of one or more of the above stress-related states, indicating that genetics and development define vulnerability, whereas environment may determine the triggering and/or severity of a disease.

The prenatal life, infancy, childhood, and adolescence are periods of increased plasticity for the stress system and, therefore, are particularly sensitive to stressors. Excessive or sustained activation of the stress system during these critical periods may have profound effects on its function (1, 3, 111, 112). These environmental triggers or stressors may have not a transient, but rather a permanent effect on the organism, reminiscent of the organizational effects of several hormones exerted on certain target tissues, which last long after cessation of the exposure to these hormones. Also, sufficiently strong or prolonged stressors may have permanent effects on the organism even if they occur later in life, such as in the adult posttraumatic stress disorders.

These effects of early environment on the development of the HPA axis responses to stress reflect a naturally occurring plasticity whereby factors such as maternal care are able to program rudimentary, biologic responses to threatening stimuli. Developmental programming of CNS responses to stress in early life is likely to be of adaptive value to the adult. Such programming would afford an appropriate HPA response and would minimize the need for a long period of adaptation in adult life.

CONCLUSIONS

The stress system coordinates the adaptive response of the organism to stressors and plays an important role in maintenance of basal and stress-related homeostasis. Activation of the stress system leads to behavioral and peripheral changes that improve the ability of the organism to adapt and increase its chances for survival. Inadequate and/or prolonged response to stressors may impair growth and development and may result in a variety of endocrine, metabolic, autoimmune, and psychiatric disorders. The development and severity of these conditions primarily depend on genetic, developmental, and environmental factors. CRH antagonists may be useful in states characterized by chronic hyperactivity of the stress system, such as melancholic depression and chronic anxiety, whereas CRH agonists may be useful in conditions characterized by chronic hypoactivity of the stress system, such as atypical depression, postpartum depression, and the fibromyalgia/chronic fatigue syndromes (113–116).

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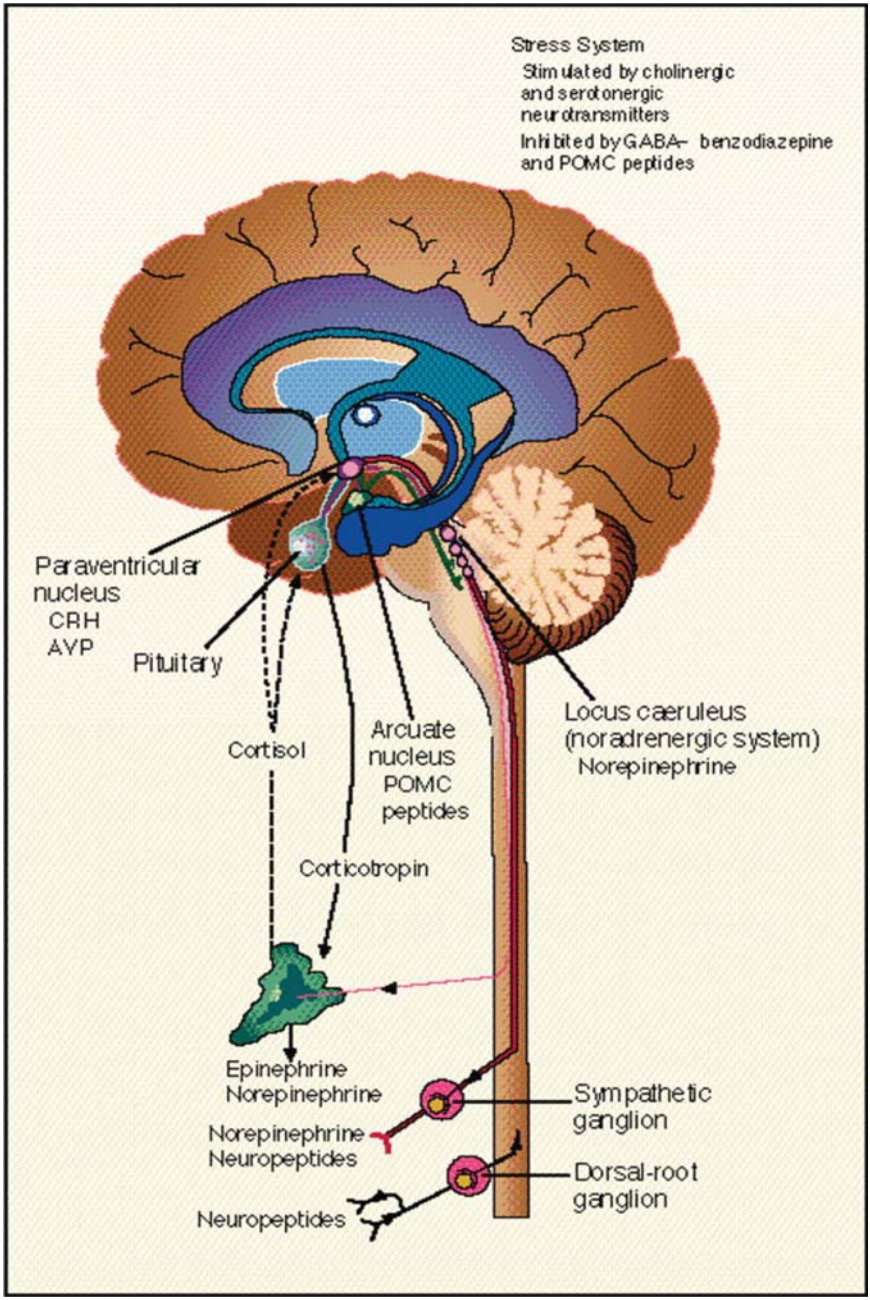

Figure 1 Schematic representation of the central and peripheral components of the stress system, their functional interrelations, and their relation to other central nervous system components involved in the stress response. Adapted from Chrousos (80).

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