Q J Med 2000; **93**:323–333

Review

QJM

The stress response and the hypothalamic-pituitary-adrenal axis: from molecule to melancholia

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Summary

Organisms survive by maintaining equilibrium with their environment. The stress system is critical to this homeostasis. Glucocorticoids modulate the stress response at a molecular level by altering gene expression, transcription, and translation, among other pathways. The effect is the inhibition of the functions of inflammatory cells, predominantly mediated through inhibition of cytokines, such as IL-1, IL-6, and TNF-α. The central effectors of the stress response are the corticotrophin-releasing hormone (CRH) and locus coeruleus-norepinephrine (LC-NE)/sympathetic systems. The CRH system activates the stress response and is subject to modulation by cytokines, hormones, and neurotransmitters. Glucocorticoids also modulate the growth, reproductive and thyroid axes. Abnormalities of stress system activation have been shown in inflammatory diseases such as rheumatoid arthritis, as well as behavioural syndromes such as melancholic depression. These disorders are comparable to those seen in rats whose CRH system is genetically abnormal. Thus, the stress response is central to resistance to inflammatory and behavioural syndromes. In this review, we describe the response to stress at molecular, cellular, neuroendocrine and behavioural levels, and discuss the disease processes that result from a dysregulation of this response, as well as recent developments in their treatment.

Introduction

Organisms survive by maintaining a dynamic equilibrium with their environment. The organization of this homeostasis exists at molecular, cellular, physiological and behavioural levels. Stress is a state of threat to this equilibrium, and adaptation to stress, or allostasis, confers a survival advantage. Successful adaptation requires not only the ability to respond to stress, but also the ability to control the stress response appropriately.

This stress system is tonically active, but both physical and emotional stressors that exceed a critical threshold increase its activity further. The hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic and adrenomedullary (sympathetic) systems are the peripheral limbs of the stress system. Increased system activation as a result of stress leads to central and peripheral changes, which facilitate behavioural adaptation and redirection of energy to the central nervous system, muscle, and stressed body sites. These changes serve to promote homeostasis. HPA axis activation results in glucocorticoid secretion. The principal role of glucocorticoids during the stress response is thought to be restraint of the effectors of the stress response.

We review the response to stress from a molecular to a behavioural level and discuss the disease processes that may result from a dysregulation of this response.

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The molecular response to stress

Glucocorticoids are the effectors of the HPA limb of the stress system. Stress and non-stress activities of glucocorticoids are regulated through two different types of glucocorticoid receptors. The type 1, high-affinity or mineralocorticoid receptor (MR) mediates non-stress circadian fluctuations in glucocorticoids and is primarily activational. The type 2, low-affinity or glucocorticoid receptor (GR), mediates stress levels of glucocorticoids, and is inhibitory in some systems and activational in others.[1] Glucocorticoid affinity for the MR is 10 times that of the GR.[2] Glucocorticoid receptors have a widespread distribution throughout tissues.

The glucocorticoid cytoplasmic receptor protein belongs to the phylogenetically conserved superfamily of nuclear hormone receptors.[3] The receptor contains three major functional domains. The carboxy-terminal binds glucorticoid. This binding leads to the dissociation of heat-shock protein, which induces a conformational change in the glucocorticoid receptor molecule. This, in turn, leads to nuclear translocation of the glucocorticoid receptor. In the nucleus, the midregion binds to specific sequences of DNA known as glucocorticoid-responsive elements (GREs). This binding facilitates the activation of target genes by the aminoterminal sequence[4] (Figure 1).

Glucocorticoids may modulate immune responses in numerous ways, including through gene expression, transcription, translation, post-translational processing, protein secretion, and cell progenitor proliferation and differentiation. Cytokine inhibition accounts for many of the inhibitory effects on the immune response during stress.

Glucocorticoids inhibit cytokine production by altering mRNA stability at the level of gene expression. Their actions may be mediated directly (Type 1 mechanism) or indirectly (Type 2 mechanism).[5] For example, glucocorticoids directly decrease transcription of the genes for interleukin-6 (IL-6) and interleukin-1β, thus decreasing their production by immune cells. In contrast, the immune response is indirectly suppressed by glucocorticoids through inhibition of pro-inflammatory transcription factors such as nuclear factor-κB (NF-κB) and activating protein-1 (AP-1).[6]

NF-κB is a heterodimer, which is found in the cytoplasm bound to IκBα and IκBβ. These proteins prevent NF-κB from entering the nucleus.[7] NF-κB is activated by many stressors (viral infection, oxidants, cytokines, and antigens).[8] Activation leads to the release of IκB, allowing passage of NF-κB into the nucleus, where it binds to specific sequences in the promoter regions of target genes. NF-κB increases the expression of the genes for many cytokines, enzymes, and adhesion molecules in inflammatory diseases.[9] In turn, pro-inflammatory cytokines such as IL-1β and tumour necrosis factor-α (TNF-α) activate NF-κB, thus perpetuating local inflammatory responses (Figure 1).[9] Glucocorticoids are potent inhibitors of the activation of NF-κB, which may account for many of their anti-inflammatory actions.

Generalized glucocorticoid resistance can result from quantitative or qualitative defects in the GR of a system.[10] More recently, a polymorphism in the glucocorticoid receptor gene has been described which may result in increased glucocorticoid sensitivity.[11] There are also numerous molecular determinants of glucocorticoid sensitivity.

The cellular response to stress

Glucocorticoids inhibit the functions of virtually all inflammatory cells (Table 1). This inhibition is mediated by altering the transcription of cytokine genes (for example, TNF, IL-1, and IL-6), and by inhibiting the production of arachidonic-acid-derived pro-inflammatory substances such as leukotrienes and prostaglandins.[12]

Many substances activate the stress response. Among these, TNF-α, IL-1, and IL-6 are the most important, and are produced at inflammatory sites in a cascade-like fashion.[13] These cytokines can stimulate the HPA-axis independently or synergistically. All three cytokines have autocrine effects in that they stimulate their own secretion from the cells that produce them. TNF-α and IL-1 stimulate IL-6 secretion, but IL-6 inhibits TNF-α and IL-1 secretion.[14] IL-6 acts synergistically with glucocorticoids to stimulate the hepatic production of acute-phase proteins.[15]

Glucocorticoids inhibit the production of TNF-α, IL-1, and IL-6, but there exists a hierarchy of sensitivity, with TNF having the greatest sensitivity and suppression occurring at physiological levels. IL-1 has intermediate sensitivity, suppression occurring only at supraphysiological levels, and IL-6 is relatively resistant. Differential regulation of cytokine production by type 1 and type 2 glucocorticoid receptors may explain this differential glucocorticoid sensitivity.[16] Glucocorticoids induce lympholysis through 'apoptosis', or steroid-hormone-receptor-mediated cell death. This is mediated by the synthesis of endogenous non-lysosomal endonucleases.[17]

Lympholysis and redistribution of T-lymphocytes cause lymphopenia in the presence of corticosteroids.[18] Glucocorticoids inhibit lymphocyte proliferation and activation by directly inhibiting IL-2 and IL-2 receptor production, and by indirectly reducing lymphocyte IL-2 synthesis through reduced monocyte IL-1 synthesis.[19]

Circulating monocytes and their secretion of IL-1,

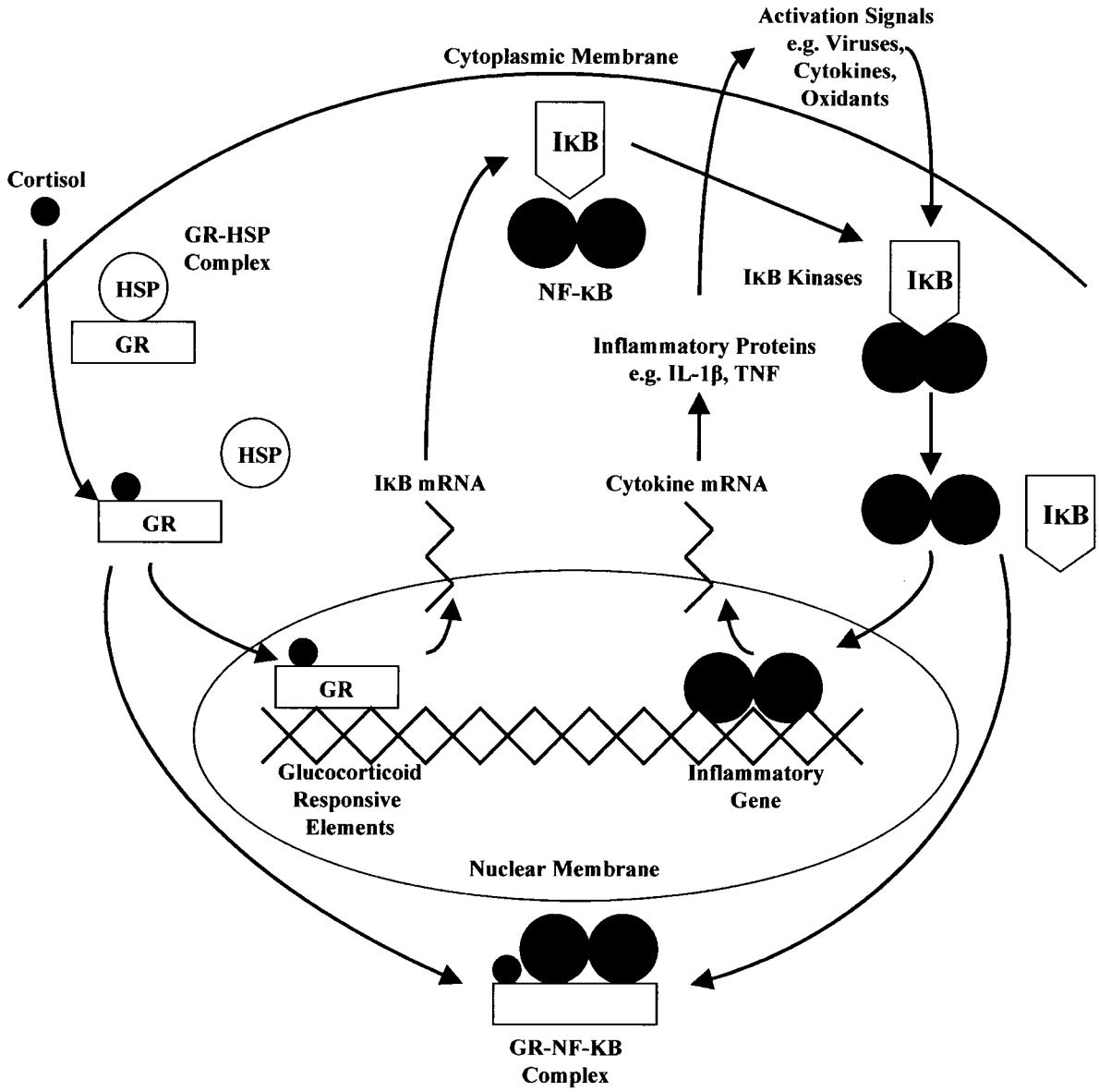

Figure 1. Cortisol binds to the glucocorticoid receptor/heat-shock protein (GR-HSP) complex in the cytoplasm, leading to the dissociation of heat shock protein (HSP), and the nuclear translocation of the glucocortiocid-glucocorticoid receptor complex. In the nucleus, the glucocortiocid-glucocorticoid receptor complex binds to glucocorticoid-responsive elements and activates target genes. This activation decreases transcription of certain genes (e.g. IL-1β/TNF genes), and increases transcription of other genes (e.g. IκB). Nuclear factor-kappa B (NF-κB) is bound to IκB in the cytoplasm. Activation signals such as cytokines lead to the dissociation of NF-κB from IκB, and the passage of NF-κB to the nucleus, where it increases the expression of genes for many cytokines, enzymes and adhesion molecules. These pro-inflammatory mediators further activate NF-κB in an amplifying loop, thus perpetuating local inflammatory responses. Glucocorticoids interrupt this process both by binding to activated NF-κB directly and preventing its nuclear binding, and by increasing the transcription of IκB, which also binds to activated NF-κB, further limiting its effects.

IL-6, TNF-α, and monocyte chemotactic-activating factors are reduced by high concentrations of glucocorticoids.[20–23] Impaired synthesis of collagenase, elastase, and tissue plasminogen activator reduces the degradation of extracellular matrix and fibrin by monocytes.[24]

Glucocorticoids deplete both circulating and tissue eosinophils. Eosinophil survival is reduced through inhibition of GM-CSF, which is produced by IL-1-activated endothelial cells.[25] Eosinophil adherence to endothelial cells is reduced by IL-1 inhibition. Basophil numbers are reduced by 80% with higher concentrations of glucocorticoids, and the IgE-induced release of histamine and leukotrienes is impaired.[26] Decreased T-lymphocyte cytokine release inhibits mast cell expansion, and endothelial adherence is also reduced.[27,28]

In contrast, neutrophil concentrations rise in blood

Table 1 Glucocorticoid effects on immune cells

Cell type	Effect
Lymphocytes	Reduce circulating numbers
	Inhibit proliferation /activation (by inhibiting IL-2 and other cytokines)
	Induce lympholysis through apoptosis
	Suppress natural killer cell activity
Monocytes	Reduce circulating numbers
	Inhibit secretion of IL-1, IL-6, TNF-α, and monocyte chemotactic activating factors
	Impair synthesis of collagenase, elastase, and tissue plasminogen activator
Eosinophils	Reduce circulating numbers
	Reduce survival (reduce endothelial GM-CSF release)
	Reduce endothelial adherence (by IL-1 inhibition)
Basophils	Reduce circulating numbers
	Impair histamine and leukotriene release
	Inhibit mast cell expansion
	Reduce endothelial adherence
Neutrophils	Increase circulating numbers
	Reduce chemotaxis (decrease IL-1, IL-8, and leukotriene B4)
	Reduce endothelial adherence

in the presence of glucocorticoids due to impaired endothelial cell adhesion, and consequent impaired diapedesis and migration to inflammatory sites.[29] The local release of neutrophil attracting factors (e.g. IL-1, IL-8, and leukotriene B4) is also reduced. Other glucocorticoid effects include reduced endothelial cell adhesion and reduced synthesis of prostaglandin, leukotrienes, and platelet-activating factor because of impaired induction of the protein lipocortin.[30]

The neuroendocrine response to stress

The central effectors of the stress response are the corticotrophin-releasing hormone (CRH) and locus coeruleus-norepinephrine (LC-NE)/sympathetic systems (Figure 2). CRH and noradrenergic neurons of the central stress system innervate and stimulate each other in a positive feedback mechanism, such that activation of one system leads to activation of the other.[31] CRH and norepinephrine collateral fibres inhibit presynaptic CRH and α_1-noradrenergic receptors respectively.[32]

CRH is a 41-amino-acid peptide that is found in the hypothalamus and many other brain regions, as well as the adrenal gland, placenta, ovary, human lymphocyte, and at inflammatory sites.[33–36] Cytokines and inflammatory mediators stimulate hypothalamic CRH release, which leads to pituitary adrenocorticotrophic (ACTH) hormone secretion into the peripheral circulation.[37] ACTH, in turn, leads to adrenal glucocorticoid production and release.This adrenocorticosteroid response controls the immune response by inhibiting further cytokine production. CRH may also play a role in the onset of parturition, by triggering a surge in fetal cortisol.[38] The activity of the HPA-axis exhibits diurnal variation and is increased during stress.

Arginine vasopressin (AVP) alone has little effect on ACTH secretion, but acts synergistically with CRH to promote pituitary ACTH release,[39] and hypothalamic pro-opiomelanocortin (POMC)-derived opioid peptide release.[40] These peptides, such as β-endorphin and dynorphin, enhance analgesia, and, with ACTH, inhibit the stress response by inhibiting further hypothalamic CRH secretion, an effect that is blocked by naloxone.[41] CRH, AVP, and noradrenergic neurons are stimulated by the serotonergic and cholinergic systems of the brain and inhibited by the gamma-aminobutyric acid-benzodiazepine (GABA-BDZ) and opioid peptide systems of the brain, as well as by glucocorticoids, ACTH, and CRH itself.[32] ACTH and β-endorphin originate from the pituicyte and from arcuate nucleus POMC neurons, and are involved in short negative feedback loops on the CRH system.[42]

In contrast to their central effects, CRH and AVP have pro-inflammatory effects at inflammatory sites, where immune cells and inflammatory exudates contain high concentrations of immunoreactive CRH and CRH receptors.[35,36] CRH has been detected in the synovial fluid of patients with rheumatoid arthritis, and in thyroid follicular cells of patients with autoimmune thyroiditis.[43,44] CRH levels at inflammatory sites may rise to concentrations similar to those found in the hypophyseal portal system, but are usually undetectable in the peripheral circulation during stress.[36] Rapid uptake, catabolism, or binding may account for this gradient. Thus, CRH has central anti-inflammatory and opposing peripheral pro-inflammatory effects.

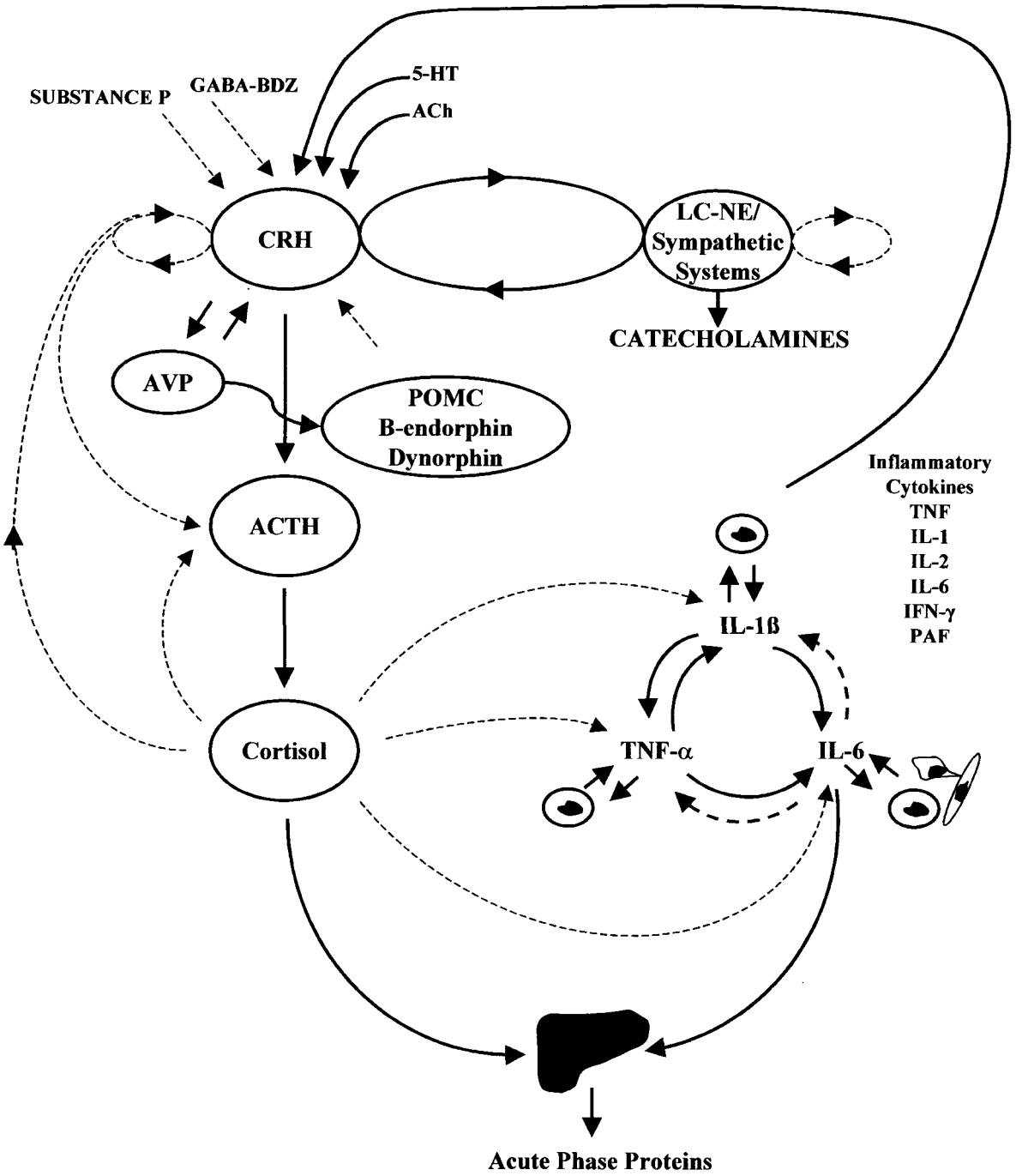

Figure 2. The corticotrophin-releasing hormone (CRH) and locus coeruleus-norepinephrine (LC-NE) systems of the brain are the central effectors of the stress response, and participate in a positive reverbatory feedback loop, whereby activation of one tends to activate the other. The CRH system is inhibited by cortisol, substance P, GABA-BDZ, pro-opiomelanocortin (POMC) and other opioids, and CRH itself, and is activated by 5-hydroxytryptamine (5-HT), acetylcholine (ACh), the LC-NE sympathetic systems, arginine vasopressin (AVP), and inflammatory cytokines. Activation results in the production of CRH. CRH stimulates AVP secretion, and acts in synergy with AVP to stimulate pituitary adrenocorticotrophin (ACTH) release, which stimulates adrenal cortisol production. Tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6 are produced from inflammatory sites in a cascade-like fashion, and are the most important activators of the CRH system. All three cytokines stimulate their own production. IL-1β and TNF stimulate IL-6 production, but IL-6 inhibits IL-1β and TNF production, and acts in concert with glucocorticoids to stimulate the hepatic secretion of acute-phase proteins. Glucocorticoids inhibit the production of all three cytokines, but TNF-α is the most sensitive, with IL-6 being relatively resistant. IFN-α, interferon-α; PAF, platelet-activating factor. Broken lines represent inhibition; Solid lines represent stimulation.

Cytokines found within the central nervous system play an important part in neuronal cell death.[45] The human central nervous system contains neuronal pathways and receptors for cytokines (e.g. IL-1) in areas that control the acute-phase response.[46] Most cytokines are large molecules, and would not be expected to cross the blood-brain barrier with ease. However, IL-1 stimulates the production of endothelial cell prostaglandins (PGE2, PGI2), which in turn stimulate the secretion of CRH from nerve terminals in the median eminence, which lies outside the blood brain barrier.[47] IL-1 may cross the blood-brain barrier at relatively leaky parts, such as the organum vasculosum of the lamina terminalis, or during disease states such as infection or inflammation which may impair the barrier. IL-1 may also signal centrally via secondary messengers such as nitric oxide and prostaglandins, or via the vagus and other nerves.[48] IL-1, IL-6, and TNF, as well as other cytokines, activate the HPA-axis, but this effect is blocked by glucocorticoids.[1]

IL-6 is a potent stimulator of ACTH and cortisol secretion, leading to higher levels of these hormones than are found with maximally-stimulating doses of CRH alone.[49] This may result from IL-6-induced AVP secretion, which acts synergistically with CRH to produce higher ACTH levels.[39] Also, IL-6 may act directly on the pituitary and adrenal glands, and may sensitise the adrenals to ACTH.[50] At high doses, IL-6 increases plasma AVP levels, leading to suggestions that IL-6 may play a role in the syndrome of inappropriate ADH secretion. IL-6 also inhibits IL-1β and TNF-α production, and glucocorticoids up-regulate the expression of the IL-6 receptor.[14,51] IL-6 production is resistant to glucocorticoid suppression when compared to other cytokines.[16] Thus, as well as being pro-inflammatory, IL-6 may also have anti-inflammatory effects.

At high concentrations or with prolonged exposure, inflammatory cytokines can stimulate pituitary ACTH and adrenal cortisol secretion directly.[49] Cytokines may also induce glucocorticoid resistance. For example, the affinity of cortisol for the glucocorticoid receptor is reduced in the presence of IL-2 and IL-4. T-cells obtained by bronchoalveolar lavage from patients with glucocorticoid-resistant asthma have high levels of IL-2 and IL-4 gene expression, which result in glucocorticoid receptor binding defects.[52]

Other endocrine interactions

Growth, reproductive function, and the thyroid axis are also influenced by stress system activation. In the acute setting of stress, glucocorticoids stimulate the growth hormone gene, leading to enhanced growth hormone secretion.[53] However, with more prolonged stress, growth hormone release is suppressed by CRH-induced elevations in somatostatin levels.[54] This results in an inverse relationship between the diurnal concentrations of cortisol and growth hormone. Also, glucocorticoids directly inhibit growth hormone effects at target tissues by inhibiting insulin-like growth factor-1 (IGF-1) and other growth factors.[55] The effects of stress on the growth axis may account for the delay in growth often seen in chronic disease and emotional deprivation in childhood.

CRH, β-endorphin, and glucocorticoids inhibit GnRH secretion from the hypothalamus. Glucocorticoids also suppress pituitary gonadotrophin release and inhibit gonadal tissue.[56] Patients with illnesses associated with increased HPA-axis activity, such as anorexia nervosa, hyperthyroidism, and malnutrition, may experience abnormalities of menstrual and reproductive function.[57–59]

The CRH-stimulated increase in somatostatin inhibits TSH production and secretion. IL-6 also inhibits the secretion of TSH.[60] In the periphery, elevated circulating levels of glucocorticoid inhibit the conversion of T4 to T3. These changes lead to the characteristic biochemical picture of 'sick euthyroid' syndrome in patients with chronic stress system activation.[61]

The behavioural response to stress

Both physical and emotional stressors activate homeostatic mechanisms. The CRH system is central to this process, and is found throughout the brain. The intraventricular administration of CRH in rats leads to activation of the pituitary-adrenal axis and the sympathetic nervous system. This activation leads to increased blood glucose, heart rate, and blood pressure. Also, observation of the rats' behaviour reveals increased arousal and vigilance, anorexia, reduced libido, changes in motor activity, and increased tolerance of pain.[62]

The stress response is intended to be of limited duration. In this way, its catabolic and immunosuppressive effects are homeostatic and without serious sequelae. Melancholic depression seems to represent an exaggerated and prolonged form of the hyperarousal seen with stress system activation, and patients with this condition show behavioural patterns that are similar in ways to rats treated with CRH.[63,64] In these patients, cortisol excretion is increased, and the ACTH response to endogenous CRH is decreased.[65] Bone mineral density may be reduced, in keeping with a chronic hypercortisolaemic state.[66] The defect appears to be at or above hypothalamic level in hypercortisolaemic

patients with melancholia, as evidenced by normal pituitary corticotroph function.[63,64] Alterations in hippocampal serotonin 1A levels and in the mineralocorticoid/glucocorticoid receptor balance may be one of the methods by which stress may trigger and maintain depressive episodes. Other conditions associated with increased and prolonged activation of the HPA axis include anorexia nervosa, obsessive-compulsive disorder and panic disorder.[67–69]

In contrast, hypoactivation of the stress system/HPA axis, resulting in chronically reduced CRH secretion, may cause pathological hypoarousal. The Lewis rat provides an animal model wherein the hypofunctioning CRH neuron, and its consequent state of CRH deficiency, leads to susceptibility to inflammatory and autoimmune disease and abnormal behavioural responses.[70,71] Examples of this HPA-axis hypoactivity in man include seasonal affective disorder, chronic fatigue syndrome, and nicotine withdrawal.[72–74] CRH deficiency after nicotine withdrawal might account for the weight gain and hyperphagia seen in patients at this time. Similarly, CRH suppression from chronic hypercortisolaemia in Cushing's syndrome might explain the weight gain and hyperphagia that characterize this condition.

Other disturbances in the system

The integrity of the immune response is central to resistance and susceptibility to inflammatory and behavioural syndromes.

An exaggerated HPA-axis response, as is seen in genetically CRH-hyper-responsive Fischer rats, and its consequent hypercortisolaemia, may increase susceptibility to infection and tumours, but reduce susceptibility to inflammatory and autoimmune disease. On the other hand, a blunted HPA-axis response and its consequent hypocortisolaemia may enhance resistance to infection and tumours, but increase susceptibility to inflammatory and autoimmune disorders. This state of CRH deficiency in the Lewis rat leads to increased susceptibility to inflammatory disease, and abnormal behavioural responses similar to those seen in atypical depression.[70,71] AVP levels are chronically increased. Furthermore, reconstitution of the HPA-axis by hypothalamic transplantation from Fischer to Lewis rats virtually eradicates the Lewis rat peripheral inflammatory response.[48]

Early reports in humans show that HPA-axis abnormalities are also seen in autoimmune diseases such as rheumatoid arthritis. These patients have a blunted circadian cortisol rhythm, and have inappropriately low or normal ACTH and cortisol levels, despite elevated TNF-α, IL-1β, and IL-6 levels.[75] AVP levels are also raised, as they are in the Lewis rat, and adrenal responses to surgery are blunted.[76] Patients with rheumatoid arthritis often experience symptoms of dysthymia, fatigue and depression. Although these symptoms might be secondary to the disease process, they are also consistent with behavioural responses associated with a state of CRH deficiency, as seen in the Lewis rat. Patients with chronic fatigue syndrome also exhibit features of dysfunctional HPA axis activity, as evidenced by low 24-h urinary free cortisol and evening basal cortisol levels, in spite of attenuated but clear ACTH responses to CRH.[73] Treatment with low-dose hydrocortisone may improve fatigue in this condition.[77]

Chronic HPA axis activation results in protective adaptation of the axis. For example, the immune suppression seen in Cushing's disease is milder than would be expected for this degree of hypercortisolaemia. Hypothalamic substance P inhibits CRH secretion, and may be the substance explaining the inhibition of CRH neuron activity seen in inflammation.[78] Also, inflammatory cytokines may block the stimulatory effects of CRH and ACTH on the pituitary and adrenal cortex.[79] This is seen in septic shock, AIDS, and African trypanosomiasis, in which adrenal responses to stress and ACTH are blunted.[80–82]

An excessive HPA axis response has been hypothesized to contribute to deterioration in memory, resulting from prolonged exposure of hippocampal neurons to increased levels of glucocorticoids.[83] Repeated and prolonged exposure to glucocorticoids causes hippocampal neurons to atrophy. However, this atrophy may be a reversible phenomenon. Evidence for increased HPA-axis activity has been demonstrated in patients with Alzheimer's type dementia.[84]

Patients with systemic lupus erythematosis (SLE) exhibit high cortisol catabolism, and consequently are corticosteroid-resistant when compared with other autoimmune diseases in terms of therapeutic steroid requirement.[85] Other diseases associated with resistance to glucocorticoids include steroid-resistant asthma and AIDS.[86,87]

In contrast, essential hypertension has been associated with a mild form of generalized glucocorticoid hypersensitivity. This may be due to an abnormally sensitive glucocorticoid receptor, or to impaired 11-β-hydroxysteroid dehydrogenase activity, which would reduce cortisol metabolism at target organ level. In patients with sepsis, there is an increased sensitivity to the antiproliferative actions of glucocorticoids.[88] This hypersensitivity may be counteracted at the site of inflammation by high local concentrations of cytokines, which allows an adequate local immune response in spite of elevated cortisol levels.

The diurnal variation in cortisol concentration

correlates with variations in immune function. For example, the delayed hypersensitivity reaction is maximal in the evening, when plasma cortisol concentration is lowest, and decreases in the morning when cortisol concentration rises. Changes in the activity of inflammatory disease over time might result from corresponding changes in HPA axis activity.

Future perspectives

Advances in our understanding of the complex pathways of the stress system have led to new therapeutic perspectives in the treatment of autoimmune and inflammatory diseases, as well as behavioural syndromes. CRH antagonists, which impair HPA axis activation, have already been used in animal studies.[38] CRH agonists or CRH-binding-protein antagonists might restore the integrity of the HPA-axis in patients with inflammatory or autoimmune diseases in whom it is hypofunctional.[32] Agents such as naloxone and type 1 glucocorticoid receptor antagonists might block inhibitory signals to the CRH neuron, thus potentiating its release.[47] Serotonin 1A agonists activate the HPA-axis via a CRH-specific mechanism,[89] and could be therapeutic in disease processes associated with a hypofunctional HPA-axis. Substance P antagonists that cross the blood brain barrier could block the inhibitory effect of substance P on CRH release. Benzodiazepines such as alprazolam inhibit CRH release in a dose-dependent fashion,[90] and thus might enhance the inflammatory response.

Peripherally, the inhibitory effect of IL-6 on TNF-α and IL-1 production could be of therapeutic value in septic shock. Treatment of diseases such as Crohn's disease and rheumatoid arthritis with monoclonal antibodies to TNF and TNF-receptor Fc fusion protein has already shown promising results.[91,92] IL-2 receptor blockade reduces the frequency of acute rejection in kidney transplant recipients.[93] Further developments in these treatments is likely to expand our ability to control autoimmune and inflammatory diseases in which HPA axis dysregulation plays a pivotal role.

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