or to catecholamine-induced interleukin-6 (IL-6) secretion. These include glucocorticoid-induced accumulation of visceral fat, leading to hyperinsulinism, insulin resistance, hypertension, and hyperlipidemia, and glucocorticoid- and IL-6-induced osteoporosis and immunosuppression, naturally all influenced also by the genetic and acquired properties of the end-organ. The former set of effects could explain the significant loss of life expectancy in patients with depression, even after exclusion of suicide deaths, most likely the result of earlier cardiovascular and cancer deaths in these patients.

It is not only excessive activity and/or stress reactivity of the stress system that produces pathology, but also defective function of this system can be equally detrimental. Thus, one should mention major states in which one or more components of the stress system are hypoactive and/or hyporesponsive, such as atypical/seasonal depression, the chronic fatigue/fibromyalgia syndromes and several autoimmune diseases with inadequate glucocorticoid responses to inflammatory stimuli. Also, one should mention transient, albeit frequent conditions, such as the postpartum blues, and the nicotine- and steroid-withdrawal syndromes, which ensue upon abrupt discontinuation of nicotine or glucocorticoid intake, respectively. All of these states are characterized by hypoarousal, fatigue, and irritability. Recently, first degree relatives of alcoholics were found to have a potentially deficient stress system, a state that alcohol may overcorrect, by causing the known chronic activation of the stress system observed in chronic active alcoholics.

It is certain that genetic abnormalities of the stress system may be responsible for a large portion of human misery. It is also certain that prenatal stress and a deprived, exploitive, or hypercritical childhood environment perpetuate the misery by constitutionally affecting the stress system of individuals, who then themselves, by begetting children and exposing them to similar toxic conditions, become a crucial link of an ever-continuing vicious cycle. The advances in our understanding of the molecular biology, physiology, and pathophysiology of the stress system will hopefully allow us not only to isolate the key genes of the stress networks and to define individual vulnerability risks for a host of human disorders, but also to initiate medical preventive measures, pharmacotherapy, and, in the more distant future, gene therapy. A parallel crucial effort should be to break the sociobiological vicious cycle of stress that plagues humanity and causes immeasurable losses.

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Neuroendocrinology and Pathophysiology of the Stress System

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INTRODUCTION

Life exists by maintaining a complex dynamic equilibrium, or *homeostasis*, that is constantly challenged by intrinsic or extrinsic adverse forces or stressors.[1] *Stress*, a term borrowed from physics by W. Cannon and H. Selye and set to mean the mutual actions of forces that take place across any section of the body,[2,3] is a state of *threatened homeostasis*. The human body reacts to stress by activating a complex repertoire of behavioral and physiologic responses, the familiar "fight or flight" response described by Walter Cannon in the early 1900s.[4] Successful adaptive responses can be specific to a stressor or can be relatively nonspecific, when a stressor of any kind exceeds a threshold magnitude. Alterations in the ability of the organism to respond to stressors, with the responses being either excessive or inadequate in magnitude and duration, may lead to disease, a concept introduced by ancient Greek medicine 2 1/2 millennia ago.[1,5,6] Thus, when the activity of the stress response system is plotted against a stressor's potency, one's dose response curve may be shifted to the left of that of a normally reactive individual while another's may be shifted to the right. The former denotes an excessive reaction, the latter a defective one.[1] Similarly, one's sense of well-being or performance ability corresponds to an inverted U-shaped curve that covers the range of stress system activity. Shifts either to the left or to the right of this range, respectively, result in hypoarousal or hyperarousal (anxiety) and a suboptimal sense of well being and/or diminished performance.[1,4]

Stress responses of individuals are determined by a multiplicity of factors, several of them inherited, as quantitative genetics of human complex behaviors indicate.[7] It has been estimated that about two-thirds of reliable variance in measured personality

traits is due to genetic influences.[8] Nevertheless, development is an important modifier of the stress response, since it influences the timing and strength of the counteracting forces. It is for this reason that infancy, childhood, and adolescence, associated with increased biological dependency and physiological and psychological immaturity, entail increased vulnerability to maladaptive stress responses. The latter, in turn, may alter normal personality development and affect physiological functions, such as growth, metabolism, reproductive function, and immune responses, leading to growth, metabolic, psychiatric, autoimmune, and other disorders.[1,9–12]

NEUROENDOCRINOLOGY OF THE STRESS RESPONSE

The adaptive stress response is characterized by both *behavioral* and *physical* changes. The former include increased arousal and alertness, heightened attention, and suppression of sexual and feeding behaviors. The latter lead to redirection of energy, i.e., oxygen and nutrients, to the stressed body site and the central nervous system (CNS), where they are needed most.[4] The proper activation of all changes is coordinated by the central and peripheral limbs of the stress system.[1] The central components of this system constantly receive information from higher centers of the CNS, the periphery, and the environment, and peripheral actions. Thus, the stress system is an extremely complex, albeit highly efficient and flexible, physiologic network that helps coordinate the dynamic equilibrium of the organism.

The parvocellular corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) neurons of the paraventricular nuclei (PVN) of the hypothalamus, along with the CRH neurons of the paragigantocellular and other nuclei of the medulla, and the catecholaminergic neurons of the locus ceruleus (LC) and other cell groups of the medulla and the pons, are the central coordinators of the stress system, while the hypothalamic-pituitary-adrenal (HPA) axis and the efferent sympathetic/adrenomedullary system represent its peripheral limbs.[13] Reciprocal neural connections exist between the CRH and catecholaminergic neurons of the CNS,[14,15] and there are autoregulatory ultrashort negative feedback loops on the CRH neurons exerted by CRH and on the catecholaminergic neurons exerted by norepinephrine via collateral fibers and presymaptic receptors.[16] Both CRH and noradrenergic neurons are stimulated by serotonin and acetylcholine, and inhibited by glucocorticoids, gamaaminobutyric acid (GABA), corticotropin (ACTH), and opioid peptides.[17–19]

CRH and AVP, produced by parvocellular neurons of the PVN, reciprocally innervate and are innervated by opioid peptide [propiomelanocortin (POMC)] producing neurons of the arcuate nucleus of the hypothalamus. Thus, activation of the stress system stimulates hypothalamic POMC-peptide secretion, which reciprocally inhibits the activity of the stress system and, in addition, through projections to the hindbrain and spinal cord, produces analgesia.[20] CRH stimulates and is permissive for pituitary ACTH secretion. On the other hand, AVP is a potent synergistic factor of CRH but has very little ACTH secretagogue activity by itself.[21] During stress, CRH and AVP secretion increases, resulting in increased ACTH and cortisol secretion. Other factors are also recruited during the various types of stress, potentiating the activity of the HPA axis. These include angiotensin II, cytokines, and lipid mediators of inflammation.[22]

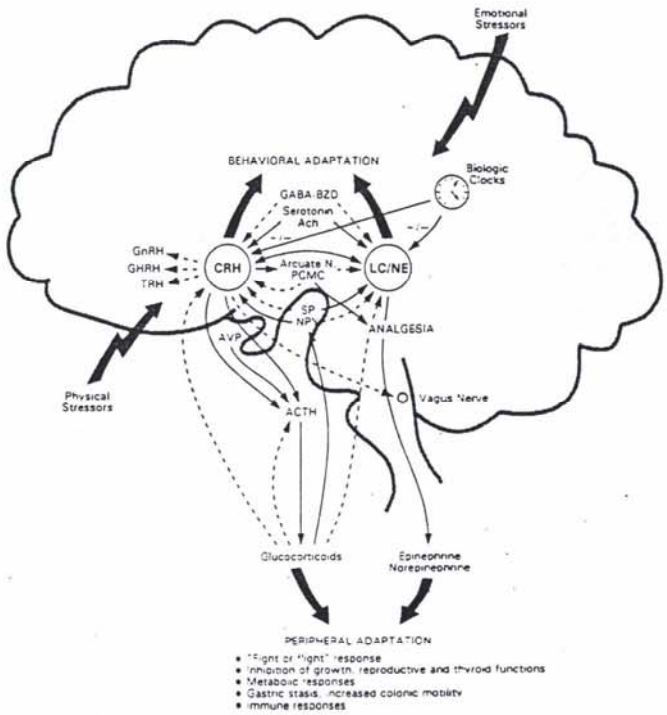

FIGURE 1. A simplified representation of the central and peripheral components of the stress system, their functional interrelations, and their relations to other CNS systems involved in the stress response. *Solid lines* represent direct or indirect activation and *dashed lines* represent direct or indirect inhibition. LC = locus ceruleus, NE = norepinephrine, SP = substance P, NPY = neuropeptide Y, AVR = vasopressin.

Circulating ACTH is the key regulator of glucocorticoid secretion by the adrenal cortex, but other hormones, some of them originating in the adrenal medulla, participate as well.[23] Glucocorticoids are the final effectors of the HPA axis and participate in the control of whole body homeostasis and the organism's response to stress. They also play a key regulatory role on the basal activity of the HPA axis and on the termination of the stress response by exerting negative feedback at the CNS components of the stress system.[24]

The sympathetic division of the autonomic nervous system provides a rapidly responding mechanism that controls mostly the acute response of the organism to a stressor. Peripherally, it widely innervates vascular smooth muscle cells, as well as the kidney, gut, and many other organs, and the adrenal medulla. In addition to acetylcholine, norepinephrine, and epinephrine, both the sympathetic and the parasym-

pathetic divisions of the autonomic nervous system (ANS) secrete a variety of neuropeptides, such as neuropeptide Y (NPY), somatostatin, galanin, enkephalin, and neurotensin, as well as adenosine triphosphate (ATP) and nitric oxide (NO).[25] The particular combination of these substances in the neurons of the ANS during the stress response is strongly affected by the CNS and the interaction with the HPA axis.

THE STRESS SYSTEM AND REGULATION OF AFFECT

Activation of the stress system occurs in diametrically opposed situations, such as pleasure and dysphoria.[4] Indeed, self-driven activation of the stress system—an important component of human development—is associated with pleasure, if adaptive and controlled, and *dysphoria,* if maladaptive and uncontrolled. Activation of the stress response during spontaneous threatening situations that are beyond the control of an individual are associated with dysphoria. The teleology of this phenomenon is sound, for this is the mechanism by which the individual avoids or learns to avoid situations that may be detrimental to one's existence. The crucial nature of the stress system in human survival is underscored by the fact that it is activated during both feeding and sexual activity, *sine qua non* functions for individual and species preservation.

The mechanism(s) by which the type of stress-activated mood depends on the context is complex, and mediated through the interactions of the stress system with at least three other elements of the CNS:[1,4] (a) the mesosocortical and mesolimbic dopamine systems which include the prefrontal cortex and nucleus accumbens and are involved in anticipatory and motivational/reiforcement and reward phenomena, respectively,[26] (b) the amygdala/hippocampus complex involved in emotional stressors, such as conditioned fear,[27] (c) the arcuate opioid peptide-secreting neurons mentioned above[16] which alter sensitivity to pain and perhaps influence emotional tone.

Several disorders seem to represent dysregulation of the generalized stress response, which in this state seems to escape the usual counterregulatory elements that serve to make it a self-limiting process.[5] In melancholic depression, for example, the cardinal symptoms are the hyperarousal (anxiety) and suppression of feeding and sexual behaviors (anorexia, loss of libido), and excessive and prolonged redirection of energy (tachycardia, hypertension), all of which are extremes of the classic manifestations of the "generalized" stress response. The dysphoria that accompanies this condition may represent a response to uncontrolled stressor and could be due to tachyphylaxis of the mesocorticolimbic system to chronic activation of the stress system. In addition, in depressive individuals, cognition, memory, and attention are focused obsessively on depressive ideas, again representing maladaptive increases in attention span that normally should focus on solving problems related to real stressors.

Both the HPA axis and the sympathetic system appear chronically activated in melancholic depression.[1,5] Chronic activation of the HPA axis has been shown also in a host of other conditions, such as anorexia nervosa,[28] panic anxiety,[29] obsessive-compulsive disorder,[30] chronic active alcoholism,[31] alcohol and narcotic withdrawal,[32]

excessive exercising,[33] malnutrition,[34] and more recently, in sexually abused girls.[35] In addition, animal data are rather confirmatory of the association of chronic activation of the HPA axis and affective disorders. Traumatic separation of infant rhesus monkeys and laboratory rats from their mothers causes behavioral agitation and elevated plasma ACTH and cortisol responses to stress that are sustained later in life.[36,37] Such activation of the CRH system was originally thought to be an epiphenomenon.[38] Administration of CRH to experimental animals, however, with its profound effect on totally reproducing the stress response, suggested that CRH may participate in the initiation and/or propagation of a vicious cycle.[1] On the other hand, atypical or seasonal depression in the dark months of the year, the postpartum period, the period following the cessation of smoking, and the chronic fatigue and fibromyalgia syndromes, represent hypoarousal states: in these conditions, CRH secretion is decreased and symptoms, such as increase in appetite and weight gain, somnolence, and fatigue are seen.[1,39]

Adolescence was defined as a period of "storm and stress" in older studies. More recent reports indicate that the vast majority of teenagers do not experience significant distress during adolescence.[10] However, there is general agreement that adolescence is a challenging period of life, during which significant physical, psychological and social changes take place.[4] The adolescents are in a chronic state of "threatened homeostasis" and their adaptive responses are crucial for a successful and happy adulthood. Dysregulation of the stress system in adolescence, by the mechanisms indicated above, could be the reason behind the emergence of a number of disorders during this period, such as schizophrenia, depression, anorexia nervosa, and substance abuse.

STRESS AND ENDOCRINE FUNCTIONS: EFFECTS ON THE GROWTH, GONADAL, AND THYROID AXES

Growth and reproduction are directly linked to the stress system, and both are profoundly influenced by the HPA axis. The reproductive axis is inhibited at all levels by various components of the stress system.[40] Thus, CRH suppresses the secretion of gonadotropin hormone releasing hormone (GnRH) by the arcuate neurons of the hypothalamus either directly or via the stimulation of arcuate POMC peptide-secreting neurons. Moreover, glucocorticoids exert inhibitory effects at the level of the GnRH neuron, the pituitary gonadotroph, and the gonads themselves and render target tissues of sex steroids resistant to these hormones. Suppression of gonadal function caused by chronic HPA activation has been demonstrated in highly trained runners of both sexes[4,41] and ballet dancers.[42] These subjects have increased evening plasma cortisol and ACTH levels, increased urinary free cortisol excretion, and blunted ACTH responses to exogenous CRH; males have low luteinizing hormone (LH) and testosterone levels, and females have amenorrhea.[41,42] Characteristically, obligate athletes go through withdrawal symptoms and signs if, for any reason, they have to discontinue their exercise routine. This syndrome is possibly the result of withdrawal from the daily exercise-induced elevation of opioid peptides.[1] The interaction between CRH and the gonadal axis appears to be bidirectional. We recently demonstrated the presence of estrogen-responsive elements in the promoter area of

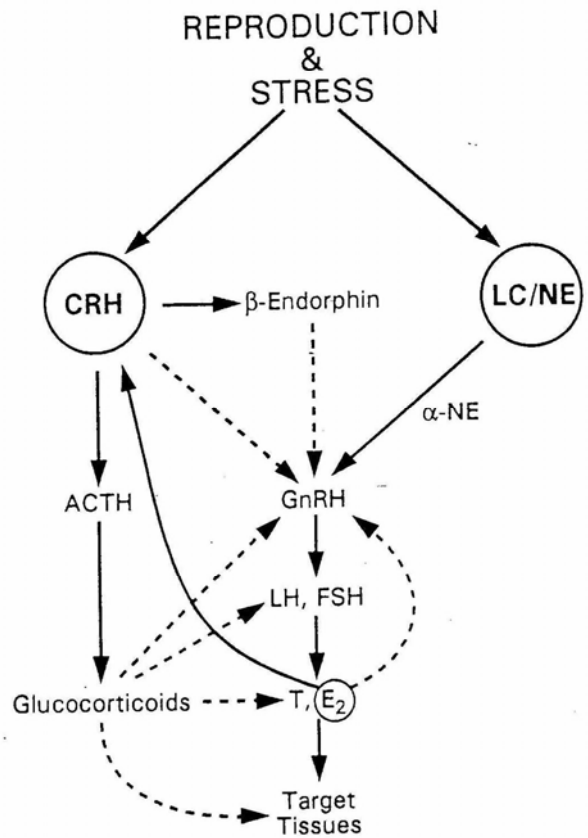

FIGURE 2. A schematic representation of the interactions between the stress system and the reproductive axis. Here, and in the figures that follow, *solid lines* represent direct or indirect activation, and *dashed lines,* direct or indirect inhibition.

the CRH gene and direct stimulatory estrogen effects on CRH gene expression.[43] This finding implicates CRH, and therefore, the HPA axis, as a potentially important target of ovarian steroids and a potential mediator of gender-related differences in the stress response.

In parallel to the gonadal axis, the stress system suppresses thyroid axis function. During stress, there is suppressed secretion of TSH and decreased conversion of the relatively inactive thyroxine (T4) to the potent triidothyronine (T3) in peripheral tissues. This situation is similar to what is observed in the "euthyroid sick" syndrome,

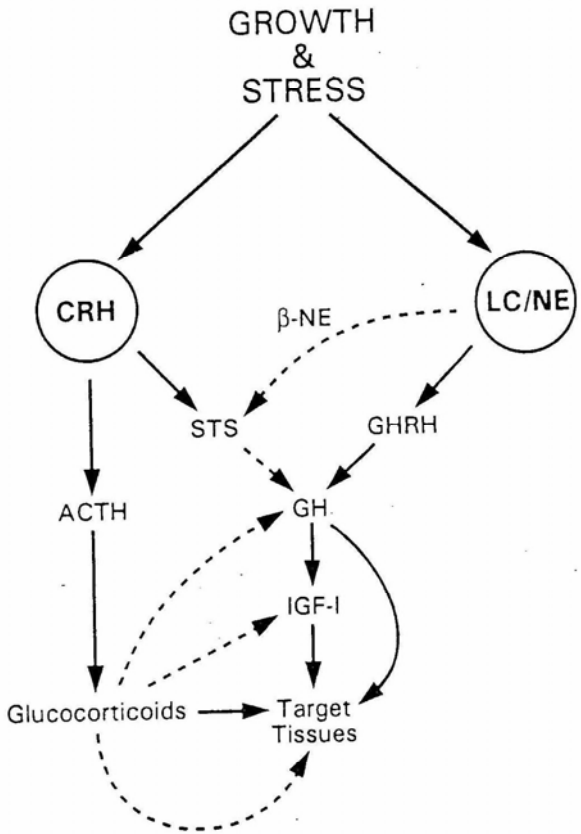

FIGURE 3. A schematic representation of the interactions between the stress system and the somatotropic (growth) axis.

a phenomenon that serves to conserve energy during stress.[44] The mediators of these changes in thyroid function include glucocorticoids, somatostatin, and cytokines.[1,4] Accordingly, patients with melancholic depression, anorectics, and highly trained athletes have significantly lower thyroid hormone concentrations than nonexercising controls.[4]

The growth axis is inhibited at many levels during stress, also. Thus, prolonged activation of the HPA axis leads to suppression of growth hormone (GH) and inhibition of insulin-like growth factor-I (IGF-I) effects on target tissues.[45] CRH-induced increases of somatostatinergic tone have been implicated as a potential mechanism of

stress-induced suppression of GH secretion. It is noteworthy that acute elevations of GH concentrations in plasma may occur at the onset of the stress response in man and after acute administration of glucocorticoids, presumably through stimulation of the GH gene by its glucocorticoid-responsive elements (GREs).

Psychosocial dwarfism (PD) is a term describing severe childhood or adolescent short stature and/or delayed puberty due to emotional deprivation or psychological harassment.[4,46] Decreased GH secretion that is reversible after separation of the child from the responsible environment is a characteristic finding in this condition.[47] Psychosocial dwarfism is also associated with a variety of behavioral abnormalities, such as depression and bizarre eating behaviors.[4,48] PD was first studied in infants in foundling homes or orphanages who failed to thrive, had decreased growth, and even died. It was hypothesized that this failure to thrive resulted from lack of attention and stimulation and/or deficient nutrition. Later it was shown that weight gain was independent of food intake, whereas with a caring and attentive environment, growth advanced and the psychological profile improved.[4] In addition to low GH secretion, these patients had a dysfunctional thyroid axis, resembling the "euthyroid sick" syndrome.

Infantile malnutrition is characterized by hypercortisolism, decreased responsiveness to CRH, and incomplete dexamethasone suppression, and the euthyroid sick syndrome pattern of abnormalities, which are restored after nutritional rehabilitation. It is noteworthy, that in this condition, increases rather than decreases of GH secretion are present, resulting from starvation-induced hyposecretion of IGF-I.[34] Premature infants are especially at risk for delayed growth and/or development, especially after a prolonged hospitalization in the intensive care nursery. The condition is similar to PD, but is known as "reactive attachment disorder of infancy."[49] Interestingly, activation of the fetal HPA axis is also associated with fetal growth retardation.[50]

STRESS AND METABOLISM

Long-term administration of glucocorticoids or endogenous Cushing syndrome is associated with visceral obesity, insulin resistance, hypertension, and elevated cholesterol and triglyceride levels.[51] Thus, hypercortisolism resembles the "metabolic syndrome X" (MS-X) in both its somatic and biochemical phenotypes. Interestingly, MS-X was recently associated with increased urinary free cortisol excretion, suggesting that glucocorticoids may represent a common denominator of both states.[51,52] Moreover, both hypercortisolism and MS-X are associated with increased atherosclerosis and resultant cardiovascular morbidity and mortality. The association between chronic, experimentally induced psychosocial stress and a hypercortisolism/MS-X-like state, with increased incidence of atherosclerosis was recently reported in cynomolgus monkeys.[53] In these animals, chronic, stress-induced activation of the HPA axis and therefore hypercortisolism apparently leads to visceral obesity, insulin resistance, and suppression of growth hormone secretion, all converging to the development of varying degrees of the physical and biochemical phenotype of the "MS-X?".[54,55] Low turnover osteoporosis is almost invariably seen in association with hypercortisolism, adult GH deficiency and the chronic stress model mentioned above, reflecting the detrimental effect of the combination of high cortisol and low GH and/or IGF-

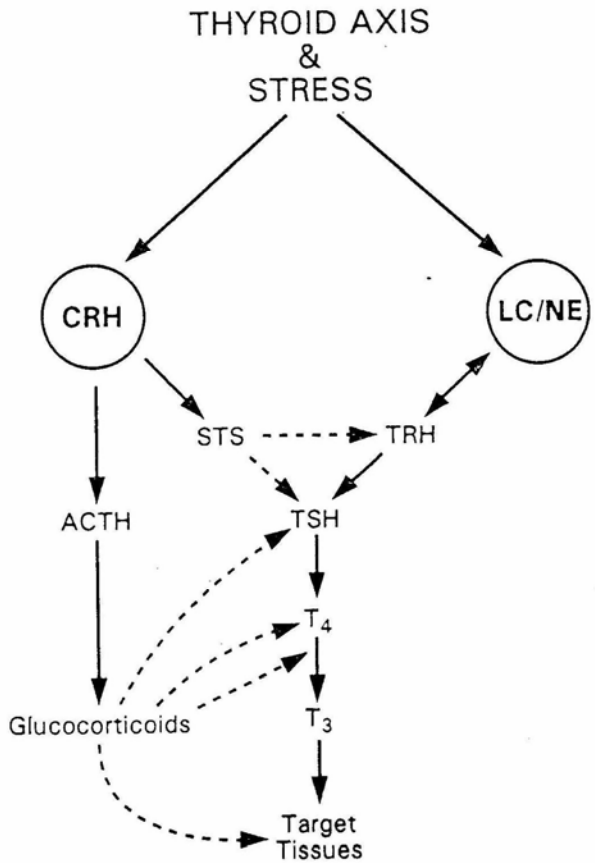

FIGURE 4. A schematic representation of the interactions between the stress system and thyroid function.

I concentrations at the level of the osteoblasts.[56,57] Osteoporosis may be further potentiated by the stress-related hypogonadism and could be responsible for the increased prevalence of osteoporosis refractory to estrogen replacement in depressed menopausal women.

Since increased gluconeogenesis is a characteristic feature of the "fight or flight" response[1,2] and glucocorticoids induce insulin resistance,[51] activation of the HPA axis may contribute to the poor control of diabetic patients during periods of emotional stress and inflammatory and other diseases. Indeed, activation of the HPA axis was recently demonstrated in type II diabetic patients that had developed diabetic

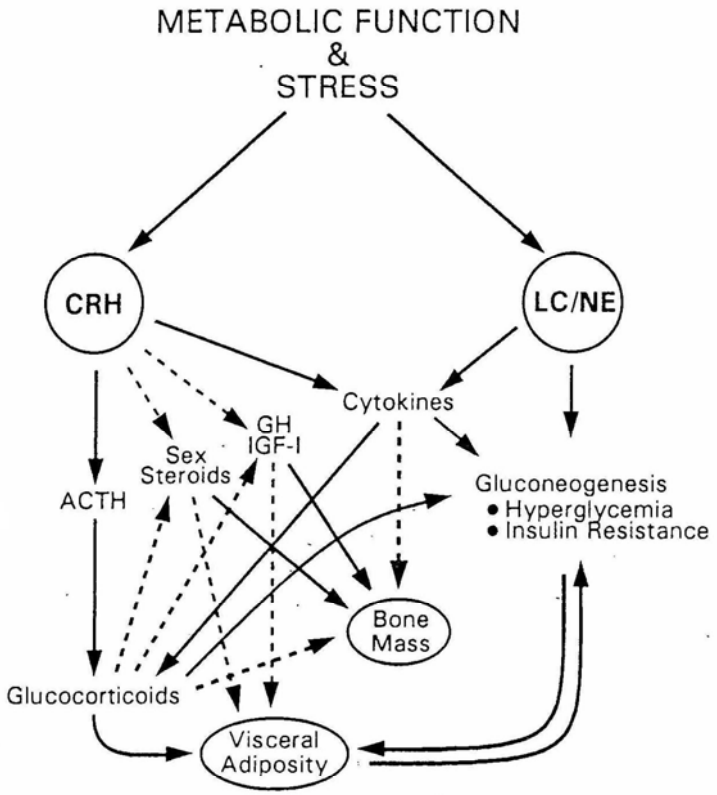

FIGURE 5. A schematic representation of the interactions between the stress system and metabolic function.

neuropathy.[58] Increased visceral adiposity is also associated with poor control of diabetes mellitus, thus suggesting that activation of the stress system in this disorder participates in a vicious cycle of increasing insulin needs, hyperglycemia, and hypercholesterolemia.

STRESS AND GASTROINTESTINAL FUNCTION

Several lines of evidence suggest that activation of the stress system influences gastrointestinal (GI) function. During stress, gastric emptying is delayed while colonic motor activity increases in animals and humans.[59] Innervation by the vagus nerve and the peripheral limbs of autonomic nervous system provides the network for rapid

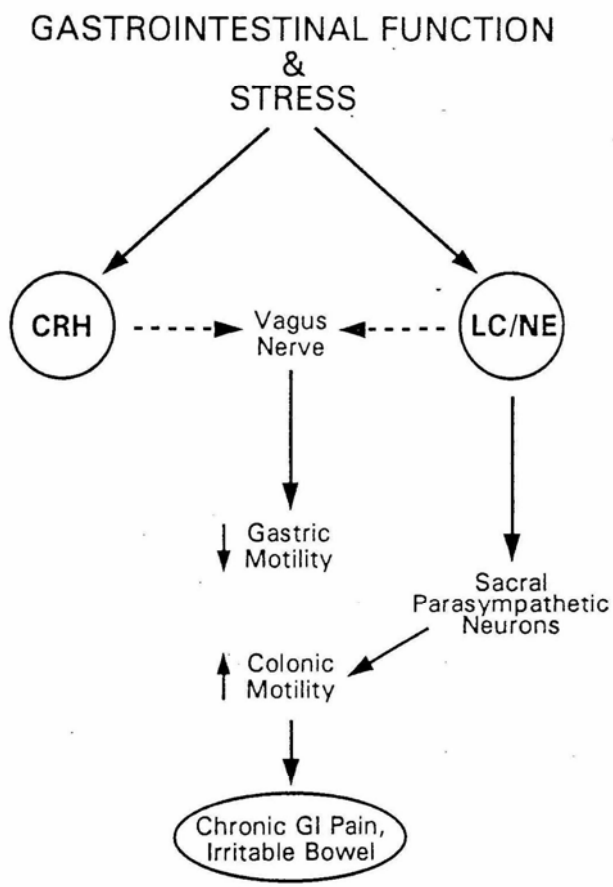

FIGURE 6. A schematic representation of the interactions between the stress system and gastrointestinal function.

responses of the GI system to stress.[60,61] In addition, the presence of APUD cells and direct secretion of a number of neuropeptides, such as somatostatin and vasoactive intestinal peptide (VIP), in the vascular system supplying the GI tract, provide a direct link with the neuroendocrine and, perhaps, the immune system.[60] More recently, CRH microinjected into the PVN was shown to reproduce the stress responses of the GI system in the animal model: CRH inhibited gastric emptying and stimulated colonic transit and fecal excretion, and this effect was abolished by the intrathecal administration of a CRH-antagonist.[59,61] It appears that these selective responses of the GI motor function to PVN CRH–gastric stasis and increased colonic motility–

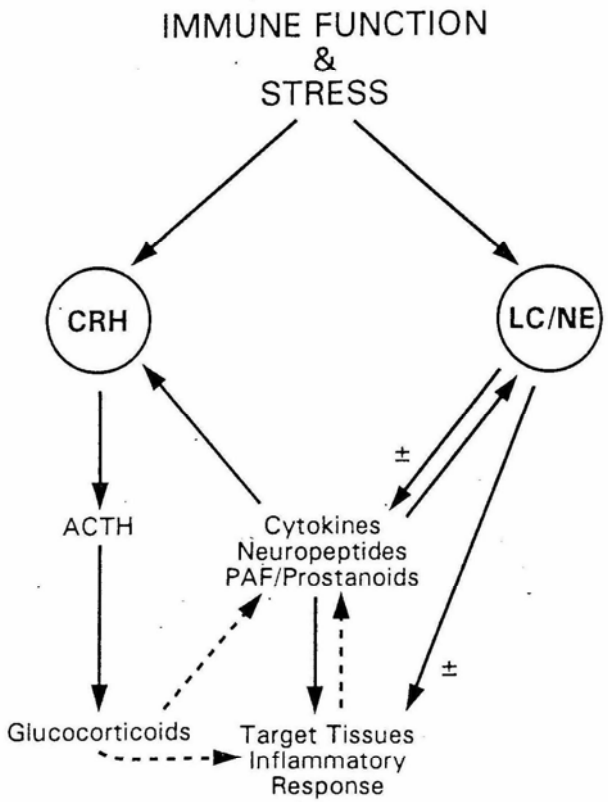

FIGURE 7. A schematic representation of the interactions between the stress system and immune function.

are mediated through the simultaneous inhibition of the vagus nerve and stimulation of the sacral parasympathetic system by CRH and the LC/noradrenergic neurons, respectively. Moreover, CRH may be implicated in mediating the gastric stasis observed during the stress of surgery and/or anesthesia. Interleukin (IL) 1β, a potent cytokine that is found increased during surgery and in the immediate postoperative period, inhibits gastric motility. Intrathecal administration of CRH antagonist prevented the surgery-induced rise of IL-1β in rats,[62] thus, suggesting that CRH may be the mediator for IL-1β-induced gastric stasis.

One area of recent interest relates to the association of chronic stress and GI illness. In a study of selectively referred patients with chronic GI pain, a high incidence of physically and sexually abused women was reported.[63] Sexual abuse

and posttraumatic stress disorder share the same degree of chronic activation of the HPA axis with patients with melancholic depression.[35] Thus, CRH could be the hidden link between the symptoms of chronic pain and history of abuse.[64] Similarly, CRH may be implicated in the stress-induced colonic hypermotility of patients with irritable bowel syndrome. Chronic activation of the HPA axis and/or the LC/noradrenergic system may also explain the observed lower pain tresholds for visceral sensation in patients with functional GI disorders,[65] by depletion of opioid-induced, stress-related analgesia.

STRESS AND IMMUNE FUNCTION

That activation of the HPA axis occurs during the stress of an infectious disease, autoimmune inflammatory process, and accidental or operative trauma has been known for years. The mechanisms of this association, however, have only recently been unravelled. The three "inflammatory cytokines" tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) cause stimulation of the HPA axis *in vivo*, alone, or in synergy with each other.[66] This is mediated through stimulation of hypothalamic CRH and AVP secretion and by direct effects at the pituitary and adrenocortical levels. IL-6, the main endocrine cytokine, causes major elevations of ACTH and cortisol, well above those observed with maximal stimulatory doses of CRH, suggesting that AVP and potentially other secretagogues are also stimulated by this cytokine. Glucocorticoids and prostanoid-synthesis inhibitors suppress the stimulatory effects of cytokines on the HPA axis.[67] Thus, glucocorticoids—the end-hormones of the HPA axis—play a major role in the stress-induced suppression of immune/inflammatory reaction.

The efferent sympathetic/adrenomedullary system also participates in the effects of stress on the immune/inflammatory reaction, both by being reciprocally connected with the CRH system and by transmitting neural signals from the periphery to the immune system. This is mediated through a dense innervation of both primary and secondary lymphoid organs, and by reaching all sites of inflammation via the postganglionic sympathetic neuron.[68] The sympathetic system, when activated, causes systemic secretion of IL-6, which by directly inhibiting the other 2 inflammatory cytokines, TNF-α and IL-1, and activating the HPA axis, participates in the stress-induced suppression of the immune-inflammatory reactions.[66,67] Activation of the sympathetic system during stress, and the effects of immunosuppression that follows, correlate well with such clinical observations as the suppression of immune system during psychological stress, the reactivation of autoimmune diseases during the post-partum period or following cure of Cushing syndrome, and the decreased ability of the stressed organism to fight neoplasms.[69]

The HPA axis and the immune system are functioning in balance in the physiologic state. An excessive HPA axis response to inflammatory stimuli would mimic a hypercortisolemic state and would lead to increased susceptibility of an individual to infections or neoplasias. On the other hand, a defective HPA axis response to inflammatory stimuli would reproduce the glucocorticoid-deficient state and lead to increased susceptibility to autoimmune/inflammatory diseases. Indeed, such properties were seen in a paired animal model, the Fischer and Lewis rats, selected out of

TABLE 1. States Associated with Dysfunctional HPA Axis[a]

Increased HPA Axis Activity	Decreased HPA Axis Activity
Chronic stress	Adrenal insufficiency
Melancholic depression	Atypical/seasonal depression
Anorexia nervosa	Chronic fatigue syndrome
Obsessive-compulsive disorder	Fibromyalgia
Panic disorder	Hypothyroidism
Excessive exercise	Nicotine withdrawal
Chronic active alcoholism	Post-glucocorticoid therapy
Alcohol and narcotic withdrawal	Post-Cushing syndrome
Diabetes mellitus	Postpartum period
Central obesity (metabolic syndrome X)	Post-chronic stress
Sexual abuse	Rheumatoid arthritis
Hyperthyroidism	
Premenstrual tension syndrome	
Cushing syndrome	
Pregnancy	

[a]Updated from Reference 1.

Sprague-Dawley rats, respectively for their resistance or susceptibility to inflammatory disease.[70] Accordingly, several lines of evidence suggest that patients with rheumatoid arthritis have a mild form of central hypercortisolism, as they have reduced 24-hour urinary free cortisol excretion, and blunted adrenal responses to surgical stress.[71,72] As in the case of atypical depression, chronic fatigue, and fibromyalgia, rheumatoid arthritis and other autoimmune diseases represent disorders in which the activity of the HPA axis is decreased, rather than increased.

CONCLUSIONS

Stress and related concepts can be traced as far back as written science and medicine. The stress system is essential for individual and species survival. Normal stress system function is crucial for maintenance of mental and physical health. Dysregulation of the stress system entails pathophysiology. Chronic stimulation or decreased activity of the HPA axis, a main constituent of the stress system, is observed in various pathophysiologic states (TABLE 1) that cut across the traditional boundaries of medical disciplines to include psychiatric, endocrine/metabolic, and inflammatory disorders.

SUMMARY

The human organism is in a state of dynamic equilibrium, *homeostasis*. The *stress system* is activated when homeostasis is challenged by extrinsic or intrinsic forces, the *stressors*. This system, whose central component is the central nervous system (CNS) and includes corticotropin-releasing hormone (CRH) and noradrenergic neurons, respectively, in the hypothalamus and the brain stem, has as its peripheral limbs the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic (sympathetic) nervous system. Normal development and preservation of life and species are dependent on a normally functioning stress system. Maladaptive neuroendocrine responses, i.e., dysregulation of the stress system, may lead to disturbances in growth and development, and cause psychiatric, endocrine/metabolic, and/or autoimmune diseases or vulnerability to such diseases.

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Definitions of Stress and Sympathetic Neuronal Responses

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The origin of the concept of stress in biology, intuitively borrowed from the physical definition of stress as a deforming force, is unknown, but well over a century ago the term was used with reference to factors that disrupt normal physiological or psychological function. A newer concept of stress was conceived by Hans Selye, who did much to popularize the use of the term as a state in which demands of life have produced a stereotypic syndrome with broad biological effects, including disease. A field of stress research has emerged in which there have been both semantic and substantive scientific controversies regarding Selye's concepts. In this brief review, I will describe the evolution of thought about biological stress, discuss the similarities and differences between physical and biological stresses and strains, and describe a strategy for testing Selye's hypotheses regarding a single response pattern common to all stresses.

DEFINITIONS OF STRESS

Scientific investigations of stress stem from the recognition, by Claude Bernard over 150 years ago, that to sustain life, it is necessary to maintain a relatively constant internal environment. During the first third of this century, Walter Cannon elucidated the mechanisms for maintaining physiological parameters within appropriate tolerable limits and coined the term "homeostasis" to describe the stable state maintained by these mechanisms.[1] He recognized also that above a "critical stress" level, corrective efforts could become overwhelmed to produce a "breaking strain" that results in failure to maintain homeostasis.[2] Cannon suggested that "breaking strain" might be identified as the point at which "the alteration becomes so great as to cause secondary, irrelevant effects" and proposed two methods to determine homeostatic efficiency. In the first, a standard severe stress is applied and the time that passes is measured before a breaking strain is reached, i.e., "secondary, irrelevant effects" appear. This he called the *fixed stress* method. In the second method, the intensity of the stress is gradually increased until the breaking strain is revealed. This he called the method of *variable stress.*

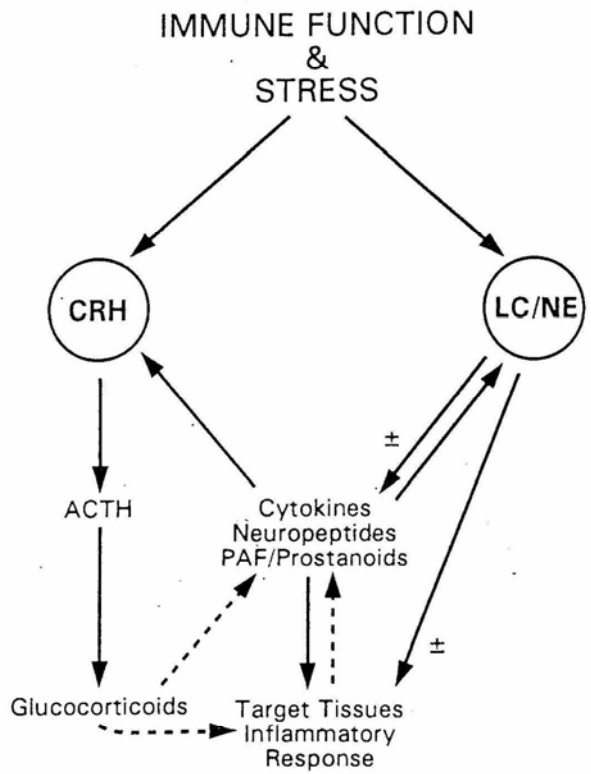

FIGURE 7. A schematic representation of the interactions between the stress system and immune function.

are mediated through the simultaneous inhibition of the vagus nerve and stimulation of the sacral parasympathetic system by CRH and the LC/noradrenergic neurons, respectively. Moreover, CRH may be implicated in mediating the gastric stasis observed during the stress of surgery and/or anesthesia. Interleukin (IL) 1β, a potent cytokine that is found increased during surgery and in the immediate postoperative period, inhibits gastric motility. Intrathecal administration of CRH antagonist prevented the surgery-induced rise of IL-1β in rats,[62] thus, suggesting that CRH may be the mediator for IL-1β-induced gastric stasis.

One area of recent interest relates to the association of chronic stress and GI illness. In a study of selectively referred patients with chronic GI pain, a high incidence of physically and sexually abused women was reported.[63] Sexual abuse

and posttraumatic stress disorder share the same degree of chronic activation of the HPA axis with patients with melancholic depression.[35] Thus, CRH could be the hidden link between the symptoms of chronic pain and history of abuse.[64] Similarly, CRH may be implicated in the stress-induced colonic hypermotility of patients with irritable bowel syndrome. Chronic activation of the HPA axis and/or the LC/noradrenergic system may also explain the observed lower pain tresholds for visceral sensation in patients with functional GI disorders,[65] by depletion of opioid-induced, stress-related analgesia.

STRESS AND IMMUNE FUNCTION

That activation of the HPA axis occurs during the stress of an infectious disease, autoimmune inflammatory process, and accidental or operative trauma has been known for years. The mechanisms of this association, however, have only recently been unravelled. The three "inflammatory cytokines" tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) cause stimulation of the HPA axis *in vivo*, alone, or in synergy with each other.[66] This is mediated through stimulation of hypothalamic CRH and AVP secretion and by direct effects at the pituitary and adrenocortical levels. IL-6, the main endocrine cytokine, causes major elevations of ACTH and cortisol, well above those observed with maximal stimulatory doses of CRH, suggesting that AVP and potentially other secretagogues are also stimulated by this cytokine. Glucocorticoids and prostanoid-synthesis inhibitors suppress the stimulatory effects of cytokines on the HPA axis.[67] Thus, glucocorticoids—the end-hormones of the HPA axis—play a major role in the stress-induced suppression of immune/inflammatory reaction.

The efferent sympathetic/adrenomedullary system also participates in the effects of stress on the immune/inflammatory reaction, both by being reciprocally connected with the CRH system and by transmitting neural signals from the periphery to the immune system. This is mediated through a dense innervation of both primary and secondary lymphoid organs, and by reaching all sites of inflammation via the postganglionic sympathetic neuron.[68] The sympathetic system, when activated, causes systemic secretion of IL-6, which by directly inhibiting the other 2 inflammatory cytokines, TNF-α and IL-1, and activating the HPA axis, participates in the stress-induced suppression of the immune-inflammatory reactions.[66,67] Activation of the sympathetic system during stress, and the effects of immunosuppression that follows, correlate well with such clinical observations as the suppression of immune system during psychological stress, the reactivation of autoimmune diseases during the post-partum period or following cure of Cushing syndrome, and the decreased ability of the stressed organism to fight neoplasms.[69]

The HPA axis and the immune system are functioning in balance in the physiologic state. An excessive HPA axis response to inflammatory stimuli would mimic a hypercortisolemic state and would lead to increased susceptibility of an individual to infections or neoplasias. On the other hand, a defective HPA axis response to inflammatory stimuli would reproduce the glucocorticoid-deficient state and lead to increased susceptibility to autoimmune/inflammatory diseases. Indeed, such properties were seen in a paired animal model, the Fischer and Lewis rats, selected out of