Pediatric Stress: Hormonal Mediators and Human Development

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Abstract

Stress activates the central and peripheral components of the stress system, i.e., the hypothalamic-pituitary-adrenal (HPA) axis and the arousal/sympathetic system. The principal effectors of the stress system are 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 event(s), given that prenatal life, infancy, childhood and adolescence are critical periods characterized by increased vulnerability to stressors. The developing brain undergoes rapid growth and is characterized by high turnover of neuronal connections during the prenatal and early postnatal life. These processes and, hence, brain plasticity, slow down during childhood and puberty, and plateau in young adulthood. Hormonal actions in early life, and to a much lesser extent later, can be organizational, i.e., can have effects that last for long periods of time, often for the entire life of the individual. Hormones of the stress system and sex steroids have such effects, which influence the behavior and certain physiologic functions of individuals for life. Exposure of the developing brain to severe and/or prolonged stress may result in hyperactivity/hyperreactivity of the stress system, with resultant amygdala hyperfunction (fear reaction), decreased activity of the hippocampus (defective glucocorticoid-negative feedback, cognition), and the mesocorticolimbic dopaminergic system (dysthymia, novelty-seeking, addictive behaviors), hyperactivation of the HPA axis (hypercortisolism), suppression of reproductive, growth, thyroid and immune functions, and changes in pain perception. These changes may be accompanied by abnormal childhood, adolescent and adult behaviors, including excessive fear ('inhibited child syndrome') and addictive behaviors, dysthymia and/or depression, and gradual development

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of components of the metabolic syndrome X, including visceral obesity and essential hypertension. Prenatal stress exerted during the period of sexual differentiation may be accompanied by impairment of this process with behavioral and/or somatic sequelae. The vulnerability of individuals to develop varying degrees and/or components of the above life-long syndrome is defined by as yet unidentified genetic factors, which account for up to 60% of the variance. CRH has marked kindling and glucocorticoids have strong consolidating properties, hence both of these hormones are crucial in development and can alone produce the above syndrome. CRH and glucocorticoids may act in synergy, as in acoustic startle, while glucocorticoids may suppress or stimulate CRH, as in the hypothalamus and amygdala, respectively. A CRH type 1 receptor antagonist, antalarmin, inhibits both the development and expression of conditioned fear in rats, and has anxiolytic properties in monkeys. Profound stressors, such as those from sexual abuse, may elicit the syndrome in older children, adolescents and adults. Most frequently, chronic dysthymia and/or depression may develop in association with gastrointestinal complaints and/or the premenstrual tension syndrome. A lesser proportion of individuals may develop the classic posttraumatic stress disorder, which is characterized by hypocortisolism and intrusive and avoidance symptoms; in younger individuals it may present as dissociative personality disorder.

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 adaptive central nervous system and peripheral responses, the 'fight or flight response' [1, 2]. Successful adaptation is usually specific to a stressor, but can become relatively 'nonspecific' if a stressor of any kind exceeds a threshold in magnitude and/or duration. Alterations in the ability of the organism to respond to stressors, as for example inadequate, excessive or prolonged responses, may lead to disease.

The adaptive response of an individual to stress is determined by a multiplicity of genetic, environmental and developmental factors. Prenatal life, infancy, childhood and adolescence are critical periods characterized by increased vulnerability to stressors [3]. Excessive and/or prolonged in duration stressors may affect personality development and behavior, and may have adverse consequences on physiologic functions, such as growth, metabolism, reproduction and the inflammatory/immune response.

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

Neuroendocrinology of the Stress Response

Neuroendocrine Effectors of the Stress Response: 'The Stress System'

The stress response is subserved by a complex physiologic system, the stress system, which is located in both the central nervous system (CNS) and the periphery of the body [1–3].

The central components of the stress system are located in the hypothalamus and the brainstem and include (i) the parvocellular neurons of corticotropin-releasing hormone (CRH); (ii) the CRH neurons of the paragigantocellular and parabranchial nuclei of the medulla and the locus coeruleus (LC); (iii) the arginine vasopressin (AVP) neurons of the paraventricular nuclei (PVN) of the hypothalamus, and (iv) other mostly noradrenergic (NE) cell groups in the medulla and pons, including the LC.

The peripheral components of the stress system include (i) the peripheral limbs of the hypothalamic-pituitary-adrenal (HPA) axis, (ii) the efferent sympathetic-adrenomedullary system, and (iii) components of the parasympathetic system.

The central neurochemical circuitry responsible for activation of the stress system has been studied extensively and is illustrated in figure 1. There are multiple sites of interaction among the various components of the stress system. Reciprocal 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
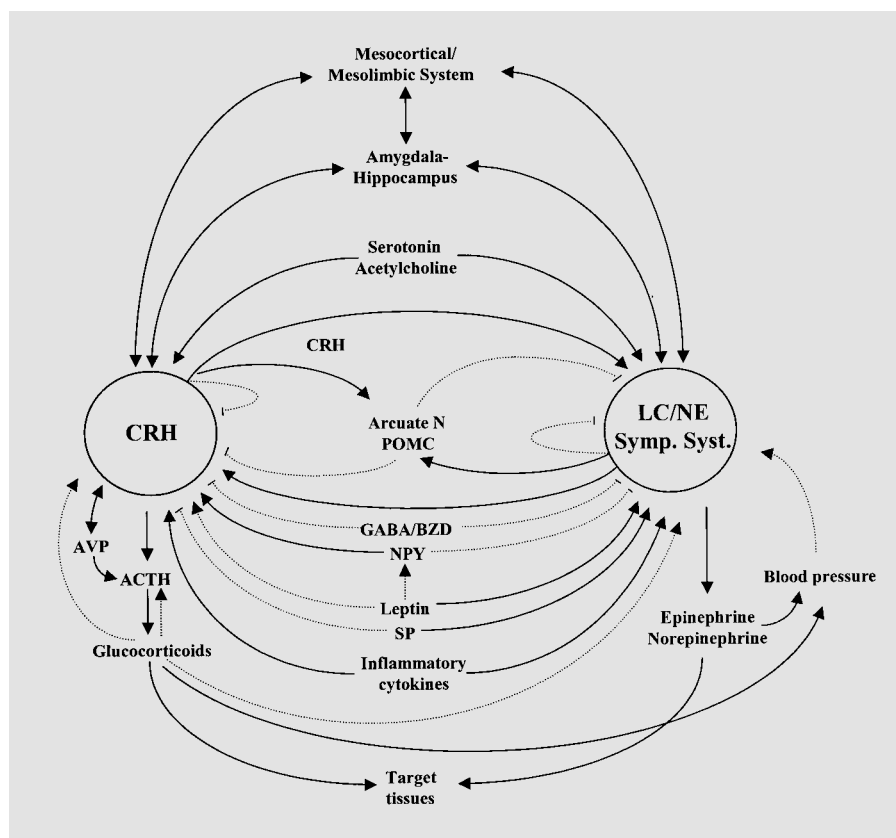
Fig. 1. Schematic representation of the central and peripheral components of the stress system, their functional interrelations and their relation to other CNS components involved in the stress response. Activation is represented by solid lines and inhibition by dashed lines (adapted from Chrousos and Gold [2]).

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, glucocorticoids [7, 14].

CRH, the principal hypothalamic regulator of the pituitary-adrenal axis, has a much broader role in coordinating the stress response than previously recognized [15, 16]. CRH is permissive for secretion of adrenocorticotropin hormone (ACTH), whereas AVP has very little ACTH secretagogue activity despite the fact that it is a potent synergistic factor of CRH [17, 18]. 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. In nonstressful situations, both CRH and AVP are secreted in the portal system in a circadian and highly concordant, pulsatile fashion [19–22]. The amplitude of the CRH and AVP pulses increases early in the morning, resulting in increases primarily in the amplitude of ACTH and cortisol pulsatile secretion. These diurnal variations are perturbed by changes in lighting, feeding schedules and activity, and are disrupted when a stressor is imposed.

During acute stress, there is an increase in the amplitude and synchronization of the PVN CRH and AVP pulsations in the hypophyseal portal system. In response to strong physical stressors, AVP of magnocellular neuron origin is also secreted into the hypophyseal portal system via collateral fibers and the systemic circulation via the posterior pituitary [22, 23]. 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 principal target organ of ACTH. ACTH is the key regulator of glucocorticoid and adrenal androgen secretion by the zona fasciculata and reticularis, respectively, and it participates in the control of aldosterone secretion by the zona glomerulosa. Other

Table 1. Behavioral and physical adaptation during acute stress (adapted from Chrousos and Gold [2])

Behavioral adaptation	Physical adaptation
Adaptive redirection of behavior	*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
	Containment of the stress response

hormones, cytokines and neuronal information from the autonomic nerves of the adrenal cortex may also participate in the regulation of cortisol secretion [22, 24–26].

Glucocorticoids are the final effectors of the HPA axis. These hormones are pleiotropic and exert their effects through their ubiquitously distributed intracellular receptors [27, 28]. 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. The inhibitory glucocorticoid feedback on CRH and ACTH secretion serves to limit the duration of the total tissue exposure to glucocorticoids, thus minimizing the catabolic, lipogenic, anti-reproductive and immunosuppressive effects of these hormones.

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

Adaptive Responses to Stress

The stress system receives and integrates a diversity of cognitive, emotional, neurosensory and peripheral somatic 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 (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 and euphoria. It also includes enhanced analgesia, elevations in core temperature and inhibition of vegetative functions, such as appetite, feeding and reproduction. A concomitant physical adaptation also occurs principally to promote an adaptive redirection of energy: 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, left ventricular ejection fraction and arterial blood pressure), 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, while digestive function, growth, reproduction and immunity are inhibited [3, 29].

During stress, the organism also activates restraining forces, which prevent an over-response from both the 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 become chronically deficient or excessive and may thus contribute to the development of pathology. In contradistinction to homeostasis, this chronic state of poorly maintained equilibrium has been called 'allostasis'.

Stress is often of a magnitude and nature that allow the perception of control by the individual. In such cases, stress can be pleasant and rewarding. For example, stress associated with the seeking of novelty is pivotal for the emotional and intellectual development of an individual. On the other hand, stress of nature, magnitude or dura-

tion that are beyond the adaptive resources of an individual may be associated with a perception of loss of control and dysphoria. Activation of the stress system also occurs during feeding and sexual activity, both important functions for preservation of self and species [1, 3, 29].

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 elements: the mesocorticolimbic dopaminergic or 'reward' system, the amygdala-hippocampus complex and the hypothalamic arcuate nucleus proopiomelanocortin (POMC) neuronal system. 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, 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 the stress system and are activated by it during stress [30, 31]. The mesocortical system, which includes dopaminergic neurons of the ventral tegmentum that send projections to the prefrontal cortex, is involved in anticipatory phenomena and cognitive functions. The mesolimbic system, which consists of dopaminergic neurons of the ventral tegmentum that innervate the nucleus accumbens, plays a principal role in motivational/reinforcement/reward phenomena. Euphoria or dysphoria is likely to be mediated by the mesocorticolimbic system, which is also considered the target of several substances of abuse, such as cocaine. Of interest, activation of the prefrontal cortex, which is part of the mesocortical dopaminergic system, is associated with inhibition of the stress system [32].

Amygdala-Hippocampus Complex. The amygdala-hippocampus complex is activated during stress primarily by ascending catecholaminergic neurons originating in the brainstem, and by the end-hormone of the HPA axis, glucocorticoids, but also by inner emotional stressors, such as fear [33]. 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. The hippocampus exerts tonic and stimulated inhibitory effect 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, 34]. 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 and produce analgesia through projections to the hind brain and spinal cord, where they inhibit ascending pain stimuli.

Activation of the LC-NE-noradrenergic and PVN/CRH systems increases the core temperature. Intracerebroventricular administration of norepinephrine and CRH result in elevations in core temperature, most likely through prostanoid-mediated actions on the septal and hypothalamic temperature-regulating centers [35, 36]. In addition, CRH has 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].

The appetite-satiety centers in the hypothalamus are also influenced by stress. Acute elevations in CRH concentrations cause anorexia. By contrast, fasting-stimulated increases in neuropeptide Y (NPY), an orexiogenic substance, stimulate CRH secretion [37], while at the same time they inhibit the LC-NE-sympathetic system and activate the parasympathetic system, thereby facilitating digestion and storage of nutrients [38]. 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 through specific melanocortin receptors type 4 [39, 40].

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 anti-growth, anti-reproductive, 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, which are outlined below and are due to increased and prolonged secretion of CRH and glucocorticoids (table 2).
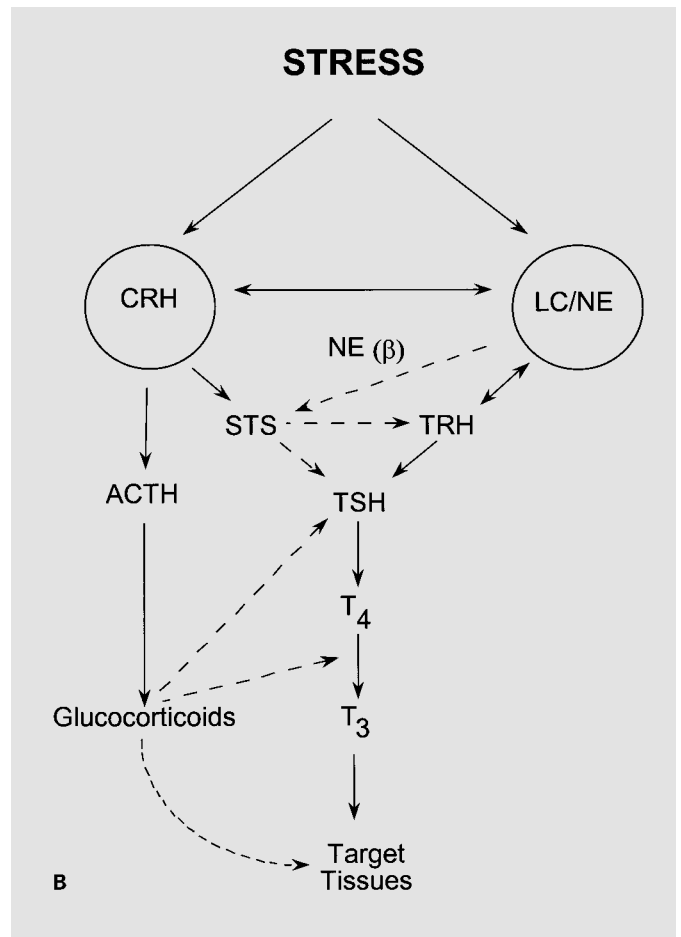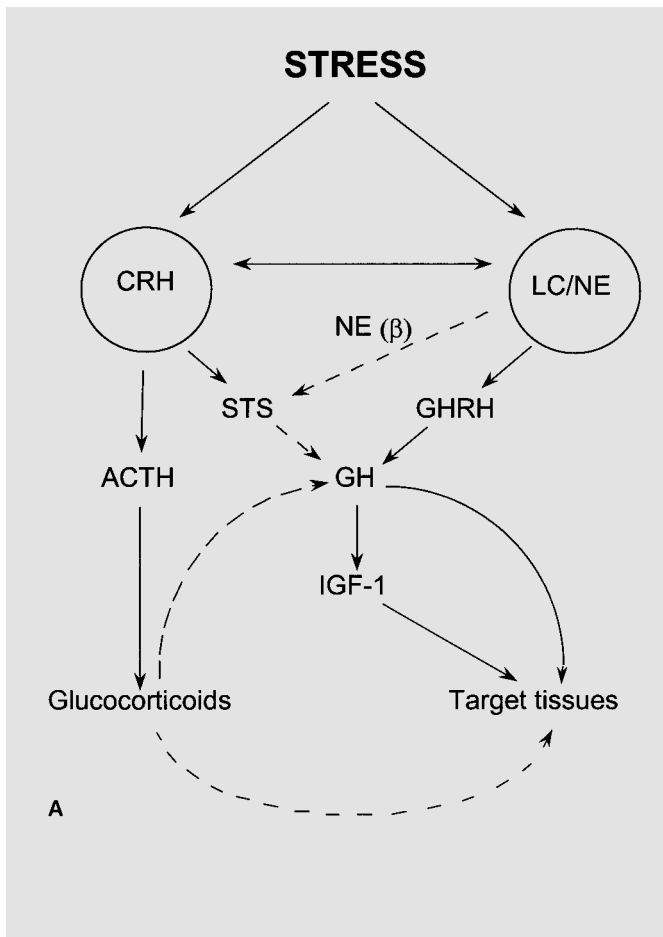
Table 2. States associated with altered HPA axis activity and altered regulation or dysregulation of behavioral and/or peripheral adaptation (adapted from Chrousos and Gold [2])

| 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's syndrome cure
Alcohol and narcotic withdrawal	Premenstrual tension syndrome
Diabetes mellitus	Postpartum period
Central 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's syndrome	
Pregnancy (last trimester)	
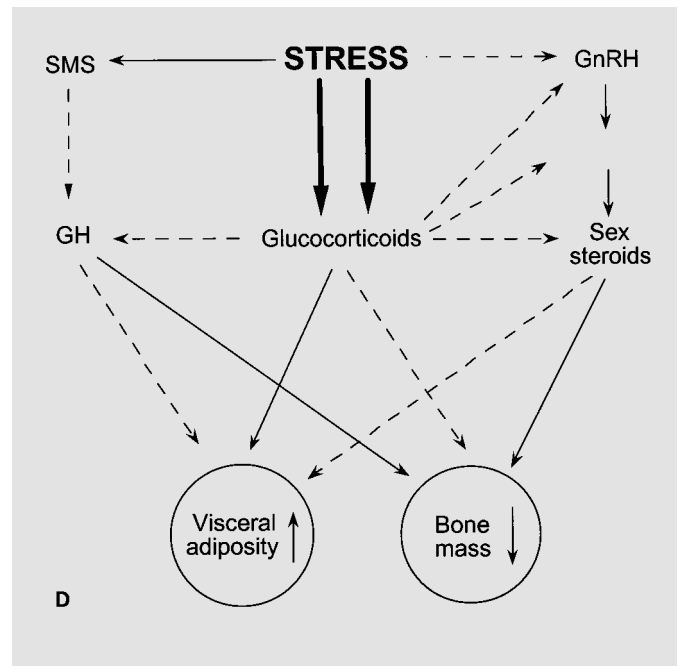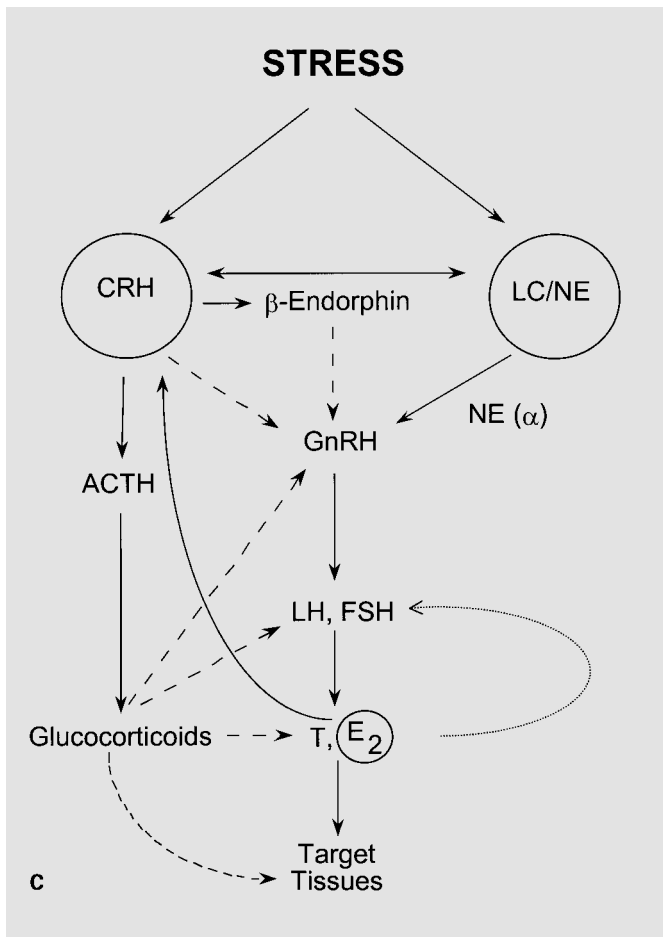
Fig. 2. Schematic representation of the interactions between the stress system and (**A**) the GH/IGF-I axis, (**B**) the thyroid axis, (**C**) the hypothalamic-pituitary-gonadal axis, and (**D**) metabolic functions (adapted from Chrousos and Gold [2]).

Growth and Development

The growth axis is inhibited at many levels during stress (fig. 2A). 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 [41–43]. Children with Cushing's syndrome have delayed or arrested growth and achieve a final adult height, which is on average 7.5–8.0 cm below their predicted height [43]. The molecular mechanisms by which glucocorticoids render tissues resistant to IGF-I and other growth factors are complex. A major mechanism is the inhibition of growth factor third messengers, such as the cJun-Fos heterodimer or AP-1 transcription factor, by protein-protein interactions between this factor and the ligand-bound, activated glucocorticoid receptor [44] (fig. 3).

In addition to these direct effects of glucocorticoids, which are pivotal in the suppression of growth observed in prolonged stress, 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. It is worth noting, however, that 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 glucocorticoid-responsive elements (GREs) in its promoter region [45].

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 disorders have diminished GH responses to intravenously administered clonidine, while children with anxiety disorders may have short stature [46, 47]. Furthermore, nervous pointer dogs,

Fig. 3. A simplified model of glucocorticoid-mediated transcriptional modulation. Hormone binding results in dissociation of the glucocorticoid receptor from the hsp complex, and translocation of the ligand bound receptor to the nucleus. Within the nucleus, the receptor can act in two ways: As indicated on the left, it can bind to glucocorticoid responsive elements (GREs) in the regulatory region of target genes and induce stimulation or inhibition of their transcriptional activity. As indicated on the right, the glucocorticoid receptor can also interact with, and inhibit other transcription factors important for growth or immune functions, such as the cJun-Fos heterodimer and the NF-κB factor, respectively (adapted from Bamberger et al. [44]).
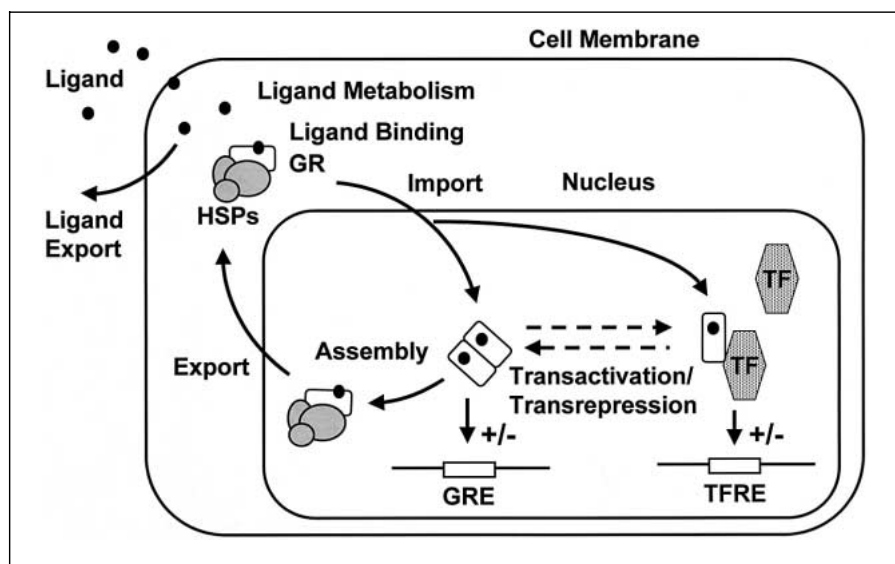
an animal model of anxiety with both panic and phobic components, have low IGF-I concentrations and decreased growth velocity compared to normal animals. That the tissue resistance to GH and/or IGF-I of chronically stressed animals can be restored following hypophysectomy or adrenalectomy, underlines the importance of glucocorticoids in chronic stress-induced growth suppression [48].

'Psychosocial short stature', a term used to describe severely compromised height in children or adolescents due to emotional deprivation and/or physical/psychologic abuse, represents another example of the detrimental effects of a chronically hyperactive stress system on growth. These children typically present with a significant decrease in GH secretion, which is fully restored within a few days following separation of the child from the adverse environment [49, 50]. The condition is also associated with a variety of emotional, behavioral or psychiatric manifestations. In addition to low GH secretion, these patients have impaired thyroid function and biochemical findings reminiscent of those of the euthyroid sick syndrome. Although very little is known about the HPA function of these children, the HPA axis is likely to be chronically activated, which may participate in the pathophysiology of the rest of the documented endocrine abnormalities.

Infantile malnutrition is characterized by hypercortisolism, diminished responses to CRH stimulation, incomplete suppression of the HPA axis by dexamethasone and alterations in the thyroid function reminiscent of the euthyroid sick syndrome. All these abnormalities are restored following nutritional rehabilitation [3, 51]. It is worth noting that this condition is characterized by an increase (rather than decrease) in GH secretion, which is due to starvation-induced hyposecretion of IGF-I, a potent negative feedback regulator of GH secretion [52].

Premature infants are especially at risk for delayed growth and/or development, especially after prolonged hospitalization in the intensive care unit. The condition is similar to psychosocial short stature and is also known as 'reactive attachment disorder of infancy' [53]. Interestingly, activation of the fetal HPA axis may also result in growth retardation in utero, as evidenced by the elevated CRH, ACTH and cortisol concentrations documented in small-for-gestation infants [54].

The 'inhibited child syndrome' usually involves a hyperactive or hyperreactive amygdala generating excessive and prolonged fear and hence anxiety, an activated stress system resulting in the expected peripheral physiologic responses, a tachyphylactic or labile mesocorticolimbic dopaminergic system generating dysphoria and/or a hypoactive hippocampus unable to inhibit and limit the activity of the stress system and amygdala [55] (fig. 4). This alteration in the interrelation of the above systems is expected to make such a child vulnerable to conditions characterized by a chronically hyperactive or hyperreactive stress, such as chronic anxiety, melancholic depression, eating disorders, substance and alcohol abuse, juvenile delinquency, personality and conduct disorders, as well as psychosomatic conditions, such as chronic fatigue
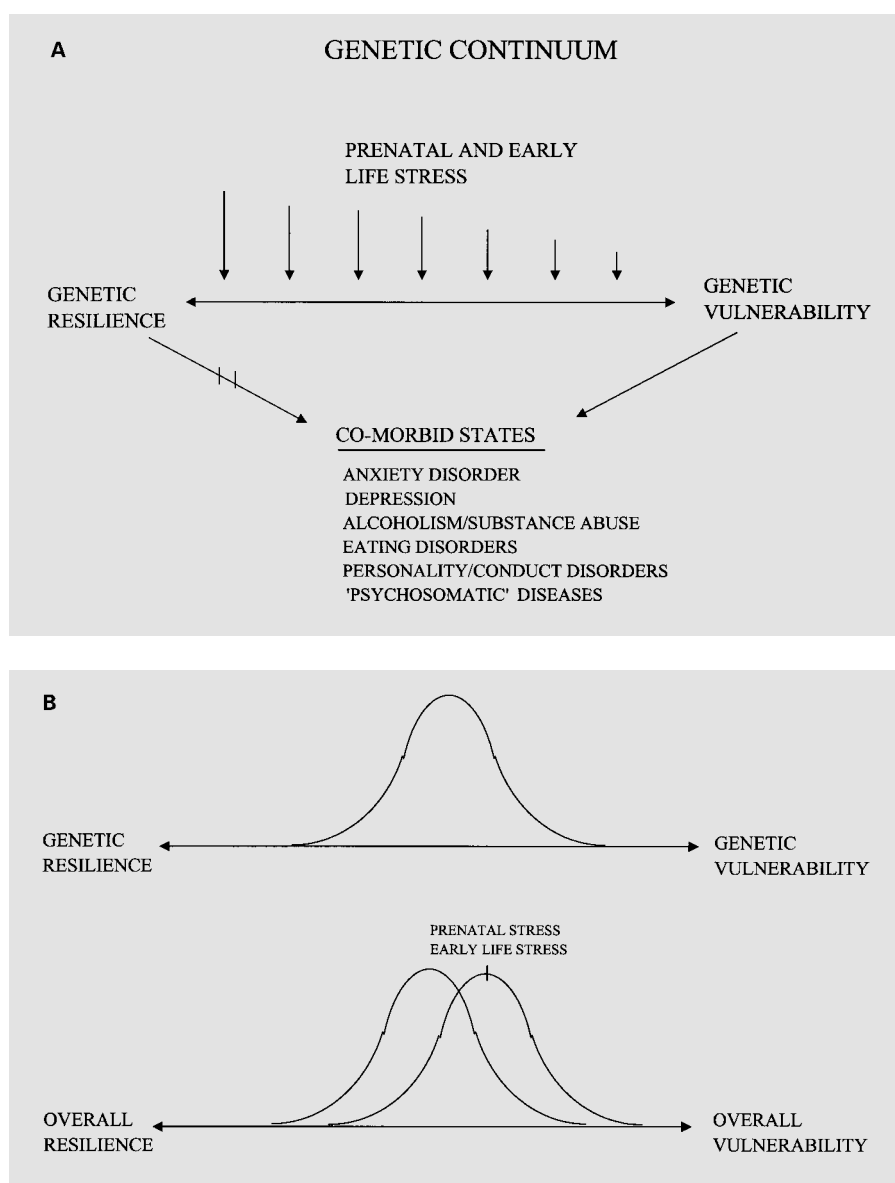
A GENETIC CONTINUUM

PRENATAL AND EARLY
LIFE STRESS

GENETIC
RESILIENCE

GENETIC
VULNERABILITY

CO-MORBID STATES

ANXIETY DISORDER
DEPRESSION
ALCOHOLISM/SUBSTANCE ABUSE
EATING DISORDERS
PERSONALITY/CONDUCT DISORDERS
'PSYCHOSOMATIC' DISEASES

B

GENETIC
RESILIENCE

GENETIC
VULNERABILITY

PRENATAL STRESS
EARLY LIFE STRESS

OVERALL
RESILIENCE

OVERALL
VULNERABILITY

Fig. 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 [128]).

syndrome. The predicted somatic consequences of this hyperactive stress system include delayed growth and puberty, components of the metabolic syndrome X, such as visceral obesity, insulin resistance, hypertension, dyslipidemia, cardiovascular disease and osteoporosis.

Thyroid Function

A corollary phenomenon to growth axis suppression is the stress-induced inhibition of thyroid function (fig. 2B). Activation of the HPA axis is associated with decreased production of thyroid-stimulating hormone (TSH) and inhibition of peripheral conversion of the relatively inactive thyroxine to the biologically active triiodothyronine [56]. Although the exact mechanism for these alterations is not known, they may be caused by the increased concentrations of CRH-induced somatostatin and glucocorticoids and may help to conserve energy during stress (the 'euthyroid sick' syndrome). Somatostatin suppresses both TRH and TSH, while glucocorticoids inhibit the 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, 29].

Reproduction

The reproductive axis is inhibited at all levels by various components of the HPA axis (fig. 2C). CRH suppresses the secretion of gonadotropin-releasing hormone (GnRH) either directly or indirectly, via stimulation of arcuate POMC peptide-secreting neurons [57, 58]. Glucocorticoids, on the other hand, 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 [57–60].

The inflammatory cytokines, which are elevated during inflammatory stress, also suppress reproductive function by inhibiting both the pulsatile secretion of GnRH 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 [61].

Leptin plays a major permissive role in the activity of the hypothalamic-pituitary-gonadal axis. Low concentrations of leptin have been implicated in the gonadal suppression observed in starvation and anorexia nervosa [59]. It has been suggested that elevations in leptin concentrations that take place peripubertally may serve as the peripheral signal that notifies the hypothalamus of the adequacy of caloric resources, necessary for reproductive function [62].

Suppression of gonadal function caused by chronic activation of the HPA axis has been demonstrated in highly trained runners of either sex and ballet dancers [63, 64]. These subjects demonstrate elevated plasma concentrations of cortisol and 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 gonadal axis appears to be bidirectional. Estrogen-responsive elements are present in the promoter region of the CRH gene and estrogen stimulates CRH gene expression [65]. These findings implicate the CRH gene as 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.

Pregnancy in the third trimester is characterized by hypercortisolism of a degree similar to that observed in severe depression, anorexia nervosa and mild Cushing's syndrome. This is the only known physiologic state in humans in which circulating CRH concentrations are sufficiently high to result in activation of the HPA axis [59, 66, 67].

Metabolism

Glucocorticoids not only have profound inhibitory effects on the secretion of GH and sex steroids but also antagonize the actions of these hormones on fat tissue catabolism (lipolysis) and muscle and bone anabolism (fig. 2D) [3]. 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. Indeed, the phenotype of central obesity, decreased lean body mass and osteoporosis is observed in patients with Cushing's syndrome, some patients with melancholic depression (pseudo-Cushing's syndrome) and patients with the (dys)metabolic syndrome X (visceral obesity, insulin resistance, dyslipidemia, hypertension, hypercoagulation, sleep apnea), many of whom display increased HPA axis activity and demonstrate similar clinical and biochemical manifestations [68–71]. Recently, patients with melancholic depression and a normal body mass index were found to have decreased muscle mass, osteopenia/osteoporosis and dysmetabolic syndrome manifestations [72].

The association between chronic stress and hypercortisolism and a metabolic syndrome X-like state has been reported in cynomolgus monkeys. In these animals, chronic stress-induced activation of the HPA axis and hypercortisolism lead to visceral obesity, insulin resistance and suppression of GH secretion, all responsible for the development of varying degrees of the clinical and biochemical manifestations of the metabolic syndrome X, along with severe coronary atherosclerosis [70, 71].

Given that increased gluconeogenesis is a cardinal feature of the stress response and that glucocorticoids induce insulin resistance, activation of the HPA axis may 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 recently 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 directly 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. Osteoporosis may be further amplified by the stress-induced hypogonadism and the reduced concentrations of sex steroids. Increased prevalence of osteoporosis has been demonstrated in young women with depression or a previous history of depression [74].

Gastrointestinal Function

CRH is involved in the central mechanisms that operate to influence gastrointestinal function during stress. PVN CRH induces inhibition of gastric acid secretion and emptying, while 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. Thus, 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 be implicated 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, thus forming a vicious cycle, which may explain the chronicity of the condition.

Another area of interest relates to the association of chronic stress and gastrointestinal (GI) illness. In a study of patients referred with chronic GI pain, a high incidence of physically and sexually abused women was reported. Sexually abused women suffer from chronic activation of the HPA axis, similar to that of patients with melancholic depression [78]. Thus, CRH hypersecretion may be a link between chronic GI pain and a history of abuse. Chronic activation of the HPA axis and/or the LC-NE-sympathetic system due to depletion of the opioid-peptide system responsible for stress-induced analgesia may also explain the observed lower pain threshold for visceral sensation in patients with functional GI disorders.

Immune Function

Activation of the HPA axis has profound inhibitory effects on the immune/inflammatory response, since virtually all the components of the immune response are inhibited by cortisol [79, 80]. 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. Thus, a circadian activity of several immune factors has been demonstrated in reverse-phase synchrony with that of plasma glucocorticoid concentrations [81].

During stress, the activated ANS also exerts systemic effects on immune organs by inducing the secretion of IL-6 in the systemic circulation [82]. Despite its inherent inflammatory activity, IL-6 plays a major role in the overall control of inflammation, by stimulating glucocorticoid secretion [83, 84] 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 [85].

The combined effects of glucocorticoids and catecholamines on the monocyte/macrophage and dendritic cell 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 [86]. This suggests that stress-related immunosuppression refers mostly to innate and cellular immunity, facilitating diseases related to deficiency of such type immune responses, such as common cold, tuberculosis and certain tumors [86].

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 SNS, and relative immunosuppression [87, 88]. Patients suffering from this 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 [89]. Patients with melancholic depression have a marked increase in the number of PVN CRH neurons on autopsy. Whether this is genetically determined, environmentally induced, or both, is unclear at the present time.

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 to controls [90]. In addition, they excrete significantly higher amounts of catecholamines and their metabolites, and show lower basal and CRH-stimulated ACTH levels and significantly reduced total ACTH responses compared to controls; however, their total and free basal and CRH-stimulated plasma cortisol concentrations and 24-hour urinary free cortisol concentrations 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 [90, 91].

A spectrum of other conditions may also be associated with increased and prolonged activation of the HPA axis. These include anorexia nervosa [92], malnutrition [51], obsessive-compulsive disorder, panic anxiety [93], excessive exercise [63, 64], chronic active alcoholism [94], alcohol and narcotic withdrawal [95], diabetes mellitus types I and II [71, 73], central (visceral) obesity [70] and perhaps, hyperthyroidism.

It is of interest that 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 [37–40]. 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. Also, glucocorticoids have been associated with leptin resistance [96], while Zucker rats are leptin receptor deficient with concurrent hypercorticosteronism and decreased LC-NE-sympathetic system activity [97].

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 [98]. Similarly, patients with fibromyalgia often complain about fatigue and have been shown to have decreased 24-hour urinary free cortisol excretion [99]. 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 [100]. 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. It is interesting that 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, 59, 101].

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. By 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 [79, 86]. 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 [102].

Patients with depression or anxiety have been found to be more vulnerable to tuberculosis, presenting both increased prevalence and a more fulminant course of the disease [103]. Similarly, stress was associated with increased vulnerability to the common cold virus. A compromised innate and T-helper-1-driven immunity would predispose an individual to these conditions. Also, there is an increasing body of evidence to suggest that patients with rheumatoid arthritis, a T-helper-1-driven inflammatory disease, have a mild form of central hypocortisolism, as indicated by the normal 24-hour cortisol excretion despite the major inflammatory stress, and diminished HPA axis responses to surgical stress [104]. Thus, dysfunction of the HPA axis may play a role in the development and/or perpetuation of T-helper-1-type of autoim-

mune disease. The same theoretical concept may explain the high incidence of T-helper-1 autoimmune disease, such as rheumatoid arthritis and multiple sclerosis that occurs following cure of hypercortisolism, in the postpartum period, and in patients with adrenal insufficiency, who do not receive adequate replacement therapy [86, 105, 106].

The Interplay of Genetic and Developmental Predisposition, and Environmental Influences in Defining the Stress Response and Its Long-Term Consequences

Genetics vs. Development vs. Environment and the Stress Response

The above stress-related pathologic conditions may occur comorbidly, in parallel with each other, and in varying combinations and degrees. Proper 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 can emerge as a function of genetic inheritance, developmental and environmental factors, and can be considered the endpoint of converging influences. For example, the enhanced vulnerability for depression derives from genetic, developmental and behavioral modes of transmission: children of depressed parents commonly inherit not only a genetic predisposition for depression, but often the compromised maternal environment and suboptimal care that a depressed parent may provide to the fetus and infant. Thus, depending on the genetic background of the individual and his/her exposure to adverse stimuli in prenatal and early postnatal life (developmental influences), one might fail to cope with life stressors and may thus develop any of these states in any combination and any degree of severity [55].

The stress response of an individual is determined by multiple factors, several of which are inherited, as indicated by quantitative genetics of human complex behaviors [1, 3, 107, 108]. It has been estimated that up to two thirds of reliable variance in measured personality traits are due to genetic influences. Genetic polymorphisms, the clinically significant alterations in the expression of genes involved in the regulation of the stress system, 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 very complex genetic background continuum in our population that ranges from extreme resilience to extreme vulnerability to these stress-related comorbid states (fig. 5). Thus, 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 (fig. 5A).

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 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 (anxiety), respectively, and a suboptimal sense of well-being or diminished performance [55]. Developmental influences, when propitious, may shift an individual towards a more resilient response to stress while, when negative, may have the opposite effect (fig. 5B). Therefore, the development in human beings of one or more of the above stress-related states can be altered by a supportive or an adverse environment. This suggests that genetics and development define vulnerability, while environment may determine the triggering of a disease.

Transitional Life Stages and Stress Effects: Organizational vs. Regulatory Effects of Stress Hormones

The prenatal life, infancy, childhood and adolescence are periods of increased plasticity for the stress system and are, therefore, 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, 109, 110]. 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
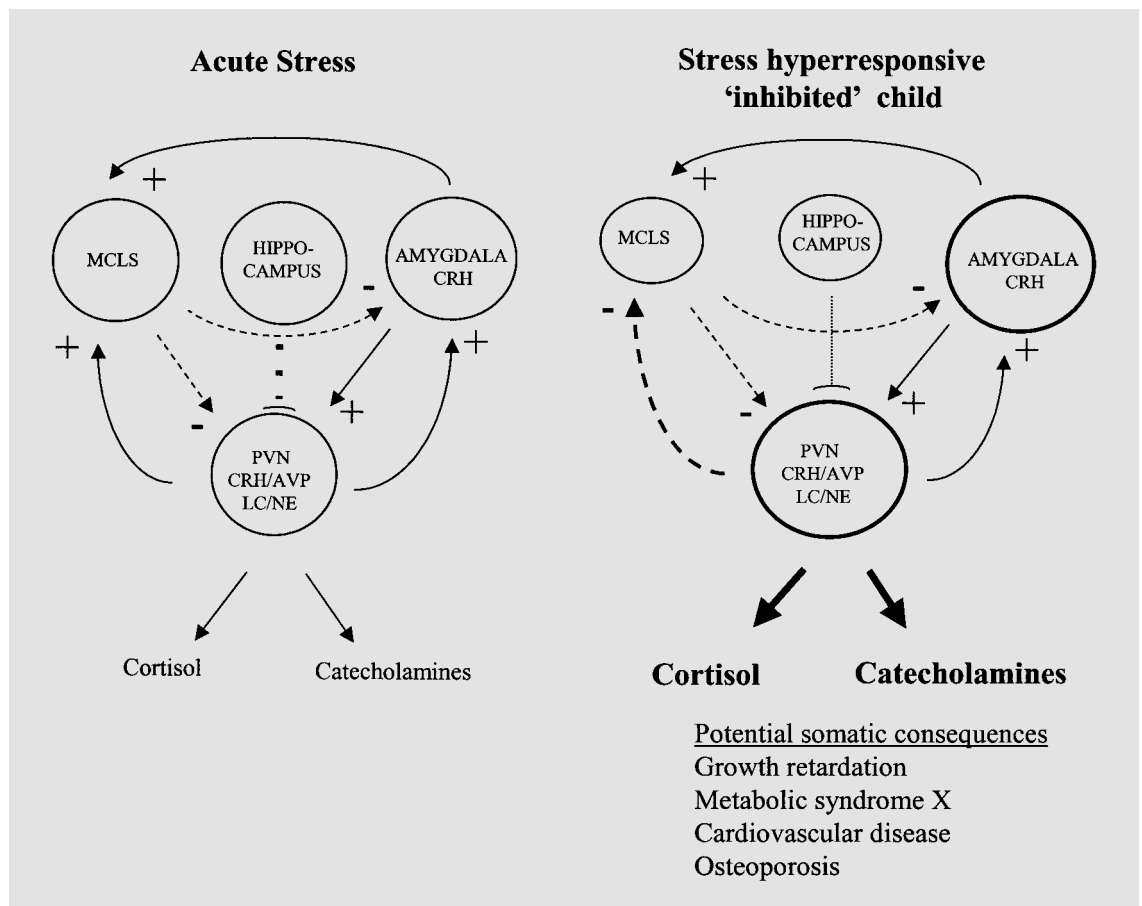
Fig. 5. Central neurocircuity in the *stress-hyperresponsive/inhibited child* leading to a hyperactive stress system in comparison with the central neurocircuity of the normal stress response. The hyperfunctioning amygdala, hypofunctioning hippocampus and/or hypofunctioning mesocorticolimbic dopaminergic system could predispose an individual to anxiety, melancholic depression and their somatic consequences. Solid lines represent activation, whereas dashed lines indicate inhibition (adapted from Chrousos and Gold [55]).

stressors may have permanent effects on the organism even if they occur later in life, such as in the adult post-traumatic stress disorders.

That prenatal life is particularly sensitive to the development of the 'organizational' effects of stress is indicated by the fact that maternal stress during the third week of pregnancy results in demasculinization and feminization of the sexual performance of male offspring in both mice and rats [111, 112]. This behavioral effect reflects the stress-induced alterations in the brain of male offspring, such as diminished sex-specific differences in neural volume, reduced fetal hypothalamic aromatase and alterations in brain monoamines thought to be involved in regulation of sexual activity. Prenatal stress may also alter masculine function directly by suppressing the two (fetal

vs. perinatal) testosterone surges that may be necessary for masculinization of brain and behavior [113]. This testosterone suppression may in turn be glucocorticoid-mediated, given that high levels of stress suppress testosterone concentrations in a wide variety of mammals and this suppression may be mimicked by direct administration of such agents as ACTH and dexamethasone. Indeed, prenatal administration of dexamethasone demasculinizes sexual behavior of the male offspring, duplicating the effect of prenatal stress, while dexamethasone and corticosterone may affect sexual differentiation by altering the anogenital distance [114].

In addition to prenatal life, infancy plays an important role in determining individual differences in vulnerability to stress-induced illnesses. Early life events permanently

influence the development of central CRF systems, which in turn mediate the expression of behavioral/emotional, autonomic and endocrine responses to stress [115]. In rodent and nonhuman primate populations, maternal deprivation in infancy is associated with enhanced neural CRF gene expression and increased stress reactivity. In adulthood, these animals show greater activation of the HPA axis, the sympatho-adrenomedullary systems and the central monoaminergic systems, and thus, greater vulnerability to stress-induced illness [115]. These animals display increased levels of glucocorticoids, decreased levels of GH, decreased glucocorticoid receptor binding in the hippocampus, hypothalamus and frontal cortex, and decreased negative feedback sensitivity [115, 116]. In addition, they demonstrate (i) a twofold increase in CRF mRNA levels in the central nucleus of the amygdala, (ii) increased CRF-like immunoreactivity at the level of the amygdala, LC and the neighboring parabrachial nucleus, and (iii) increased CRF receptor levels in the LC and the raphe nucleus. These findings suggest that maternal separation-induced changes in CRF systems might regulate both noradrenergic and serotonergic responses to stress [116]. Indeed, PVN levels of noradrenaline during stress are elevated in maternal separation animals [116, 117]. As expected, these animals are highly fearful in behavioral tests of novelty, which include reduced exploration or feeding in a novel environment, and increased acoustic startle responsivity, all of which are mediated by CRF effects on noradrenergic release [116, 118]. Administration of the CRH type 1 receptor antagonist, antalarmin, inhibits the development of conditioned fear in rats [119], while in rhesus monkeys it inhibits a repertoire of behaviors associated with anxiety and fear, and increases exploratory and sexual behaviors, which are normally suppressed during stress [120]. Furthermore, antalarmin significantly diminishes the increase in CRH concentrations in the CSF, as well as the pituitary-adrenal, sympathetic and adrenomedullary responses to stress, without causing hypotension or any Addisonian crises [120].

In contradistinction to the effects of maternal separation on stress reactivity, postnatal handling during the first few weeks of life results in decreased stress reactivity in adulthood [115, 116, 121, 122]. As adults, rats exposed to brief periods of postnatal handling daily show reduced ACTH and adrenal corticosterone (the principal glucocorticoid in the rat) responses to stress compared with nonhandled animals; these differences are apparent in animals tested as late as 26 months of age, indicating that the handling effect on HPA function persists throughout life. Also, postnatally handled animals show enhanced gluco-corticoid negative-feedback sensitivity compared with nonhandled rats, and therefore decreased hypothalamic CRH and AVP mRNA expression. The handling effect on feedback sensitivity is mediated by an increase in glucocorticoid receptor (GR) expression in the hippocampus, a region that has been strongly implicated in glucocorticoid negative-feedback regulation. The increased hippocampal GR gene expression is, therefore, a central feature of the handling effect on HPA responsivity to stress, resulting in increased feedback inhibition of CRH and AVP synthesis, and reduced pituitary ACTH release during stress [121, 122]. Tactile stimulation derived from mothers also serves to decrease HPA activity and to stimulate the release of GH, thus protecting the animals against the highly catabolic effects of adrenal glucocorticoids during a period of rapid development [116]. It is, therefore, evident that individual differences in parental care are related to the health of the offspring. Parental rearing that results in enhanced reactivity to stress appears to increase the risk for illness in later life. The cornerstone of this argument is the fact that increased levels of stress hormones, notably the glucocorticoids and catecholamines, can promote the development of multiple forms of chronic illnesses [115, 116].

Another example that illustrates the fact that the quality of the early family environment can serve as a major source of vulnerability in later life is that individuals who are the victims of physically or sexually abusive families are at considerably greater risk for mental illness in adulthood [123]. Persistent emotional neglect or conditions of harsh, inconsistent discipline, also serve to increase the risk of depression and anxiety disorders to a level comparable to that observed in more obvious cases of abuse [124]. Indeed, low scores on parental bonding scales, reflecting cold and distant parent-child relationships, significantly increase the risk of depression in later life [125]. Children need not be beaten to be compromised, and the risk is not unique to mental health. Individuals who as undergraduate students rated their relationship with parents as cold and detached had a fourfold greater risk of chronic illness, including not only major depressive disorder, alcoholism and posttraumatic stress disorder, but also heart disease and type II diabetes [126]. This higher stress vulnerability may be mediated by persistent alterations in neurobiological systems that are known to be stress-responsive. CNS CRH systems are likely involved in mediating the effects of stress early in life on the development of certain psychiatric disorders in adulthood. For example, abused women without major depressive disorder exhibit greater than usual ACTH responses to CRH

administration, whereas abused women with major depressive disorder and depressed women without early life stress demonstrate blunted ACTH responses. Following ACTH stimulation, abused women without major depressive disorder exhibit lower baseline and stimulated plasma cortisol concentrations. These findings suggest sensitization of the anterior pituitary and counterregulatory adaptation of the adrenal cortex in abused women without major depressive disorder. On subsequent stress exposure, women with a history of childhood abuse may hypersecrete CRH, resulting in down-regulation of adenohypophyseal CRH receptors and symptoms of depression and anxiety [127].

These findings provide a biologic basis for the link between early life trauma and illness in later life as well as ample evidence that early life events can alter the development of individual differences in stress reactivity. These effects of early environment on the development of HPA responses to stress reflect a naturally occurring plasticity whereby factors such as maternal care are able to program rudimentary, biologic responses to threatening stimuli. Such plasticity allows the development of defensive systems to the unique demands of the environment. Developmental 'programming' of CNS responses to stress in early life is likely to be of adaptive value to the adult within a certain extent. Such programming would afford an appropriate HPA response and minimize the need for a long and perhaps unaffordable period of adaptation in adult life.

Conclusions

The concept of a hormone as a chemical messenger, which allows local, regional, or distant cellular communication, has been challenged by new concepts that merge the views of separate signaling mechanisms via classic hormones and neurochemical and cytokine networks into an integrated pattern, which forms the basis of a clearer understanding of homeostasis and its disturbances throughout the human life-span.

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