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Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress

Constantine Tsigos[a,c], George P. Chrousos[b,c,*]

[a]*Hellenic National Diabetes Center, Athens, Greece*
[b]*Pediatric and Reproductive Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bldg. 10, Rm. 9D42, Bethesda, MD 20892-1583, USA*
[c]*Athens University Medical School, Athens, Greece*

Abstract

The stress system coordinates the adaptive responses of the organism to stressors of any kind.[1] The main components of the stress system are the corticotropin-releasing hormone (CRH) and locus ceruleus–norepinephrine (LC/NE)-autonomic systems and their peripheral effectors, the pituitary–adrenal axis, and the limbs of the autonomic system. Activation of the stress system leads to behavioral and peripheral changes that improve the ability of the organism to adjust homeostasis and increase its chances for survival. The CRH and LC/NE systems stimulate arousal and attention, as well as the mesocorticolimbic dopaminergic system, which is involved in anticipatory and reward phenomena, and the hypothalamic β-endorphin system, which suppresses pain sensation and, hence, increases analgesia. CRH inhibits appetite and activates thermogenesis via the catecholaminergic system. Also, reciprocal interactions exist between the amygdala and the hippocampus and the stress system, which stimulates these elements and is regulated by them. CRH plays an important role in inhibiting GnRH secretion during stress, while, via somatostatin, it also inhibits GH, TRH and TSH secretion, suppressing, thus, the reproductive, growth and thyroid functions. Interestingly, all three of these functions receive and depend on positive catecholaminergic input. The end-hormones of the hypothalamic–pituitary–adrenal (HPA) axis, glucocorticoids, on the other hand, have multiple roles. They simultaneously inhibit the CRH, LC/NE and β-endorphin systems and stimulate the mesocorticolimbic dopaminergic system and the CRH peptidergic central nucleus of the amygdala. In addition, they directly inhibit pituitary gonadotropin, GH and TSH secretion, render the target tissues of sex steroids and growth factors resistant to these substances and suppress the 5′ deiodinase, which converts the relatively inactive tetraiodothyronine (T_4) to triiodothyronine (T_3), contributing further to the suppression of reproductive, growth and thyroid functions. They also have direct as well as insulin-mediated effects on adipose tissue, ultimately promoting visceral adiposity, insulin resistance, dyslipidemia and hypertension (metabolic syndrome X) and direct effects on the bone, causing ''low turnover'' osteoporosis. Central CRH, via glucocorticoids and catecholamines, inhibits the inflammatory reaction, while directly secreted by peripheral nerves CRH stimulates local inflammation (*immune* CRH). CRH antagonists may be useful in human pathologic states, such as melancholic depression and chronic anxiety, associated with chronic hyperactivity of the stress system, along with predictable behavioral, neuroendocrine, metabolic and immune changes, based on the interrelations outlined above. Conversely, potentiators of CRH secretion/action may be useful to treat atypical depression, postpartum depression and the fibromyalgia/chronic fatigue syndromes, all characterized by low HPA axis and LC/NE activity, fatigue, depressive symptomatology, hyperalgesia and increased immune/inflammatory responses to stimuli.

Keywords: Stress; Glucocorticoids; Corticotropin-releasing hormone or factor (CRH or CRF)

* Corresponding author. Tel.: +1-301-496-5800; fax: +1-301-402-0884.
E-mail address: chrousog@mail.nih.gov (G.P. Chrousos).

[1] ''Stress'' is defined as a state of disharmony or threatened homeostasis. The concepts of stress and homeostasis can be traced back to ancient Greek history, however, the integration of these notions with related physiologic and pathophysiologic mechanisms and their association with specific illnesses are much more recent.

In the present overview, we focus on the cellular and molecular infrastructure of the physiologic and behavioral adaptive responses to stress and we define the pathophysiologic effects of the dysregulation of the stress response, which may result in vulnerability to several disease entities, such as anxiety or depression and chronic inflammatory processes.

Physiology of the stress response

Life exists by maintaining a complex dynamic equilibrium or *homeostasis* that is constantly challenged by intrinsic or extrinsic adverse forces, the *stressors* [1]. Under favorable conditions, individuals can be invested in vegetative and pleasurable functions that enhance their emotional and intellectual growth and development and the survival of their species, such as food intake and sex. In contrast, activation of the stress response during threatening situa-

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tions that are beyond the control of the individual can be associated with dysphoria and eventually emotional or somatic disease [2,3].

When faced with excessive stress, whether physical or emotional, a subject's adaptive responses attain a relatively stereotypic nonspecific nature, referred to by Selye as "the general adaptation syndrome." We now know that the adaptive responses have some specificity toward the stressor that generates them, which, however, is progressively lost as the severity of the stressor increases. During stress, attention is enhanced and the brain focuses on the perceived threat. Cardiac output and respiration are accelerated, catabolism is increased and blood flow is redirected to provide the highest perfusion and fuel to the aroused brain, heart and muscles [1].

The brain circuits that initiate and maintain the stress response are illustrated in Fig. 1. The central control stations of the stress system are located in the hypothalamus and the brain stem and include the parvocellular corticotropin-releasing hormone (CRH) and arginine–vasopressin (AVP) neurons of the paraventricular nuclei (PVN) of the hypothalamus, and the locus ceruleus (LC)–norepinephrine system (central sympathetic system) [2,3]. The hypothalamic–pituitary–adrenal (HPA) axis, together with the efferent sympathetic/adrenomedullary system, represent the effector limbs, via which the brain influences all body organs during exposure to threatening stimuli (Fig. 1) [6,7]. The brain also differentially activates a subset of vagal and sacral parasympathetic efferents that mediate the gut responses to stress [8].

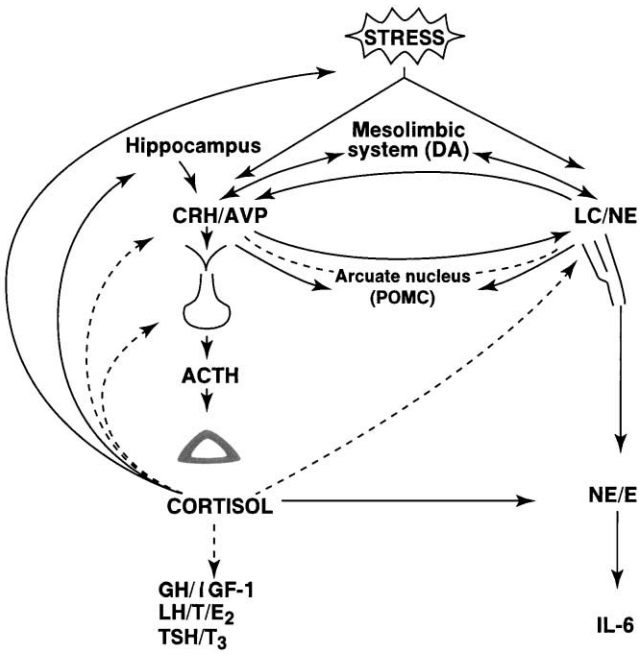

Fig. 1. A simplified schematic representation of the central and peripheral components of the stress system, their functional interrelations and their relations to other central systems involved in the stress response. The CRH/AVP neurons and central catecholaminergic neurons of the LC/NE system reciprocally innervate and activate each other. The HPA axis is controlled by several feedback loops that tend to normalize the time-integrated secretion of cortisol, yet glucocorticoids stimulate the fear centers in the amygdala. Activation of the HPA axis leads to suppression of the GH/IGF-1, LH/testosterone/E2 and TSH/T3 axes; activation of the sympathetic system increases IL-6 secretion. Solid lines indicate stimulation; dashed lines indicate inhibition. (Adapted from Chrousos and Gold [1]).

There are mutual interactions of the central stress stations with three higher brain control areas that influence affect and anticipatory phenomena (mesocortical/mesolimbic systems); the initiation, propagation and termination of stress system activity (amygdala/hippocampus complex); and the setting of the pain sensation (arcuate nucleus) [9–11].

The HPA axis

The hypothalamus controls the secretion of ACTH from the anterior pituitary, which, in turn, stimulates the secretion by the adrenal cortex of glucocorticoid hormones, mainly cortisol in humans. The principal hypothalamic stimulus to the pituitary–adrenal axis is CRH, a 41 amino acid peptide first isolated in 1981 by W. Vale [12]. AVP is a potent synergistic factor with CRH in stimulating ACTH secretion; however, AVP has little ACTH secretagogue activity alone [13]. Furthermore, it appears that there is a reciprocal positive 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, pulsatile fashion, with a frequency of about two to three secretory episodes per hour [14]. Under resting conditions, the amplitude of the CRH and AVP pulses increase in the early morning hours, resulting finally in ACTH and cortisol secretory bursts in the general circulation [15,16]. These diurnal variations are perturbed by changes in lighting, feeding schedules and activity and are disrupted by stress.

During acute stress, the amplitude and synchronization of the CRH and AVP pulsations in the hypophyseal portal system markedly increases, resulting in increases of ACTH and cortisol secretory episodes [3]. Depending on the type of stress, other factors such as AVP of magnocellular neuron origin, angiotensin II and various cytokines and lipid mediators of inflammation are secreted and act on hypothalamic, pituitary or adrenal components of the HPA axis, potentiating its activity [17,18].

Circulating ACTH is the key regulator of glucocorticoid secretion by the adrenal cortex. Other hormones or cytokines, either originating from the adrenal medulla or coming from the systemic circulation, as well as neuronal information from the autonomic innervation of the adrenal cortex may also participate in the regulation of cortisol secretion [19,20].

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 play a key regulatory role on the basal activity of the HPA axis and on

the termination of the stress response by acting at extrahypothalamic centers, the hypothalamus and the pituitary gland [21]. The inhibitory glucocorticoid feedback on the ACTH secretory response acts to limit the duration of the total tissue exposure to glucocorticoids, thus, minimizing the catabolic, antireproductive and immunosuppressive effects of these hormones.

Glucocorticoids exert their effects through their ubiquitous cytoplasmic receptors [22,23]. On ligand binding, the glucocorticoid receptors translocate into the nucleus, where they interact as homodimers with specific glucocorticoid responsive elements (GREs) within the DNA to activate appropriate hormone-responsive genes [23]. The activated receptors also inhibit, through protein–protein interactions, other transcription factors, such as c-*jun*/c-*fos* and NF-kB, which are positive regulators of the transcription of several genes involved in the activation and growth of immune and other cells [24]. Furthermore, glucocorticoids change the stability of messenger RNAs and hence the translation of several glucocorticoid-responsive proteins, as well as the electrical potential of neuronal cells.

The autonomic axes

The autonomic nervous system provides a rapidly responding mechanism to control a wide range of functions [3]. Cardiovascular, respiratory, gastrointestinal, renal, endocrine and other systems are regulated by the sympathetic nervous system or the parasympathetic system, or both [25]. Interestingly, the parasympathetic system may assist sympathetic functions by withdrawing and can antagonize them by increasing its activity.

Sympathetic innervation of peripheral organs is derived from the efferent preganglionic fibers, whose cell bodies lie in the intermediolateral column of the spinal cord. These nerves synapse in the bilateral chains of sympathetic ganglia with postganglionic sympathetic neurons that richly innervate the smooth muscle of the vasculature, the heart, skeletal muscles, kidney, gut, fat and many other organs. The preganglionic neurons are cholinergic, whereas the postganglionic neurons are mostly noradrenergic. The sympathetic system also has a humoral contribution, providing most of the circulating epinephrine and some of the norepinephrine from the adrenal medulla. In addition to the classic neurotransmitters acetylcholine and norepinephrine, both sympathetic and parasympathetic subdivisions of the autonomic nervous system contain several subpopulations of target-selective and neurochemically coded neurons that express a variety of neuropeptides and, in some cases, ATP, nitric oxide or lipid mediators of inflammation [26]. Interestingly, CRH, neuropeptide Y (NPY) and somatostatin are colocalized in noradrenergic vasoconstrictive neurons. Transmission in sympathetic ganglia is also modulated by neuropeptides released from preganglionic fibers and short interneurons (e.g., enkephalin and neurotensin), as well as from primary afferent collaterals (e.g., substance P) [27].

Regulation of the stress response

The orchestrated interplay of several neurotransmitter systems in the brain underlies the characteristic phenomenology of behavioral, endocrine, autonomic and immune responses to stress [28]. These transmitters include CRH, AVP, opioid peptides, dopamine and norepinephrine.

CRH/AVP

Shortly after its isolation, it became apparent that CRH was implicated in other components of the stress response, such as arousal and autonomic activity. Supportive evidence was derived from intracerebroventricular or selective brain administration of CRH in rodents and nonhuman primates, which precipitated several coordinated responses characteristic of stress [29]. Moreover, brain administration of CRH peptide antagonists suppresses many aspects of the stress response. Finally, CRH type 1 receptor knockout mice were shown to have a markedly deficient ability to mount an effective stress response [30].

CRH and CRH receptors were found in many sites in the brain outside of the hypothalamus, including parts of the limbic system and the central arousal sympathetic systems (LC/NE) in the brain stem and spinal cord [31]. Stress is a potent general activator of CRH release from the hypothalamus and extrahypothalamic sites [5]. The mechanisms via which stress stimulates CRH neurons are unclear. Whether CRH or another transmitter (e.g., NE) is upstream in eliciting the neurocircuitry of stress remains to be determined.

CRH-binding sites are also found in various peripheral tissues, such as the adrenal medulla, heart, prostate, gut, liver, kidney and testes. CRH receptors belong to the G-protein-coupled receptor superfamily, and CRH binding stimulates the intracellular accumulation of cAMP. Two distinct CRH receptor subtypes designated CRH-R1 and CRH-R2 have been characterized, encoded by distinct genes that are differentially expressed [31]. CRH-R1 is the most abundant subtype found in the anterior pituitary and is also widely distributed in the brain [32]. CRH-R2 receptors are expressed mainly in the peripheral vasculature and the heart, as well as in subcortical structures in the brain.

LC/NE system

The locus ceruleus and other noradrenergic cell groups of the medulla and pons are collectively known as the LC/NE system. Brain epinephrine serves globally as an alarm system that decreases neurovegetative functions, such as eating and sleeping, and that contributes to accompanying increases in autonomic and neuroendocrine responses to stress, including HPA axis activation [28]. NE also activates the amygdala, the principal brain locus for fear-related behaviors, and enhances the long-term storage of aversively charged emotional memories in sites such as the hippocampus and striatum.

Reciprocal neural connections exist between the CRH and (LC/NE system neurons) of the central stress system, with CRH and norepinephrine stimulating each other, the latter primarily through α_1-noradrenergic receptors [3,28]. There is an ultra-short autoregulatory negative feedback loop on the CRH neurons exerted by CRH itself, just as there is a similar loop in the LC/NE neurons, by way of presynaptic CRH and α_2-noradrenergic receptors, respectively. There is also parallel regulation of both central components of the stress system by other stimulatory and inhibitory neuronal pathways. Several neurotransmitters, including serotonin and acetylcholine, excite CRH and the LC/NE neurons [32]. The negative feedback controls, include glucocorticoids, γ-amino-butyric acid (GABA), corticotropin and several opioid peptides, which inhibit both CRH and LC/NE neurons [33].

Body systems responses to stress

HPA axis–immune system interactions

It has been known for several decades that stress, whether inflammatory, traumatic or psychological, is associated with concurrent activation of the HPA axis. In the early 1990s, it also became apparent that cytokines and other humoral mediators of inflammation are potent activators of the central stress response, constituting the afferent limb of a feedback loop through which the immune/inflammatory system and the CNS communicate [34].

All three inflammatory cytokines, tumor necrosis factor-α (TNF-α), interleukin-1β and interleukin-6 (IL-6) can cause stimulation of the HPA axis alone, or in synergy with each other [34,35]. There is evidence to suggest that IL-6, the main endocrine cytokine, plays the major role in the immune stimulation of the axis, *especially in chronic inflammatory stress*.

Some of the activating effects of cytokines on the HPA axis may be exerted indirectly by stimulation of the central catecholaminergic pathways. Also, activation of peripheral nociceptive, somatosensory and visceral afferent fibers would lead to stimulation of both the catecholaminergic and CRH neuronal systems via ascending spinal pathways. Other inflammatory mediators, such as eicosanoids, platelet-activating factor (PAF) and serotonin may also participate in the activation of the HPA axis [34], via auto/paracrine and/or endocrine effects.

Conversely, activation of the HPA axis has profound inhibitory effects on the inflammatory/immune response because virtually all the components of the immune response are inhibited by cortisol. Alterations of leukocyte traffic and function, decreases in production of cytokines and mediators of inflammation, and inhibition of the latter's effects on target tissues are among the main immunosuppressive effects of glucocorticoids [34,36].

The efferent sympathetic/adrenomedullary system apparently participates in a major fashion in the interactions of the HPA axis and the immune/inflammatory reaction by being reciprocally connected with the CRH system, by receiving and transmitting humoral and nervous immune signals from the periphery, by densely innervating both primary and secondary lymphoid organs, and by reaching all sites of inflammation via the postganglionic sympathetic neurons [36]. When activated during stress, the autonomic system exerts its own direct effects on immune organs, which can be immunosuppressive, or both immunopotentiating and antiinflammatory. CRH secreted by postganglionic sympathetic neurons at inflammatory sites has proinflammatory properties (*immune CRH*); one of its key actions is to degranulate mast cells [36,37].

HPA axis—other endocrine axes interactions

Gonadal and growth axes

The systems responsible for reproduction and growth are directly linked to the stress system and both are profoundly inhibited by various components of the HPA axis, the effector of the stress response [28,37]. Either directly or through arcuate POMC neuron β-endorphin, CRH suppresses the GnRH neurons of the arcuate nucleus of the hypothalamus. Glucocorticoids exert inhibitory effects at the levels 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 axis activation has been demonstrated in highly trained athletes of both sexes, in ballet dancers, and in individuals sustaining anorexia nervosa or starvation.

During inflammatory stress, cytokines suppress reproductive function directly and indirectly by activating hypothalamic secretion of CRH and POMC-derived peptides, as well as by peripheral elevations of glucocorticoids and inhibition of steroidogenesis at both ovaries and testes [38].

The interaction between CRH and the gonadal axis appears to be bidirectional. Thus, the presence of estrogen responsive elements has been demonstrated in the promoter area of the CRH gene, as well as direct stimulatory estrogen effects on CRH gene expression [39]. This finding implicates the CRH gene as a potentially important target of ovarian steroids and a potential mediator of gender-related differences in the stress response and HPA axis activity.

The growth axis is also inhibited at many levels during stress. Prolonged activation of the HPA axis with elevations in glucocorticoids leads to suppression of growth hormone secretion and inhibition of somatomedin C and other growth hormone effects on their target tissues [40]. However, acute elevations of growth hormone concentration in plasma may occur at the onset of the stress response or after acute administration of glucocorticoids, presumably through stimulation of the GH gene by glucocorticoids through glucocorticoid-responsive elements in its promoter region

[41]. In addition to the direct effects of glucocorticoids, CRH-induced stimulation in hypothalamic somatostatin secretion may also result in GH suppression, providing another potential mechanism for stress-related suppression of GH secretion.

Similarly, activation of the HPA axis is associated with decreased production of thyroid-stimulating hormone and inhibition of the conversion of the relatively inactive thyroxin to the more biologically active triiodothyronine in peripheral tissues (the "euthyroid sick" syndrome) [42]. Both phenomena may be caused by the increased levels of glucocorticoids and may serve to conserve energy during stress. In the case of inflammatory stress, inhibition of TSH secretion may be in part through the action of cytokines both on the hypothalamus and the pituitary [35].

Metabolism

Glucocorticoids directly inhibit pituitary growth hormone, gonadotropin and thyrotropin secretion and make the target tissues of sex steroids and growth factors resistant to these hormones. Thus, glucocorticoids antagonize the beneficial actions of GH and sex steroids on fat tissue (lipolysis) and muscle and bone anabolism [43]. Chronic activation of the stress system would be expected to increase visceral adiposity, decrease lean body (muscle and bone) mass and suppress osteoblastic activity (Fig. 2). Interestingly, the phenotype of central obesity and decreased lean body mass is shared by patients with Cushing's syndrome and some patients with the combined diagnosis of melancholic depression or chronic anxiety disorder and the metabolic syndrome (visceral adiposity, insulin resistance, dyslipidemia, hypertension) or "pseudo-Cushing's syndrome" [43].

Because increased hepatic gluconeogenesis is a characteristic feature of the stress response and because glucocorticoids induce insulin resistance, activation of the HPA axis may contribute to the poor control of diabetic patients during periods of emotional stress, or concurrently with inflammatory and other diseases [44].

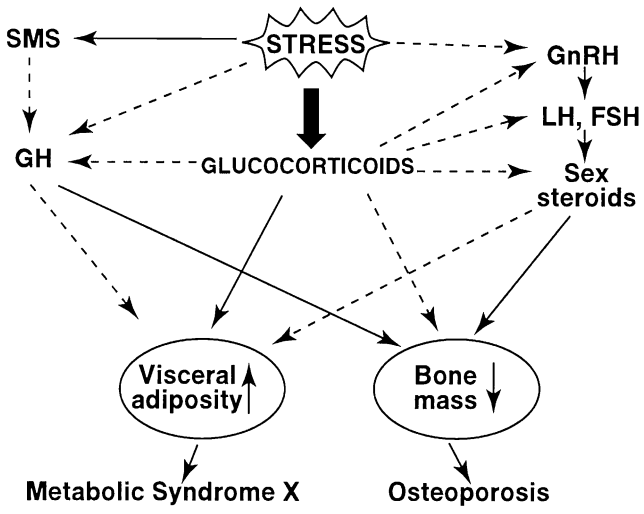

Fig. 2. Detrimental effects of chronic stress on adipose tissue metabolism and bone mass. Solid lines indicate stimulation; dashed lines indicate inhibition. (Adapted from Chrousos [28]).

Obese subjects with psychiatric manifestations ranging from those of melancholic depression to anxiety with perception of "uncontrollable" stress, frequently have mild hypercortisolism, while carefully screened obese subjects without such manifestations are eucortisolemic [3]. The former may have stress-induced glucocorticoid-mediated visceral obesity and metabolic syndrome manifestations, which in the extreme may be called a pseudo-Cushing state that needs to be differentiated from frank Cushing syndrome. Stress-induced hypercortisolism and visceral obesity and their cardiovascular and other sequelae increase the all-cause mortality risk of affected subjects by two- to three-fold and curtail their life expectancy by several years [43].

HPA axis: pathophysiology

Generally, the stress response with the resultant activation of the HPA axis is meant to be acute or at least of a limited duration. The time-limited nature of this process renders its accompanying antireproductive, antigrowth, catabolic and immunosuppressive effects temporarily beneficial rather than damaging. In contrast, chronicity of stress system activation would lead to the syndromal state that Selye described in 1936 [4]. Because CRH coordinates behavioral, neuroendocrine and autonomic adaptation during stressful situations, increased and prolonged production of CRH could explain the pathogenesis of the syndrome [28,45].

The prototypic example of chronic hyperactivation of the stress system (both HPA axis and LC/NE system) is manifested in melancholic depression, with dysphoric hyperarousal and relative immunosupression [6,7]. Indeed, cortisol secretion is increased and plasma ACTH response to exogenous CRH decreased. Hypersecretion of CRH has been shown in depression and suggests that CRH may participate in the initiation or perpetuation of a vicious cycle. Owing to a chronically hyperactive stress system, patients with melancholic depression may sustain several severe somatic sequelae, such as osteoporosis, features of the metabolic syndrome, varying degrees of atherosclerosis, innate and T-helper 1-directed immunosuppression and certain infectious and neoplastic diseases [28,43,45]. When not treated, these patients have a compromised life expectancy curtailed by 15–20 years after excluding suicides.

In addition to melancholic depression, a spectrum of other conditions may be associated with increased and prolonged activation of the HPA axis (Table 1), including anorexia nervosa with or without malnutrition, obsessive–compulsive disorder, panic anxiety, chronic active alcoholism, alcohol and narcotic withdrawal, excessive exercising, poorly controlled diabetes mellitus, childhood sexual abuse and hyperthyroidism [1,28,45].

Table 1
States associated with hyperactivation or hypoactivation of the HPA axis

Increased HPA axis activity	Decreased HPA axis activity	Disrupted HPA axis activity
Severe chronic disease		
Melancholic depression	Atypical depression	Cushing syndrome
Anorexia nervosa	Seasonal depression	Glucocorticoid deficiency
Obsessive–compulsive disorder	Chronic fatigue syndrome	Glucocorticoid resistance
	Fibromyalgia	
Panic disorder	Hypothyroidism	
Chronic excessive exercise	Adrenal suppression	
Malnutrition	Post glucocorticoid therapy	
Diabetes mellitus	Post stress	
	Nicotine withdrawal	
	Postpartum	
Hyperthyroidism	Menopause	
Central obesity	Rheumatoid arthritis	
Childhood sexual abuse		
Pregnancy		

Adapted from Chrousos and Gold [1].

Another group of states is characterized by hypoactivation of the stress system, rather than sustained activation, in which chronically reduced secretion of CRH may result in pathological hypoarousal (Table 1) [25]. Patients with atypical, seasonal depression and the chronic fatigue syndrome fall in this category [46]. Similarly, patients with fibromyalgia have decreased urinary free cortisol excretion and frequently complain of fatigue. Hypothyroid patients also have clear evidence of CRH hyposecretion [28].

Withdrawal from smoking has been associated with decreased cortisol and catecholamine secretion [1]. Decreased CRH secretion in the early period of nicotine abstinence could explain the increased appetite and weight gain frequently observed in these patients. In Cushing syndrome, the clinical picture of atypical depression, hyperphagia and weight gain, and fatigue and anergia is consistent with suppression of the CRH neuron by the associated hypercortisolism. The periods after cure of hypercortisolism or following cessation of chronic stress and the postpartum period are also associated with atypical depression, suppressed CRH secretion and decreased HPA axis activity [28].

It is believed that 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 a host of infectious agents or tumors as a result of T-helper-1 suppression, but enhanced resistance to autoimmune/inflammatory disease [34,36]. In contrast, a defective HPA axis response to such stimuli would reproduce the glucocorticoid-deficient state and would lead to relative resistance to infections and neoplastic disease, but increased susceptibility to autoimmune/inflammatory disease, such as Hashimoto's thyroiditis or rheumatoid arthritis [34]. Thus, an increasing body of evidence suggests that patients with rheumatoid arthritis have a mild form of central hypocortisolism [47]. Dysfunction of the HPA axis may actually play a role in the development or perpetuation of autoimmune disease, rather than being an epiphenomenon. The same rational may explain the high incidence of autoimmune disease in the period after cure of hypercortisolism, as well as in glucocorticoid underreplaced adrenal insufficiency.

Future directions

There has been a long search for small molecular weight CRH antagonists that could be absorbed orally and cross the blood brain barrier to treat disorders characterized by a hyperactive CRH neuron as in melancholic depression. Antalarmin, a prototype CRH receptor type 1 antagonist, shows that this concept bears merit [5,28]. This small pyrrolopyrimidine compound, binds with high affinity to the CRH receptor type 1, decreases the activity of the HPA axis and LC/NE, blocks the development and expression of conditioned fear and stress-induced colonic hyperfunction, suppresses neurogenic inflammation and blocks CRH-induced skin mast cell degranulation [28]. Chronic administration of antalarmin is not associated with glucocorticoid deficiency and permits HPA axis and LC/NE responses to severe stress.

These data suggest that such CRH antagonists may be useful in human pathological states, such as melancholic depression and chronic anxiety, associated with chronic hyperactivity of the stress system, along with predictable behavioral, neuroendocrine, metabolic and immune changes, based on the interrelations outlined above. Conversely, we will need potentiators of CRH secretion/action to treat atypical depression, postpartum depression and the fibromyalgia/chronic fatigue syndromes, all characterized by low HPA axis and LC/NE activity, fatigue, depressive symptomatology, hyperalgesia and increased immune/inflammatory responses to stimuli.

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