

## Review

# Neural immune pathways and their connection to inflammatory diseases

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## Abstract

Inflammation and inflammatory responses are modulated by a bidirectional communication between the neuroendocrine and immune system. Many lines of research have established the numerous routes by which the immune system and the central nervous system (CNS) communicate. The CNS signals the immune system through hormonal pathways, including the hypothalamic–pituitary–adrenal axis and the hormones of the neuroendocrine stress response, and through neuronal pathways, including the autonomic nervous system. The hypothalamic–pituitary–gonadal axis and sex hormones also have an important immunoregulatory role. The immune system signals the CNS through immune mediators and cytokines that can cross the blood–brain barrier, or signal indirectly through the vagus nerve or second messengers. Neuroendocrine regulation of immune function is essential for survival during stress or infection and to modulate immune responses in inflammatory disease. This review discusses neuroimmune interactions and evidence for the role of such neural immune regulation of inflammation, rather than a discussion of the individual inflammatory mediators, in rheumatoid arthritis.

**Keywords:** cytokine, hypothalamic–pituitary–adrenal axis, immune, inflammatory, neural, rheumatoid arthritis

## Introduction

The inflammatory response is modulated in part by a bidirectional communication between the brain and the immune systems. This involves hormonal and neuronal mechanisms by which the brain regulates the function of the immune system and, in the reverse, cytokines, which allow the immune system to regulate the brain. In a healthy individual this bidirectional regulatory system forms a negative feedback loop, which keeps the immune system and central nervous system (CNS) in balance. Perturbations of these regulatory systems could potentially lead to either overactivation of immune responses and inflammatory disease, or oversuppression of the immune system and increased susceptibility to infectious disease. Many lines of research have recently established the numerous routes by which the immune system and the CNS communicate. This review will focus on these regulatory systems and

their involvement in the pathogenesis of inflammatory diseases such as rheumatoid arthritis (RA). For other reviews on the involvement of these regulatory pathways in RA and other inflammatory diseases, see reviews by Eijsbouts and Murphy [1], Crofford [2], and Imrich [3].

There are two major pathways by which the CNS regulates the immune system: the first is the hormonal response, mainly through the hypothalamic–pituitary–adrenal (HPA) axis, as well as the hypothalamic–pituitary–gonadal (HPG), the hypothalamic–pituitary–thyroid (HPT) and the hypothalamic–growth-hormone axes; the second is the autonomic nervous system, through the release of norepinephrine (noradrenaline) and acetylcholine from sympathetic and parasympathetic nerves. In turn, the immune system can also regulate the CNS through cytokines.

ACTH = adrenocorticotropin; AVP = arginine vasopressin; CNS = central nervous system; CRH = corticotropin-releasing hormone; DHEA = dehydroepiandrosterone; GH = growth hormone; GR = glucocorticoid receptor; HPA = hypothalamic–pituitary–adrenal; HPG = hypothalamic–pituitary–gonadal; HPT = hypothalamic–pituitary–thyroid; IFA = incomplete Freund's adjuvant; IGF = insulin-like growth factor; IL = interleukin; NF- $\kappa$ B = nuclear factor- $\kappa$ B; PBMCs = peripheral blood mononuclear cells; RA = rheumatoid arthritis; T<sub>3</sub> = triiodothyronine; T<sub>4</sub> = thyroxine; Th = T helper cells; TNF = tumor necrosis factor; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

Conversely, cytokines released in the periphery change brain function, whereas cytokines produced within the CNS act more like growth factors. Thus, cytokines produced at inflammatory sites signal the brain to produce sickness-related behavior including depression and other symptoms such as fever [4–7]. In addition, cytokines produced locally exert paracrine/autocrine effects on hormone secretion and cell proliferation [8,9].

The interactions between the neuroendocrine and immune systems provide a finely tuned regulatory system required for health. Disturbances at any level can lead to changes in susceptibility to or severity of infectious, inflammatory or autoimmune diseases.

## Regulation of the immune system by the CNS Hormonal pathways

### HPA axis

On stimulation, corticotropin-releasing hormone (CRH) is secreted from the paraventricular nucleus of the hypothalamus into the hypophyseal portal blood supply. CRH then stimulates the expression and release of adrenocorticotropin (ACTH) from the anterior pituitary gland. Arginine vasopressin (AVP) synergistically enhances CRH-stimulated ACTH release [10,11] ACTH in turn induces the expression and release of glucocorticoids from the adrenal glands.

Glucocorticoids regulate a wide variety of immune-related genes and immune cell expression and function. For example, glucocorticoids modulate the expression of cytokines, adhesion molecules, chemoattractants and other inflammatory mediators and molecules and affect immune cell trafficking, migration, maturation, and differentiation [12,13]. Glucocorticoids cause a Th1 (cellular immunity) to Th2 (humoral immunity) shift in the immune response, from a proinflammatory cytokine pattern with increased interleukin (IL)-1 and tumor necrosis factor (TNF)- $\alpha$  to an anti-inflammatory cytokine pattern with increased IL-10 and IL-4 [14,15]. Pharmacological doses and preparations of glucocorticoids cause a general suppression of the immune system, whereas physiological doses and preparations of glucocorticoids are not completely immunosuppressive but can enhance and specifically regulate the immune response under certain circumstances. For example, physiological concentrations of natural glucocorticoids (i.e. corticosterone) stimulate delayed-type hypersensitivity reactions acutely, whereas pharmacological preparations (i.e. dexamethasone) are immunosuppressive [16].

Glucocorticoids exert these immunomodulatory effects through a cytosolic receptor, the glucocorticoid receptor (GR). This is a ligand-dependent transcription factor that, after binding of the ligand, dissociates from a protein complex, dimerizes, and translocates to the nucleus, where it binds to specific DNA sequences (glucocorticoid

response elements) to regulate gene transcription [17]. GR can also interfere with other signaling pathways, such as nuclear factor (NF)- $\kappa$ B and activator protein-1 (AP-1), to repress gene transcription; it is through these mechanisms that most of the anti-inflammatory actions are mediated [18–21]. A splice variant of GR, GR $\beta$ , that is unable to bind ligand but is able to bind to DNA and cannot activate gene transcription [22] (although this is still under some dispute), has been suggested to be able to act as a dominant repressor of GR [23,24]. Increased GR $\beta$  expression has been shown in several inflammatory diseases including asthma [25–28], inflammatory bowel disease/ulcerative colitis [29,30], and RA [31].

### HPG axis

In addition to the HPA axis, other central hormonal systems, such as the HPG axis and in particular estrogen, also modulate the immune system [32]. In general, physiological concentrations of estrogen enhance immune responses [33,34] whereas physiological concentrations of androgens, such as testosterone and dehydroepiandrosterone (DHEA), are immunosuppressive [34]. Females of all species exhibit a greater risk of developing many autoimmune/inflammatory diseases, such as systemic lupus erythematosus, RA and multiple sclerosis, ranging from a 2-fold to a 10-fold higher risk compared with males [35,36]. Animal models have provided evidence for the importance of *in vivo* modulation of the immune system by the estrogen receptors [37,38]. Knockout mouse models indicate that both estrogen receptors  $\alpha$  and  $\beta$  are important for thymus development and atrophy in a gender-specific manner [39].

In contrast, immune stress, such as occurs during inflammation, has an inhibitory effect on the HPG axis and thus gonadal function is reduced in conditions associated with severe inflammation such as sepsis and trauma. This effect is mediated either through a direct cytokine effect on hypothalamic neurons secreting luteinizing hormone releasing hormone [40,41] or through other factors such as CRH [42,43] and endogenous opioids [44]. Cytokines also affect gonadal sex steroid production by acting directly on the gonads [45].

### Hypothalamic–growth-hormone axis

Growth hormone (GH) is a modulator of the immune system [46,47]. The effects of GH are mediated primarily through insulin-like growth factor-1 (IGF-1). GH and IGF-1 have been shown to modulate the immune system by inducing the survival and proliferation of lymphoid cells [48], leading some to suggest that GH functions as a cytokine [49]. Thus, immune cells including T and B lymphocytes [50] and mononuclear cells [51] express IGF-1 receptor. After binding to these receptors, GH activates the phosphoinositide 3-kinase/Akt and NF- $\kappa$ B signal transduction pathways, leading to the expression of genes involved in the cell cycle.

The NF- $\kappa$ B pathway is also important in immunity, and therefore some of the GH effects on the immune system might be mediated through this signal transduction pathway [49]. However, the role of GH in regulation of the immune system is somewhat controversial. Studies in GH knockout animals have shown that this hormone is only minimally required for immune function [52], leading to an alternative hypothesis in which the primary role of GH is proposed to be protection from the immunosuppressive effects of glucocorticoids during stress [53].

GH might also modulate immune function indirectly by interacting with other hormonal systems. Thus, short-term increases in glucocorticoids increase GH production [54], whereas long-term high doses result in a decrease in the hypothalamic-GH axis and even growth impairment [55]. Conversely, prolonged HPA axis activation and resultant excessive glucocorticoid production, as occurs during chronic stress, also inhibits the hypothalamic-GH axis [56–58]. Consistent with this is the observation that children with chronic inflammatory disease exhibit growth retardation. During the early phase of inflammatory reactions, the concentration of GH is increased. In spite of an initial rise in GH secretion, GH action is reduced because of GH and IGF-1 resistance induced by inflammation. IL-1 $\alpha$  initially stimulates GH [59], but subsequently inhibits its secretion [60].

#### *HPT axis*

As with the interaction between the HPA axis and the immune system, there is a bidirectional interaction between the HPT axis and immune system [61]. The HPT axis has an immunomodulatory effect on most aspects of the immune system. Thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), and the thyroid hormones triiodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>) all have stimulatory effects on immune cells [62–64]. As for GH, the role of thyroid hormones in the regulation of immunity is somewhat controversial, and for the same reasons the alternative hypothesis of protection from the immunosuppressive effects of glucocorticoids has also been suggested for thyroid hormones [53]. Inflammation inhibits TSH secretion because of the inhibitory effect of cytokines on TRH [62]. IL-1 has been shown to suppress TSH secretion [59], whereas IL-2 has been shown to stimulate the pituitary-thyroid axis [65]. IL-6 and its receptor have been shown to be involved in developing euthyroid sick syndrome in patients with acute myocardial infarction [66].

In addition to direct effects of thyroid hormones on immune response, there is also interaction between the HPA and HPT axes. Hyperthyroid and hypothyroid states in rats have been shown to alter responses of the HPA axis, with hypothyroidism resulting in a reduced HPA axis response and hyperthyroidism resulting in an increased HPA axis response [67]. In agreement with this, adminis-

tration of thyroxine, inducing a hyperthyroid state, has been shown to activate the HPA axis and be protective against an inflammatory challenge in rats [68], and hypothyroidism has been shown to cause a reduction in CRH gene expression [69]. Chronic HPA axis activation also represses TSH production and inhibits the conversion of inactive T<sub>4</sub> to the active T<sub>3</sub> [70].

#### **Neural pathways**

##### *Sympathetic nervous system*

The sympathetic nervous system regulates the immune system at regional, local, and systemic levels. Immune organs including thymus, spleen, and lymph nodes are innervated by sympathetic nerves [71–73]. Immune cells also express neurotransmitter receptors, such as adrenergic receptors on lymphocytes, that allow them to respond to neurotransmitters released from these nerves.

Catecholamines inhibit production of proinflammatory cytokines, such as IL-12, TNF- $\alpha$ , and interferon- $\gamma$ , and stimulate the production of anti-inflammatory cytokines, such as IL-10 and transforming growth factor- $\beta$  [15]. Through this mechanism, systemic catecholamines can cause a selective suppression of Th1 responses and enhance Th2 responses [15,74]. However, in certain local responses and under certain conditions, catecholamines can enhance regional immune responses by inducing the production of IL-1, TNF- $\alpha$ , and IL-8 [75]. Interruption of sympathetic innervation of immune organs has been shown to modulate the outcome of, and susceptibility to, inflammatory and infectious disease. Denervation of lymph node noradrenergic fibers is associated with exacerbation of inflammation [76,77], whereas systemic sympathectomy or denervation of joints is associated with decreased severity of inflammation [77]. However, mice lacking  $\beta$ 2-adrenergic receptor from early development ( $\beta$ 2AR<sup>-/-</sup> mice) maintain their immune homeostasis [78]. Therefore, dual activation of the sympathetic nervous system and HPA axis is required for full modulation of host defenses to infection [16,79].

##### *Opioids*

Opioids suppress many aspects of immune responses, including antimicrobial resistance, antibody production, and delayed-type hypersensitivity. This occurs in part through the desensitization of chemokine receptors on neutrophils, monocytes, and lymphocytes [80,81]. Morphine decreases mitogen responsiveness and natural killer cell activity [82–86]. In addition to these direct effects, morphine could also affect immune responses indirectly through adrenergic effects, because it increases concentrations of catecholamines in the plasma [87].

##### *Parasympathetic nervous system*

Activation of the parasympathetic nervous system results in the activation of cholinergic nerve fibers of the efferent

vagus nerve and the release of acetylcholine at the synapses. Together with the inflammation-activated sensory nerve fibers of the vagus nerve (discussed below) this forms the so-called 'inflammatory reflex'. This is a rapid mechanism by which inflammatory signals reach the brain; the brain responds with a rapid anti-inflammatory action through cholinergic nerve fibers [88].

Acetylcholine attenuates the release of proinflammatory cytokines (TNF, IL-1 $\beta$ , IL-6, and IL-18) but not the anti-inflammatory cytokine IL-10, in lipopolysaccharide-stimulated human macrophage cultures through the post-transcriptional suppression of protein synthesis. This effect seems, at least in part, to be independent of the HPA axis, because direct electrical stimulation of the peripheral vagus nerve does not stimulate the HPA axis but decreases hepatic lipopolysaccharide-stimulated TNF synthesis and the development of shock during lethal endotoxemia [89].

#### *Peripheral nervous system*

The peripheral nervous system regulates immunity locally, at sites of inflammation, through neuropeptides such as substance P, peripherally released CRH, and vasoactive intestinal polypeptide. These molecules are released from nerve endings or synapses, or they may be synthesized and released by immune cells and have immunomodulatory and generally proinflammatory effects [90–92].

#### *Neuropeptides*

The HPA axis is also subject to regulation by both neurotransmitters and neuropeptides from within the CNS. CRH is positively regulated by serotonergic [93–95], cholinergic [96,97], and catecholaminergic [98] systems. Other neuropeptides, such as  $\gamma$ -aminobutyric acid/benzodiazepines (GABA/BZD) have been shown to inhibit the serotonin-induced secretion of CRH [99].

### **Regulation of the CNS by the immune system**

#### **Cytokines**

Cytokines are important factors connecting and modulating the immune and neuroendocrine systems. Cytokines and their receptors are expressed in the neuroendocrine system and exert their effects both centrally and peripherally [100–102].

Systemic cytokines can affect the brain through several mechanisms, including active transport across the blood–brain barrier [103], through leaky areas in the blood–brain barrier in the circumventricular organs [104] or through the activation of neural pathways such as the vagal nerve [105]. The blood–brain barrier is absent or imperfect in several small areas of the brain, the so-called circumventricular organs, which are located at various sites within the walls of the cerebral ventricles. These include the median eminence, the organum vasculosum of

the laminae terminalis (OVLT), the subfornical organ, the choroid plexus, the neural lobe of the pituitary, and the area postrema. In addition, in the presence of inflammation, the permeability of the blood–brain barrier might be generally altered [106–108]. Moreover, circulating IL-1 can interact with IL-1 receptors on endothelial cells of the vasculature and thereby stimulate signaling molecules such as nitric oxide or prostaglandins, which can locally influence neurons [109].

Cytokines signal the brain not only to activate the HPA axis but also to facilitate pain and induce a series of mood and behavioral responses generally termed sickness behavior [110,111]. Cytokines, such as IL-1, IL-6, and TNF- $\alpha$ , are also produced in the brain [112–114]. Thus, these brain-derived cytokines can stimulate the HPA axis. For example, IL-1 stimulates the expression of the gene encoding CRH and thereby the release of the hormone from the hypothalamus [115], the release of AVP from the hypothalamus [116], and the release of ACTH from the anterior pituitary [117]. IL-2 stimulates AVP secretion from the hypothalamus [118]. IL-6 [119] and TNF- $\alpha$  [120] also stimulate ACTH secretion. In chronic inflammation there seems to be a shift from CRH-driven to AVP-driven HPA axis response [121].

However, in contrast to these effects of peripheral cytokines on neuroendocrine responses in the CNS, cytokines produced within the brain by resident glia or invading immune cells act more like growth factors protecting from or enhancing neuronal cell death. Cytokines might therefore have a pathological consequence, because cytokine-mediated neuronal cell death is thought to be important in several neurodegenerative diseases such as neuroAIDS, Alzheimer's disease, multiple sclerosis, stroke, and nerve trauma [100–102]. In contrast, activated immune cells and cytokines might also protect neuronal survival after trauma and contribute to neural repair [122].

#### **Vagus nerve**

The vagus nerve is involved in signaling of the CNS to the immune system. The vagus innervates most visceral structures such as the lung and the gastrointestinal tract, where there may be frequent contact with pathogens. Immune stimuli activate vagal sensory neurons, possibly after binding to receptors in cells in paraganglial structures [123–126]. Administration of endotoxins and IL-1 has been shown to induce Fos expression in the vagal sensory ganglia, and vagotomy abolishes this early activation gene response [124–126]. Vagal afferents terminate in the dorsal vagal complex of the caudal medulla, which consists of the area postrema, the nucleus of the solitary tract, and the dorsal motor nucleus of the vagus. These nuclei integrate sensory signals and control visceral reflexes, and also relay visceral sensory information to the

central autonomic network [127]. Subdiaphragmatic vagotomy inhibits activation of the paraventricular nucleus and subsequent secretion of ACTH in response to lipopolysaccharides and IL-1 [128,129].

### Correlation between blunted HPA axis and disease

A blunted HPA axis has been associated with increased susceptibility to autoimmune/inflammatory disease in a variety of animal models and human studies. In general, at the baseline the HPA axis parameters do not differ in individuals susceptible and resistant to inflammatory disease. However, differences become apparent with stimulation of the axis.

#### Animal models

A blunted HPA axis has been associated with susceptibility to autoimmune/inflammatory diseases in several animal models. These include the Obese strain (OS) chickens, a model for thyroiditis [130]; MRL mice, which develop lupus [131]; and Lewis (LEW/N) rats. A region on rat chromosome 10 that links to the innate carrageenan inflammation [132] is syntenic with a region on human chromosome 17 that is known to link to susceptibility to a variety of autoimmune diseases [133] and is also syntenic with one of the 20 different regions on 15 different chromosomes shown to link to inflammatory arthritis in other linkage studies [134–136]. Several candidate genes within the rat chromosome 10 linkage region are known to have a role in hypothalamic CRH regulation as well as inflammation, including the CRH R1 receptor, angiotensin-converting enzyme, and STAT3 and STAT5a/5b [132]. However, these candidate genes either show no mutation in the coding region and no differences in regulation between susceptible and resistant strains, or show a mutation in the coding region that does not seem to have a role in expression of the inflammatory trait [137]. As in most complex illnesses and traits, the genotypic contribution to variance in the trait is small: about 35%, which is consistent with such multigenic and polygenic conditions.

Inbred rat strains provide a genetically uniform system that can be systemically manipulated to test the role of neuroendocrine regulation of various aspects of immunity. Lewis (LEW/N) rats are highly susceptible to the development of a wide range of autoimmune diseases in response to a variety of proinflammatory/antigenic stimuli. Fischer (F344/N) rats are relatively resistant to development of these illnesses after exposure to the same dose of antigens or proinflammatory stimuli. These two strains also show related differences in HPA axis responsiveness. The inflammatory-susceptible LEW/N rats exhibit a blunted HPA axis response, compared with inflammatory-resistant F344/N rats with an exaggerated HPA axis response [138–140]. Differences in the expression of hypothalamic CRH [141], pro-opiomelanocortin, corticosterone-binding

globulin [142] and glucocorticoid expression and activation [143,144] have been shown in these two rat strains.

Disruptions of the HPA axis in inflammatory resistant animals, through genetic, surgical, or pharmacological interventions, have been shown to be associated with enhanced susceptibility to, or increased severity of, inflammatory disease [139,145–148]. Reconstitution of the HPA axis in these inflammatory-susceptible animals, either pharmacologically with glucocorticoids or surgically by intracerebral fetal hypothalamic tissue transplantation, has been shown to attenuate inflammatory disease [139,149].

#### Animal models of arthritis

Several animal models exist for RA in rodents. Lewis rats develop arthritis in response to streptococcal cell walls [138,139], heterologous (but not homologous) type II collagen in incomplete Freund's adjuvant (IFA) [150], and various adjuvant oils – including mycobacteria (MTB-AIA) [109], pristine [151], and avridine, but not IFA alone [152]. Inbred dark Agouti (DA) rats develop arthritis in response to heterologous and homologous type II collagen in IFA [153–156], cartilage oligomeric matrix protein [109], MTB-AIA [152], pristine, avridine [157], and ovalbumin-induced arthritis. DBA mice develop arthritis in response to type II collagen in complete Freund's adjuvant [158,159]. For specific reviews on animal models for RA, refer to reviews by Morand and Leech [160] and Joe and Wilder [161].

A premonitory blunting of normal diurnal corticosterone levels in both Lewis and DA rats has been shown in animals susceptible to experimentally induced arthritis [162]. In adjuvant-induced arthritis, chronic activation of the HPA axis is seen 7–21 days after adjuvant injection, together with loss of circadian rhythm [163]. This chronic activation of the HPA axis was shown to be due to increased corticosterone secretion due to an increase in the pulse frequency of secretion in adjuvant-induced arthritis [164]. During this chronic activation of the HPA axis, rats with adjuvant-induced arthritis are incapable of mounting an HPA axis response to acute stress (such as noise) but are still able to respond to an acute immunological stress [165]. Adrenalectomy or glucocorticoid receptor blockade exacerbates the disease state and results in death or disease expression in surviving animals [139,166,167]. It has been suggested that mortality from such shock-like responses is due to the increased cytokine production that occurs in adrenalectomized animals exposed to proinflammatory stimuli [166,168].

In addition to the role of HPA axis dysregulation, a dual role for the sympathetic nervous system in animal models of RA has been suggested. Activation of  $\beta$ -adrenoceptors or A2 receptors by high concentrations of norepinephrine or adenosine results in increased intracellular concentra-

tions of cAMP and anti-inflammatory responses, whereas activation of  $\alpha_2$ -adrenoceptors and A1 receptors by low concentrations of norepinephrine or adenosine results in proinflammatory events, such as the release of substance P [169]. Consistent with this is the observation that  $\beta$ -adrenergic agonists attenuate RA in animal models [170,171]. Rolipram, an inhibitor of the PDE-IV phosphodiesterase, an enzyme that degrades cAMP, has been shown reduce inflammation in several rodent models [170,172–174]. The effects of rolipram have also been suggested to be mediated by catecholamines [175] or by the stimulation of the adrenal and HPA axis [176,177]. There is also a loss of sympathetic nerve fibers during adjuvant-induced arthritis [178]. The peripheral natural anti-inflammatory agent, vasoactive intestinal peptide, has been shown to reduce the severity of arthritis symptoms in the mouse model of collagen-induced arthritis [179,180].

In addition to the sympathetic nervous system, the parasympathetic nervous system is also important in immune regulation. A role of the cholinergic parasympathetic nervous system in an animal model of RA was suggested because direct stimulation of the vagus nerve was shown to inhibit the inflammatory response [181]. Impairment of the cholinergic regulation also exacerbates an inflammatory response to adjuvant in the knees of rats [182].

#### *Summary of animal model studies and therapeutic correlates*

Thus, animal models for arthritis have shown a role for the HPA axis, sympathetic, parasympathetic, and peripheral nervous systems. They have shown the necessity of endogenous glucocorticoids in regulating the immune response after exposure to antigenic or proinflammatory stimuli, and severity of inflammatory/autoimmune disease or mortality after removal of these endogenous glucocorticoids by adrenalectomy or GR blockade. Animal models have enabled genetic linkage studies, which have demonstrated the multigenic, polygenic nature of such inflammatory diseases with genes on more than 20 different chromosomes being linked to inflammatory arthritis. Finally, animal models have shown defects in the sympathetic and parasympathetic nervous system in arthritis. These findings have led to the development and testing of novel therapies (see the penultimate section, 'New therapies').

#### **Human studies**

In humans, ovine CRH, hypoglycemia, or psychological stresses have been used to stimulate the HPA axis. In such studies, blunted HPA axis responses have been shown in a variety of autoimmune/inflammatory or allergic diseases such as allergic asthma and atopic dermatitis [183–186], fibromyalgia [187–190], chronic fatigue syndrome [188,189,191,192], Sjögren's syndrome [2,193], systemic lupus erythematosus [2,194], multiple sclerosis [195,196], and RA [1,197–202]. Conversely, chronic

stimulation of the stress hormone response, such as experienced by caregivers of Alzheimer's patients, students taking examinations, couples during marital conflict, and Army Rangers undergoing extreme exercise, results in chronically elevated glucocorticoids, causing a shift from Th1 to Th2 immune response, and is associated with an enhanced susceptibility to viral infection, prolonged wound healing, or decreased antibody production in response to vaccination [203–206].

#### *Rheumatoid arthritis*

RA is more common in women than in men, with onset usually occurring between menarche and menopause [207,208]. However, the incidence of RA becomes much less gender specific in elderly men and women [207]. In women, RA activity is reduced during pregnancy but returns postpartum, suggesting a role for the hormones that are fluctuating at this time (cortisol, progesterone, and estrogen) in the regulation of RA activity [33,209–212].

Glucocorticoids have been used for therapy for RA since the 1950s [213,214], when the Nobel Prize was awarded for the discovery of this effect. They are effective because of their anti-inflammatory actions in the suppression of many inflammatory immune molecules and cells. In patients with RA, administration of glucocorticoids decreases the release of TNF- $\alpha$  into the bloodstream [215]; however, there are many debilitating side effects including weight gain, bone loss, and mood changes.

*The HPA axis in RA.* Human clinical studies are much more difficult to perform than animal models. However, some evidence exists supporting the involvement of the HPA axis in RA. Alterations in the diurnal rhythm of cortisol secretion have been documented in patients with RA [216,217]. An association between the cortisol diurnal cycle and diurnal variations in RA activity has been made, although it still remains to be determined whether this is cause or effect [218]. One of the most pertinent observations for the regulation of RA by endogenous cortisol comes from a study in which RA was exacerbated by inhibition of adrenal glucocorticoid synthesis by the  $11\beta$ -hydroxylase inhibitor metyrapone [219].

Several studies have looked for abnormalities in the HPA axis of patients with RA. In general, these point to an inappropriately low cortisol response. Subtle changes in cortisol responses have been reported in response to insulin-induced hypoglycemia [201]. However, another study, also using insulin-induced hypoglycemia, described a blunted HPA axis in patients with RA [220]. In one study, lower cortisol responses to surgical stress were shown in patients with RA compared with healthy controls and an inflammatory control group, whereas normal responses of ACTH and cortisol to ovine CRH were seen in the same patients [198]; however, these results are

complicated by the steroid therapy that these patients were taking. Other studies have shown increased peripheral ACTH levels in patients with RA without increases in cortisol [221–223], whereas other studies have shown a normal HPA axis in patients with RA [200]. Some studies have suggested that, given the inflammatory state of RA, a normal cortisol response is in fact indicative of an under-responsive HPA axis [224,225]. It has become generally accepted that lower than normal cortisol responses to stimulation are characteristic of RA [169,197,201,216,221, 223,225–227]. Most recently Straub and colleagues have shown that the most sensitive indicator of blunted HPA axis responsiveness in early, untreated PA is an inappropriately low ratio of cortisol to IL-6 in these subjects [228].

Such defects in the stress response system are in agreement with patients' descriptions of RA 'flare up' during stress [229], which are likely to be caused by imbalances of the neuroendocrine and immune systems induced by psychosocial stressors [230]. It is worth noting that psychosocial stress is important in RA disease activity [231–233]. However, this will not be reviewed here and readers are referred to reviews by Walker and colleagues [234] and Herrmann and colleagues [235].

*Glucocorticoid receptors in RA.* Quantification of the numbers of GRs by ligand binding studies has produced contrasting results. In one study, normal or even slightly elevated numbers of GRs in peripheral blood mononuclear cells (PBMCs) were seen in untreated patients with RA [236], whereas other studies have shown a decrease in the number of GR molecules in the lymphocytes of patients with RA in comparison with controls [237]. Others have also shown a downregulation of GR during early RA [238,239]. Recently, Neeck and colleagues, evaluating the expression of GR by immunoblot analysis, showed a higher expression of GR in untreated patients with RA in comparison with controls but a decreased GR expression in glucocorticoid-treated patients with RA in comparison with controls [202]. This has been confirmed by others [240]. A polymorphism in the 5' untranslated region of exon 9 of the GR gene, which is associated with enhanced stability of the dominant-negative splice variant, GR $\beta$ , has been shown in patients with RA [31]. Enhanced expression of GR $\beta$  has also been shown in the PBMCs of steroid-resistant patients with RA [241]. A polymorphism in the CRH gene has also been described as a susceptibility marker for RA in an indigenous South African population [242–244].

*Other hormone measures in RA.* Patients with RA also show abnormalities in other endocrine hormones. Like other inflammatory diseases, they have been shown to have low serum androgen levels but unchanged serum estrogen levels [245–252]. Growth retardation is a phenomenon seen in juvenile RA [253], and an impairment of the GH axis has been shown in patients with active and

remitted RA [220,225]. An increased expression of IGF-1-binding protein, resulting in a decreased concentration of free IGF-1, was also observed in patients with RA [254–256]. However, another study has attributed this difference in IGF-binding proteins to physical activity rather than inflammation [257].

An association between thyroid and rheumatoid disorders, such as RA and autoimmune thyroiditis, has been known for many years [258] although little is known about the thyroid involvement in RA. One study has shown that patients with RA have increased free T<sub>4</sub> levels, and consequently lower free T<sub>3</sub>, than normal controls [259], although other studies were unable to confirm low T<sub>3</sub> levels in patients with RA [260]. However, a higher incidence of thyroid dysfunction has been shown in women with RA [261,262].

*Sympathetic nervous system in RA.* The extent to which the sympathetic nervous system is involved in human RA is unclear. In one study, a decreased number of  $\beta$ -adrenoceptors in the PBMCs and synovial lymphocytes of patients with RA was described, suggesting a shift to a proinflammatory state [263,264]. Regional blockade of the sympathetic nervous system in patients with RA has been described to attenuate some of features of RA [265]. Others were unable to confirm this result but found defects in other aspects of this signaling pathway [266]. However, as in animal models,  $\beta$ -adrenergic agonists have been shown to attenuate RA in humans [267].

For the sympathetic nervous system to be able to modulate inflammation in RA it is necessary for the synovial tissue to be innervated by sympathetic nerve fibers. In patients with long-term RA there is a significant decrease in sympathetic nerve fibers but an increase in substance P-producing sensory nerve fibers [268,269], suggesting a decrease in the anti-inflammatory effects of the sympathetic nervous system and an increase in the proinflammatory effects of the peripheral nervous system.

#### **Peripheral neuropeptides in RA**

Consistent with these changes in peripheral and autonomic innervation in RA are findings of altered peripheral neuropeptides in RA. proinflammatory CRH is locally secreted in the synovium of patients with RA and at a lower level than in osteoarthritis [199,270]. Human T lymphocytes have been shown to synthesize and secrete CRH [271]. Inflammation in chronic RA has also been shown to be attenuated with the  $\mu$ -opioid-specific agonist morphine [272]. In animal models, infusion of substance P into the knee exacerbated RA [273].

#### **Summary of hormonal findings in RA**

Studies of patients with RA are difficult to interpret and some might be tainted by a prior use of glucocorticoids

used generally in the treatment of RA. However, these studies have generally shown a defect in cortisol secretion after HPA axis stimulation, decreased androgen levels, a blunted GH response, and dysregulation of the thyroid response. In addition there is evidence of an impaired response of the sympathetic nervous system and enhanced levels of the peripheral proinflammatory neuropeptides CRH and substance P. In some cases, a decrease in the number of GRs has been shown in RA, or reduced glucocorticoid sensitivity has been observed due to GR $\beta$  overexpression, which is consistent with relative glucocorticoid resistance in some patients. Furthermore, a polymorphism of the GR $\beta$  associated with the enhanced stability of that receptor has also been shown in RA [31]. It still remains to be fully determined whether these alterations in neuroendocrine pathways and receptors are involved in the pathogenesis of RA or whether they are a result of the inflammatory status of the disease.

### New therapies

On the basis of the principles described above, new therapeutic modalities for inflammatory diseases are being investigated. For example, recent studies have indicated a potential therapeutic role for CRH type 1-specific receptor antagonist (antalarmin) in an animal model of adjuvant-induced arthritis [274],  $\beta$ -adrenergic agonists in both animal models of RA and in a human study [170,171,267], the  $\mu$ -opioid-specific agonist morphine in chronic RA [272], and the phosphodiesterase inhibitor rolipram in several rodent models for RA [170,172–174]. Androgen replacement, DHEA therapy, could be potentially therapeutic in RA, particularly in men [275], and has proved beneficial for inflammatory diseases [276].

### Conclusion

The CNS and immune system communicate through multiple neuroanatomical and hormonal routes and molecular mechanisms. The interactions between the neuroendocrine and immune systems provide a finely tuned regulatory system required for health. Disturbances at any level can lead to changes in susceptibility to, and severity of, autoimmune/inflammatory disease. A thorough understanding of the mechanisms by which the CNS and immune systems communicate at all levels will provide many new insights into the bidirectional regulation of these systems and the disruptions in these communications that lead to disease, and ultimately will inform new avenues of therapy for autoimmune/inflammatory disease. Animal models of arthritis have shown changes in both the HPA axis and the sympathetic nervous system during inflammation. More importantly, these models have demonstrated the importance of endogenous glucocorticoids in the regulation of immunity and the prevention of lethality from an uncontrolled immune response. Furthermore, in both animals and humans, RA is associated with dysregulation of the HPA, HPT, HPG, and GH axes. There

is also evidence of an impaired regulation of immunity by the sympathetic nervous system and of defects in glucocorticoid signaling. These principles are now being used to test novel therapies for RA based on addressing and correcting the dysregulation of these neural and neuroendocrine pathways.

### Competing interests

None declared.

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