3 Hypothalamic-Pituitary-Adrenal Axis

Ioannis Kyrou, Constantine Tsigos

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3.1 Introduction

The hypothalamic-pituitary-adrenal (HPA) axis outlines the tight hormonal coupling of the hypothalamus, the anterior pituitary and the adrenal cortex (Fig. 1). A linear progression characterizes the downstream activation of the axis while reciprocal feedback loops exist at each level to fine-tune the potency of the response and ensure optimal hormone secretions. The HPA axis is a vital component of the stress system and mediates a variety of adaptive responses to stressors that threaten body homeostasis. Basal and stress-related homeostasis depend on the integrity of the HPA axis, which additionally exerts profound regulatory effects on other systems (immune, endocrine and metabolic) in order to orchestrate a response that will allow endurance against any imposed challenge and preserve the internal milieu. Dysfunction at any level of the HPA axis can cause either prolonged or inadequate activation and leads to syndromal states that consistently share various degrees of impaired response to stress.

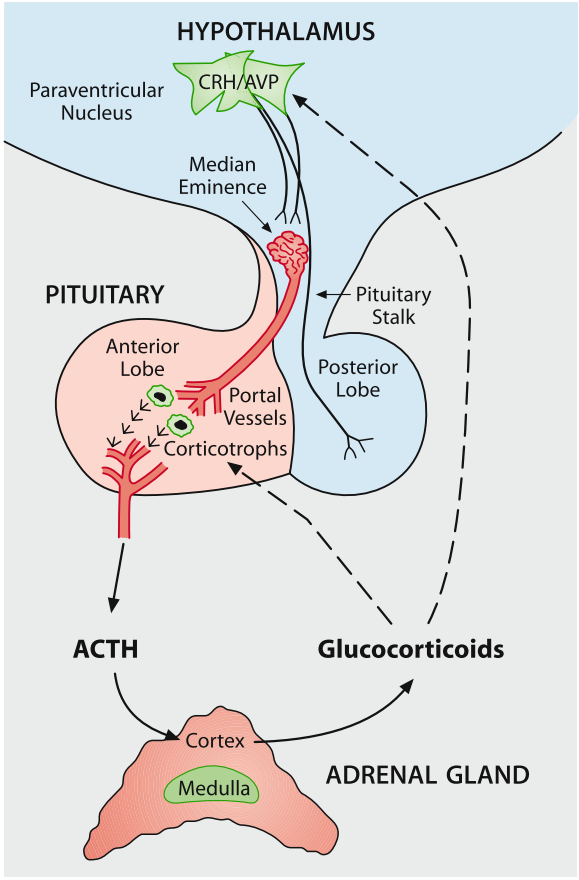

Fig. 1. A schematic representation of the components of the hypothalamic-pituitary-adrenal axis and their hormonal interactions. Stimulatory effects are represented by *solid lines* and inhibitory effects by *dashed lines* (*CRH*, corticotropin-releasing hormone; *AVP*, arginine vasopressin)

3.2 HPA Axis: A Multilevel Endocrine System

3.2.1 Hypothalamus: Corticotropin-Releasing Hormone and Arginine Vasopressin

The hypothesis that pituitary corticotropin (ACTH) secretion is controlled by a hypothalamic factor was first suggested in the late 1940s. A decade later, in vitro studies supported the existence of such a hypothalamic corticotropin-releasing factor by demonstrating that hypothalamic extracts could stimulate pituitary corticotroph cells to secrete ACTH. In 1981, Vale and his colleagues announced the sequence of a 41-amino-acid peptide from ovine hypothalami, designated corticotropin-releasing hormone (CRH), which showed greater ACTH-releasing potency in vitro and in vivo than any other previously identified endogenous or synthetic peptide.

Following the isolation of CRH, data from anatomic, pharmacologic, and behavioral studies made evident that CRH not only triggers the hormonal cascade of the HPA axis but also plays a complex role in the response to stressors. The wide distribution of CRH receptors in many extrahypothalamic sites of the brain, including parts of the limbic system and the central arousal-sympathetic systems in the brain stem and spinal cord, suggests the implication of CRH in a broader spectrum of neural circuits that control the stress response. In addition, experimental studies proved that central administration of CRH sets into motion a coordinated series of physiologic and behavioral responses, which apart from the activation of the pituitary-adrenal axis and the sympathetic nervous system, also include enhanced arousal, suppression of appetite and sexual behaviors, hypothalamic hypogonadism, and changes in motor activity, all characteristic of stress behaviors [95, 105, 110]. Conversely, central administration of CRH peptide antagonists suppresses many aspects of the stress response. Finally, CRH type 1 receptor knockout mice are characterized by a striking failure to properly answer to induced stress [108].

An intricate neuronal network regulates the secretion of hypothalamic CRH from parvicellular neurons of the paraventricular nucleus (PVN) (Fig. 2). These neurons have axons that terminate in the median eminence and secrete CRH into the hypophyseal portal system and axons that terminate in the locus ceruleus (LC)/norepinephrine (NE) sympathetic system neurons in the brainstem [28, 101]. Neurons of the latter systems send projections, mostly noradrenergic, to the PVN [30]. Thus, a reverberatory neural circuit is formed between the CRH neurons and those of the LC/NE sympathetic systems, with CRH and norepinephrine stimulating each other (Fig. 2) [16, 125]. Furthermore, CRH activates an ultra-short negative feedback loop on the CRH neurons [18], while a similar loop exists in the LC/NE-sympathetic system neurons, with norepinephrine inhibiting its own secretion via collateral branches and inhibitory α_2-noradrenergic receptors [1, 41]. In addition, neurotransmitters from parallel neuronal systems, like serotonin, acetylcholine, catecholamines (α_1-receptors) and neuropeptide Y, stimulate CRH secretion [18, 44], whereas the GABA/benzodiazepine system and endogenous opioids exert inhibitory effects [17, 82]. Regulatory opioid peptides are also produced by arcuate nucleus proopiomelanocortin (POMC) neurons that produce ACTH, α-MSH, and β-endorphin, all of which are inhibitory to CRH secretion [17, 82], and by CRH and arginine vasopressin (AVP) neurons which co-secrete dynorphin along with CRH and AVP [97]. A significant long negative feedback loop is also mediated by the glucocorticoids released from the adrenal cortex in response to ACTH in order to inhibit the prolongation of pituitary ACTH secretion and the activation of the hypothalamic CRH neurons and the LC/NE sympathetic systems [18, 71]. It is obvious that CRH secretion is tightly interweaved in the neurocircuitry of stress, which utilizes a complex network of interacting pathways in order to initiate and orchestrate an effective response to stressors.

In the hormonal cascade of the HPA axis activation, CRH exerts its effect on pituitary ACTH secretion via high-affinity transmembrane CRH receptors on the corticotrophs that couple to guanine nucleotide-binding proteins and stimulate the release of ACTH by a cAMP-dependent mechanism [2]. In addition to enhancing ACTH secretion, CRH also stimulates the de novo biosynthesis of POMC, the ACTH precursor, in corticotrophs resulting in a biphasic release of ACTH [71]. Two distinct CRH receptor subtypes (CRH-R1 and CRH-R2) have been characterized, encoded by distinct genes that are differentially expressed [21, 121]. CRH-R1 is the most abundant subtype found in anterior pituitary and is also widely distributed in the brain. The CRH-R2 subtype is expressed mainly in the peripheral vasculature and the heart, as well as in subcortical structures of the brain [132]. It is notable that CRH availability is also regulated by specific binding of the peptide to CRH binding protein [83], with which it partially colocalizes in various tissues [84].

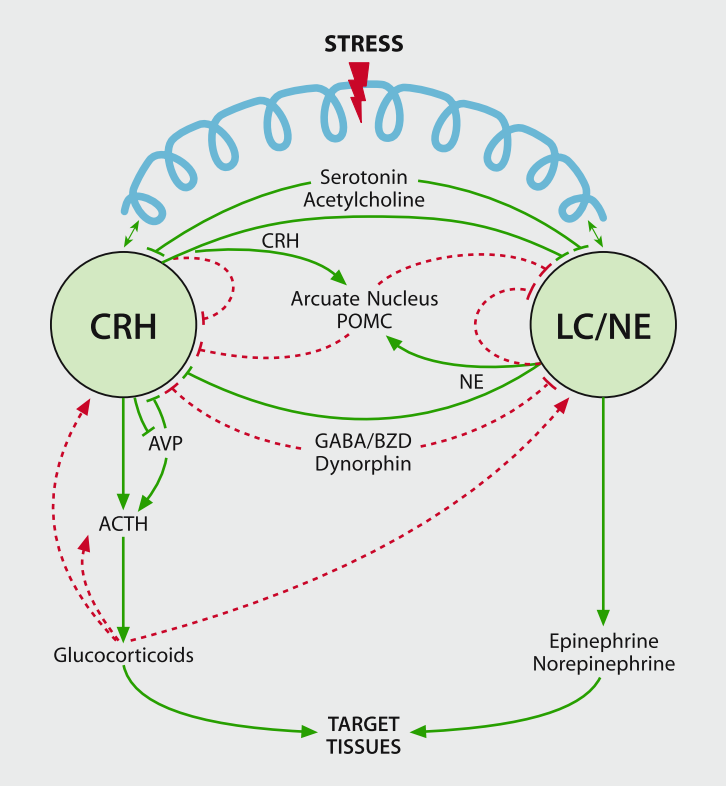

Fig. 2. A simplified, schematic representation of the intricate neuronal network that regulates the secretion of hypothalamic corticotropin-releasing hormone (*CRH*) from parvicellular neurons of the paraventricular nucleus (*PVN*). The HPA axis is tightly integrated with the main central nervous systems involved in the stress response. Activation is represented by *solid lines* and inhibition by *dashed lines* (*CRH*, corticotropin-releasing hormone; *ACTH*, corticotropin; *POMC*, pro-opiomelanocortin; *LC/NE*, locus ceruleus/norepinephrine-sympathetic system; *AVP*, arginine vasopressin; *GABA*, γ-aminobutyric acid; *BZD*, benzodiazepine)

At the level of the anterior pituitary, CRH is the most potent but not the sole regulator of the corticotroph ACTH secretion. AVP, a nonapeptide also produced by parvicellular neurons of the PVN and secreted into the hypophyseal portal system, is considered the second most important modulator of pituitary ACTH secretion [9]. Whereas CRH appears to directly stimulate the ACTH secretion, AVP and other factors, such as angiotensin II, have synergistic or additive effects [45, 94, 124]. AVP shows synergy with CRH in vivo, when the peptides are coadministered in humans [67]. Furthermore, physiologic elevations of plasma AVP in response to hyperosmolality, apparently produced by magnocellular neurons of the PVN, have additive rather than synergistic effects with CRH on stimulating ACTH secretion [91]. AVP interacts with a V1-type receptor (V1β, also referred as V3) and exerts its effects through calcium/phospholipid-dependent mechanisms [8]. In nonstressful situations, both CRH and AVP are secreted in the portal system in a pulsatile fashion, with approximately 80% concordance of the pulses [7, 40]. It has been shown that during stress, the amplitude of the pulsations increases, whereas, if the magnocellular AVP-secreting neurons are involved, continuous elevations of plasma AVP concentrations are seen. The aforementioned data support a reciprocal positive interaction between hypothalamic CRH and AVP at the corticotrophs. It is noteworthy that oxytocin, a nonapeptide produced by parvicellular neurons of the PVN like AVP, has no significant ACTH-releasing action in humans in vivo, while in the rat it appears to be an important coregulator of ACTH secretion [92]. Finally, it should be mentioned that catecholamines stimulate CRH secretion but have no direct effects on human pituitary ACTH secretion, while ghrelin, a novel GH secretagogue factor, appears to stimulate predominantly the AVP secretion [6, 64].

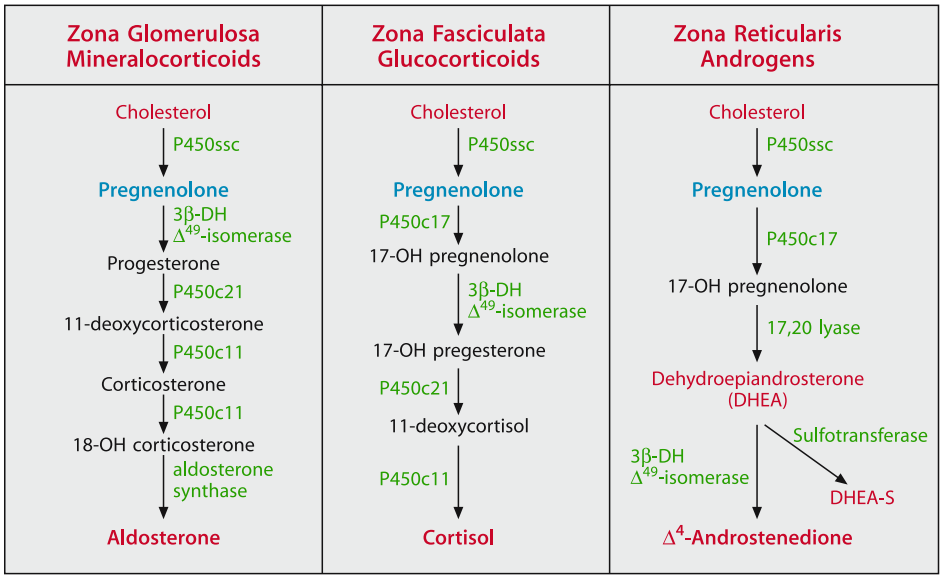

Fig. 3. The pathway of steroidogenesis in the three zones of the adrenal cortex

3.2.2 Anterior Pituitary: Adrenocorticotropin

The signal of the initial HPA axis activation is transferred to the systemic circulation by adrenocorticotropin (ACTH). ACTH is a 39-amino-acid peptide secreted from the basophilic corticotrophic cells of the anterior pituitary which are distributed in the median wedge, anteriorly and laterally, and posteriorly adjacent to the pars nervosa. ACTH is a proteolytic product of a 266-amino-acid precursor, pro-opiomelanocortin (POMC) [38]. In the human anterior pituitary, POMC is processed into ACTH and two large polypeptides, N-terminal peptide and β-lipotropin, cosecreted in the circulation in approximately equimolar amounts [65, 79]. Subsequently, normal or abnormal regulation of ACTH secretion could be inferred by changes in the secretion of co-secreted products. Small, variable amounts of β-endorphin may also be produced and secreted by the human pituitary, but further processing of ACTH to smaller fragments, such as α-MSH and corticotropin-like intermediate lobe peptide (CLIP), does not occur in humans [65, 106]. It is of interest that the POMC precursor peptide is secreted in detectable amounts [115].

The regulatory influence of CRH on pituitary ACTH secretion varies diurnally and changes during stress [66]. The plasma ACTH concentration peaks at 6 A.M. to 8 A.M., and the lowest concentrations are found at about midnight. Episodic bursts of secretion appear throughout the day [58, 128]. The central mechanisms responsible for the circadian release of CRH/AVP/ACTH in their characteristic pulsatile manner are not completely defined, but appear to be controlled by one or more central pacemakers [37]. Plasma cortisol concentrations generally follow those of ACTH, but owing to differences in bioavailability and pharmacokinetics between the two hormones, the correlation between their plasma concentrations is not perfect [54, 130]. The diurnal variation of ACTH and cortisol secretion is disrupted when a stressor is imposed or by changes in zeitgebers, e.g. lighting and activity.

The adrenal cortex is the principal target organ for ACTH, which acts as the major regulator of cortisol and adrenal androgen production by the *zonae fasciculata* (central zone) and *reticularis* (inner zone), respectively. ACTH is also essential for aldosterone biosynthesis from the *zona glomerulosa* (outer zone), although aldosterone secretion is primarily under the control of the renin-angiotensin axis [4, 111]. The biologic activity of ACTH resides in the N-terminal portion, with the first 24 amino acids necessary for maximal activity. ACTH interacts with specific high affinity cell membrane receptors (melanocortin receptor 2, MC2), expressed in all three cortical zones that couple to G-proteins to stimulate adenylyl cyclase and generate cAMP [76]. The latter activates a cAMP-dependent protein kinase, which stimulates cholesterol ester hydrolase, the key enzyme in the adrenocortical response of steroidogenesis to ACTH [51]. In addition, ACTH increases the uptake of cholesterol from plasma lipoproteins, enhances later steps in the steroidogenesis and has a trophic effect on the adrenal

cortices (Fig. 3) [58]. It should be noted that ACTH when hypersecreted stimulates the melanocytes via the skin α-MSH receptor (MC1) [76], causing skin hyperpigmentation.

3.2.3 Adrenal Cortex: Glucocorticoids

At the level of the adrenal cortex, glucocorticoids synthesized in the *zona fasciculata* are the final effectors of the HPA axis and direct the stress response toward the goal of maintaining homeostasis. Cortisol, the main endogenous glucocorticoid in humans, is secreted by the adrenals into the circulation to reach the peripheral target tissues, where it exerts its effects via specific cytoplasmic receptors. In the unbound/inactive state, the glucocorticoid receptors are found as hetero-oligomers with heat shock protein (hsp) 90 and other proteins, which include hsp 70 and immunophillin [100, 107]. The ligand-bound receptors dissociate from the hetero-oligomer, homodimerize, and translocate into the nucleus, where they interact with glucocorticoid responsive elements (GREs) of the DNA to transactivate appropriate hormone-responsive genes [85]. The activated glucocorticoid receptors also interact at the protein level with the c-jun component of the activator protein-1 (AP-1) transcription factor, preventing this factor from exerting its effect on AP-1-responsive genes [57, 133].

Glucocorticoids play a key regulatory role on the basal control of HPA axis activity and on the termination of the stress response by acting at suprahypothalamic centers, the hypothalamus, and the pituitary gland [31, 42, 63]. The presence of a direct glucocorticoid negative feedback is crucial for the attenuation of the ACTH secretory response, in order to conserve the capacity of the HPA axis to respond to subsequent stressors. In addition, this negative feedback loop limits the duration of the total tissue exposure to glucocorticoids, thus minimizing the catabolic, antireproductive, and immunosuppressive effects of these hormones. Interestingly, a dual receptor system exists for glucocorticoids in the central nervous system, including the glucocorticoid receptor type I, or mineralocorticoid receptor, which responds to low levels of glucocorticoids and is primarily activational, and the classic glucocorticoid receptor (type II), which responds to higher levels of glucocorticoids and is dampening in some systems and activational in others [31].

3.3 HPA Axis: Other System Interactions

3.3.1 HPA Axis: Immune System

Over the last few decades compiling evidence has revealed a variety of interactions between the HPA axis and the immune system, suggesting an alliance of these systems against immune challenges. In states of inflammatory or immune stress, the overall adaptive mobilization of the organism can be described as a combination of the immune system activation and the typical stress response. Cytokines and other humoral mediators of inflammation have been proven as potent activators of the central stress response and can be regarded as the afferent limb of a feedback loop that mediates the immune system and HPA axis crosstalk (Fig. 4).

The three main inflammatory cytokines, tumor necrosis factor-alpha (TNF-α), interleukin-1, and interleukin-6, are secreted in inflammatory sites in a cascade-like fashion, with TNF-α appearing first followed by IL-1 and IL-6 in tandem [5]. Although TNF-α and IL-1α are primarily auto/paracrine regulators of inflammation, both can be found in the general circulation along with IL-1β and IL-6, the main

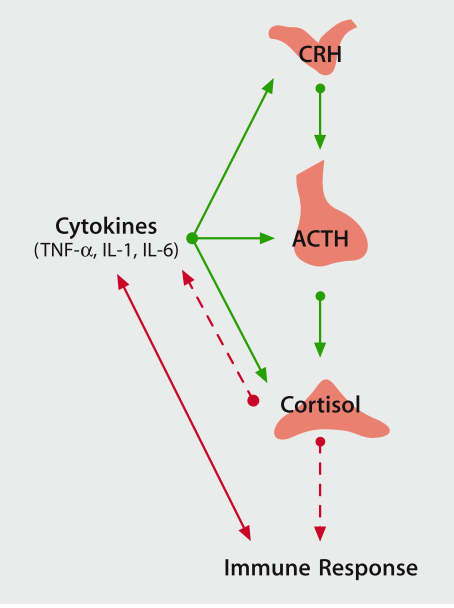

Fig. 4. A simplified, schematic representation of the interactions between the hypothalamic-pituitary-adrenal axis and the immune system. Stimulatory effects are represented by *solid lines* and inhibitory effects by *dashed lines* (*CRH*, corticotropin-releasing hormone; *ACTH*, corticotropin; *IL-1*, interleukin-1; *IL-6*, interleukin-6; *TNF-α*, tumor necrosis factor-α)

endocrine inflammatory cytokines [88]. All three inflammatory cytokines are able to directly and indirectly enhance the synthesis and secretion of CRH and AVP at the level of the hypothalamus and their effects are synergistic [13, 78, 102]. In addition, several eicosanoids and other inflammatory mediators such as platelet-activating factor (PAF), bradykinin, and serotonin show strong CRH-releasing properties [12, 44, 26]. Most striking has been the ability of interleukin-6 to acutely and chronically activate the HPA axis in humans [117]. The acute ACTH response to a single subcutaneous dose of IL-6 has been the highest ever seen in response to any stimulus, while antibodies to IL-6 almost completely block the stimulatory effect of bacterial lipopolysaccharide on the HPA axis [75, 14]. IL-6 seems to be the critical cytokine regulator in the immune stimulation of the HPA axis in chronic inflammatory stress. It is not clear, however, which of the above effects are endocrine and which are paracrine. Presence of cytokinergic neural pathways and local involvement of eicosanoids and PAF in CRH secretion are certain. Direct effects, albeit delayed, of most of these cytokines and mediators of inflammation on pituitary ACTH secretion also have been shown [43], and direct effects of these substances on adrenal glucocorticoid secretion also appear to be present [99, 131]. Finally, indirect activation of the HPA axis is also mediated through cytokine induced stimulation of the central noradrenergic stress system.

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 (Fig. 4). Glucocorticoids act as potent anti-inflammatory and immunosuppressive factors by influencing the traffic of circulating leukocytes and inhibiting vital functions of the immune cells. Furthermore, they decrease the production of cytokines and other mediators of inflammation (e.g. platelet-activating factor, nitric oxide, prostanoids), induce cytokine resistance and inhibit the expression of adhesion molecules and their receptors on the surface of immune cells [77, 26]. It is interesting that glucocorticoids and catecholamines secreted during stress exert an immunomodulative effect by suppressing the T-helper 1 (Th1) response and causing a Th2 shift, thus protecting the tissues from the potentially destructive actions of type 1 proinflammatory cytokines and other products of activated macrophages [39].

An interesting aspect of the immune response is that CRH is also secreted peripherally at inflammatory sites (peripheral or immune CRH) by postganglionic sympathetic neurons and by cells of the immune system (e.g. macrophages, tissue fibroblasts) [61]. The secretion of immune CRH has been examined both in experimental animal models of inflammation [61] and in patients with rheumatoid arthritis [29] and Hashimoto's thyroiditis [112]. Immune CRH secretion is suppressed by glucocorticoids and somatostatin [61]. Mast cells are considered as the primary target of immune CRH where, along with substance P, it acts via CRH type 1 receptors causing degranulation. Subsequently, histamine is released, causing vasodilation, increased vascular permeability and other manifestations of local inflammation. Thus, locally secreted CRH has proinflammatory properties, whereas central CRH alleviates the immune response [26, 39].

3.3.2 HPA Axis: Other Endocrine Axes

The HPA axis is closely linked to the endocrine axes that control reproduction and growth. The survival of the individual and the species in general requires adequate nourishment, growth and reproduction, which are achieved through biologically costly pathways that threaten the stability of the internal milieu. Under conditions of serious danger to survival, the stress-dependent HPA axis activation intervenes to exert multilevel inhibitory effects on the gonadal and growth axes, until the imposed challenge is counteracted.

3.3.2.1 Gonadal Axis

The reproductive axis is inhibited at all levels by various components of the HPA axis (Fig. 5) [72, 86, 95]. At the hypothalamic level, CRH suppresses the gonadotropin hormone releasing hormone (GnRH) neurons of the arcuate nucleus. CRH-induced β-endorphin secretion by the arcuate POMC neurons mediates this suppression, but direct inhibitory action of CRH is also suggested [25]. In addition, glucocorticoids exert inhibitory effects on the hypothalamic GnRH neuron, the pituitary gonadotroph, and the gonads themselves and render target tissues of sex steroids resistant to their actions [86]. Hypothalamic functional amenorrhea is a typical example of stress induced inhibition of the female reproductive axis, while suppression of the gonadal function by chronic HPA axis activation has been also demonstrated in highly trained athletes of both sexes and in individuals with anorexia nervosa or sustaining starvation [52,

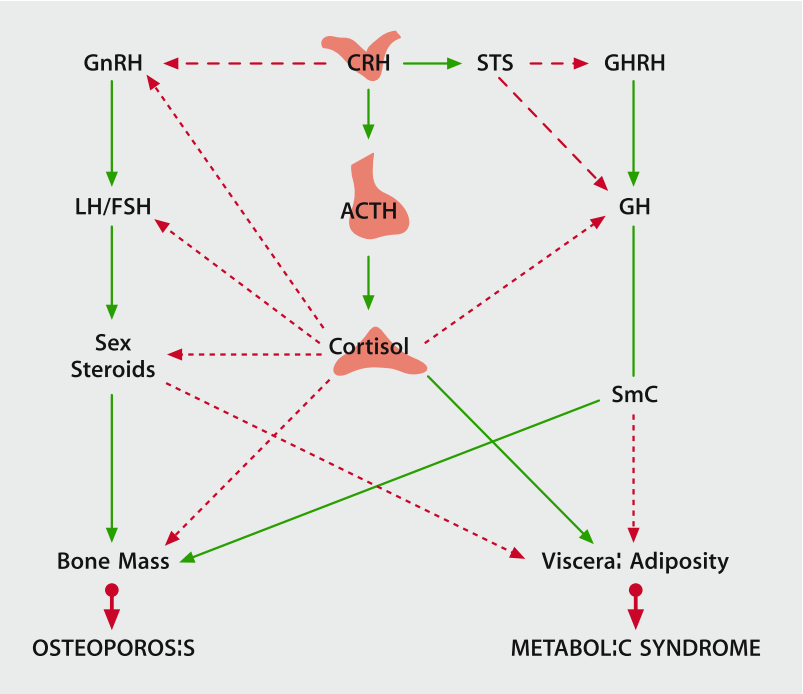

Fig. 5. A schematic representation of the regulatory effects of the hypothalamic-pituitary adrenal (*HPA*) axis on the reproductive axis, the growth axis and the metabolism. Dysfunction of the HPA axis may lead to osteoporosis and manifestations of the metabolic syndrome. Stimulatory effects are represented by *solid lines* and inhibitory effects by *dashed lines* (*CRH*, corticotropin-releasing hormone; *ACTH*, corticotropin; *GnRH*, gonadotropin-releasing hormone; *LH*, luteinizing hormone; *FSH*, follicle-stimulating hormone; *STS*, somatostatin; *GHRH*, growth hormone-releasing hormone; *GH*, growth hormone; *SmC*, somatomedin C)

68, 62]. It is interesting that during inflammation, circulating cytokines suppress the reproductive functions by activating the hypothalamic secretion of CRH and POMC-derived peptides, by enhancing the adrenocortical secretion of glucocorticoids and by inhibiting steroidogenesis at both ovaries and testes [93, 119].

Finally, a reciprocal interaction between CRH and the sex hormones is suggested by the presence of estrogen responsive elements in the promoter area of the CRH gene and by the direct stimulatory effects that estrogen exerts on CRH gene expression [126]. This finding implicates the CRH gene and consequently the HPA axis as a potentially important target of ovarian steroids and a potential mediator of gender related differences in the stress response and HPA axis activity.

3.3.2.2 Growth Axis

Growth is also sacrificed in order to preserve homeostasis under stressful conditions through a variety of inhibitory effects mediated by the HPA axis (Fig. 5) [34, 96]. Prolonged activation of the HPA axis results in increased circulating levels of glucocorticoids which suppress the secretion of growth hormone (GH) and inhibit the action of somatomedin C and other growth factors on their target tissues [15, 122, 57]. However, it should be noted that at the onset of the stress response or after acute administration of glucocorticoids an acute elevation of growth hormone concentration in plasma may occur, presumably as a result of GH gene stimulation by glucocorticoids through glucocorticoid-responsive elements in its promoter region [19]. At the level of the hypothalamus, CRH stimulates the secretion of somatostatin, which is the most potent inhibitor of the growth hormone secretion by the somatotroph cells of the anterior pituitary, providing a centrally acting mechanism of growth suppression by the HPA axis.

The anabolic function of the thyroid gland is also interrupted by the activated HPA axis in order to conserve energy during stress. Increased circulating levels of glucocorticoids suppress the pituitary production of thyroid-stimulating hormone (TSH) and

inhibit the conversion of the relatively inactive thyroxine to the more biologically active triiodothyronine in peripheral tissues (the "euthyroid sick" syndrome) [11, 36]. Inhibition of TRH and TSH secretion by CRH-stimulated increases in somatostatin might also participate in the central component of thyroid axis suppression during stress. Especially in the case of inflammatory stress, inhibition of TSH secretion is attributed in part to the direct action of cytokines on the hypothalamus and the pituitary [112, 117].

3.3.2.3 Metabolism

Glucocorticoids, the hormonal end-product of the HPA axis, exert primarily catabolic effects as part of a generalized effort to utilize every available energy resource against the challenge posed by intrinsic or extrinsic stressors. Thus, glucocorticoids increase hepatic gluconeogenesis and plasma glucose concentration, induce lipolysis (although they favor abdominal and dorsocervical fat accumulation) and cause protein degradation at multiple tissues (e.g. muscle, bone, skin) to provide amino acids that would be used as an additional substrate at oxidative pathways. In addition to their direct catabolic actions, glucocorticoids also antagonize the beneficial anabolic actions of GH, insulin and sex steroids on their target tissues [27]. This shift of the metabolism toward a catabolic state under the control of the activated HPA axis normally reverses upon retraction of the enforced stressor. Indeed, chronic activation of HPA axis would be damaging as it is expected to increase visceral adiposity, decrease lean body (muscle and bone) mass, suppress osteoblastic activity and cause insulin resistance (Fig. 5). Interestingly, the phenotype of Cushing's syndrome, characterized by abdominal and trunk fat accumulation and decreased lean body mass, in combination with manifestations of the metabolic syndrome (visceral adiposity, insulin resistance, dyslipidemia, hypertension), is present in a variety of pathophysiologic conditions, collectively described as pseudo-Cushing's states. The pseudo-Cushing's states are presumably attributed to HPA-induced mild hypercortisolism or to adipose tissue-specific hypersensitivity to glucocorticoids [27, 118].

The balance of metabolic homeostasis is also centrally affected by the neuroendocrine integration of the HPA axis to the CNS centers that control energy expenditure and intake. Indeed, CRH stimulates the POMC neurons of the arcuate nucleus which, via α-MSH release, elicit antiorexigenic signals and increase thermogenesis [89]. Conversely, glucocorticoids at the hypothalamic level enhance the intake of carbohydrates and fat and inhibit energy expenditure by stimulating the secretion of neuropeptide Y, which is the most potent appetite stimulator [20].

3.4 HPA Axis: Pathophysiology

Generally, the activation of the HPA axis is tightly regulated and is intended to be acute or at least of a limited duration. The time-limited nature of this process renders the induced adaptive antireproductive, antigrowth, catabolic and immunosuppressive effects temporarily beneficial rather than damaging and prevents significant adverse consequences [114]. In contrast, prolongation of the HPA axis activation, as documented in chronic stressful conditions, would lead to the stress syndromal state that Selye described in 1936 characterized by anorexia, loss of weight, depression, hypogonadism, peptic ulcers, immunosuppression, adrenal enlargement and involution of the thymus and lymph nodes [104]. Because CRH coordinates behavioral, neuroendocrine and autonomic adaptation during stressful situations, increased and prolonged production of CRH could explain the pathogenesis of the syndrome [120].

The prototypic example of prolonged dysregulation leading to hyperactivation of the HPA axis is manifested in melancholic depression with dysphoric hyperarousal and relative immunosuppression [46]. Indeed, cortisol excretion 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. Thus, owing to chronically hyperactive CRH neurons, patients with melancholic depression may sustain several severe somatic sequelae, such as osteoporosis, features of the metabolic syndrome, varying degrees of atherosclerosis, innate and Th-1-directed immunosuppression and certain infectious and neoplastic diseases [26]. If untreated, 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 [47], obsessive-compulsive disorder [56], panic anxiety [24], excessive exercising [70], malnutrition [73], chronic active alcoholism [129], alcohol and narcotic withdrawal [10, 90], diabetes mellitus [120], hyperthyroidism [59] and pre-

Table 1. Pathophysiology of the hypothalamic-pituitary-adrenal axis (HPA) axis

	HPA axis activity		
	Increased	Decreased	Disrupted
Severe chronic disease	+		
Melancholic depression	+		
Anorexia nervosa	+		
Obsessive-compulsive disorder	+		
Panic disorder	+		
Chronic excessive exercise	+		
Malnutrition	+		
Diabetes mellitus	+		
Chronic alcoholism	+		
Hyperthyroidism	+		
Central obesity	+		
Pregnancy	+		
Atypical depression		+	
Seasonal depression		+	
Chronic fatigue syndrome		+	
Fibromyalgia		+	
Hypothyroidism		+	
Post glucocorticoid therapy		+	
Post stress		+	
Postpartum		+	
Rheumatoid arthritis		+	
Cushing's syndrome			+
Glucocorticoid deficiency			+
Glucocorticoid resistance			+
Congenital adrenal hyperplasia			+
ACTH resistance			+

menstrual tension syndrome [87]. Notably, patients with central (upper body) obesity exhibit higher levels of circulating inflammatory cytokines [116] while a subpopulation of these patients were also found to have mild hypercortisolism [81, 27].

Pregnancy is another condition characterized by hypercortisolism of a degree similar to that observed in mild Cushing's syndrome, severe depression and anorexia nervosa. Gestation is the only known physiologic state in humans in which CRH circulates in plasma at levels high enough to cause activation of the HPA axis [103]. Although circulating CRH, which is of placental origin, is bound with high affinity to CRH-binding protein [69, 83], it appears that the circulating free fraction is sufficient to explain the observed hypercortisolism. Hypercortisolism of pregnancy is associated with suppression of hypothalamic secretion of CRH, persisting in the postpartum [49].

On the other side of the spectrum of HPA axis dysregulation, another group of states is characterized by hypoactivation, rather than sustained activation, in which chronically reduced secretion of CRH may result in pathologic hypoarousal (Table 1). Patients with seasonal depression and the chronic fatigue syndrome fall into this category [32, 127]. Similarly, patients with fibromyalgia have decreased urinary free cortisol excretion and frequently complain of fatigue [50]. Hypothyroid patients also have clear evidence of CRH hyposecretion and often present depression of the "atypical" type [60]. It is interesting that in Cushing's syndrome, the clinical manifestations of hyperphagia, weight gain, fatigue, and anergia are consistent with the suppression of the hypothalamic CRH neurons by the associated hypercortisolism [48].

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 Th-1 suppression, but enhanced resistance to autoimmune/inflammatory disease [39]. 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 [26]. Thus, an increasing body of evidence suggests that patients with rheumatoid arthritis have a mild form of central hypocortisolism [22]. Dysfunction of the HPA axis may actually play a role in the development or perpetuation of autoimmune disease, rather than being an epiphenomenon [109]. The same rationale may explain the high incidence of autoimmune disease in the period after cure of hypercortisolism, as well as in glucocorticoid underreplaced adrenal insufficiency [74].

Disruption of the HPA axis may present as a result of destructive processes involving the hypothalamus, pituitary, or adrenal glands, leading eventually to adrenal insufficiency (Table 1). On the other hand, eutopic or ectopic autonomous production of CRH, ACTH, or cortisol results in the development of Cushing's syndrome and suppression of the hypothalamic CRH neuron and normal pituitary corticotroph. It is interesting that the HPA axis of patients cured from Cushing's syndrome or after discontinuation of chronic glucocorticoid therapy requires a period of 6 months to 2 years to normalize [35]. It appears that the locus of such chronic glucocorticoid-induced adrenal suppression is primarily suprapituitary involving the CRH neuron [49].

Finally, genetic defects can cause disruption of the HPA axis. These include the various types of congenital adrenal hyperplasia due to enzymatic defects at different steps of steroidogenesis and the rare syndromes of ACTH and glucocorticoid resistance, whereby the defect lies in the ACTH and glucocorticoid receptor gene, respectively [55, 113]. All these hereditary abnormalities lead to attenuation or complete loss of the glucocorticoid negative feedback, resulting in compensatory increases of CRH and ACTH secretion [23].

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