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FEATURE REVIEW

Brain-immune interactions and disease susceptibility

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Many studies have established the routes by which the immune and central nervous (CNS) systems communicate. This network of connections permits the CNS to regulate the immune system through both neuroendocrine and neuronal pathways. In turn, the immune system signals the CNS through neuronal and humoral routes, via immune mediators and cytokines. This regulatory system between the immune system and CNS plays an important role in susceptibility and resistance to autoimmune, inflammatory, infectious and allergic diseases. This review focuses on the regulation of the immune system via the neuroendocrine system, and underlines the link between neuroendocrine dysregulation and development of major depressive disorders, autoimmune diseases and osteoporosis.
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The immune, endocrine and central nervous systems (CNS) communicate at multiple levels.[1,2] This network of connections permits the CNS to regulate the immune system through both neuroendocrine and neuronal pathways, and in turn allows the immune system to signal the brain through neural and humoral routes. Much recent work has elucidated the important role of cytokine signaling the brain in sickness behavior and depressive symptomatology,[3–7] the importance of autonomic reflex pathways in shock, inflammation and immunity,[8–13] and the role of peripheral nervous system neuropeptides in inflammation.[14–19] This review, however, will focus on neuroendocrine regulation of immunity and dysregulation of these pathways in autoimmune/inflammatory disease and associated major depressive disorder (MDD). We will first review physiological and molecular regulation of immune responses by the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid (HPT), hypothalamic-pituitary-gonadal (HPG) axes and then discuss dysregulations of these pathways in MDD, autoimmune/inflammatory diseases and osteoporosis. These pathophysiological associations may account in part for the recognized association between MDD and autoimmune diseases, as well as between MDD and osteoporosis.

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Neuroendocrine regulation of immune system

Several neuroendocrine pathways regulate the immune system, including hormones of the HPA axis, the HPG, HPT and the hypothalamic-growth-hormone axes (Figure 1).

HPA axis

Glucocorticoids are the main effectors of the HPA axis and it is through the action of these molecules that the HPA axis regulates a wide variety of immune functions affecting cell trafficking, migration, maturation and differentiation.[20,21] The modulation of the immune system by glucocorticoids occurs through cytoplasmic receptors, the glucocorticoid receptors (GRs) (NR3C1).[22] Corticosteroids suppress, enhance and modulate immune responses. The presence of this regulatory system plays an important role in susceptibility and resistance to autoimmune, inflammatory, infectious and allergic diseases.[1] Prolonged HPA axis activation and associated prolonged elevation of glucocorticoids, as occurs in chronic stress, exerts an inhibitory effect on immune function and can predispose the host to infection. In contrast, in acute stress, elevations of glucocorticoids enhance certain immune responses, such as delayed type hypersensitivity.[23] Furthermore, inappropriately low glucocorticoid responses can predispose to autoimmune and inflammatory diseases such as, inflammatory arthritis, systemic lupus erythematosus, allergic asthma and atopic dermatitis.[24,25] Glucocorticoids also alter T-helper 1(Th1)/T-helper 2 (Th2) balance, enhancing the production of Th2 cytokines (humoral immunity) and inhibiting the production of Th1 cytokines (cellular immunity). This produces a shift from a proinflammatory cytokine pattern, with

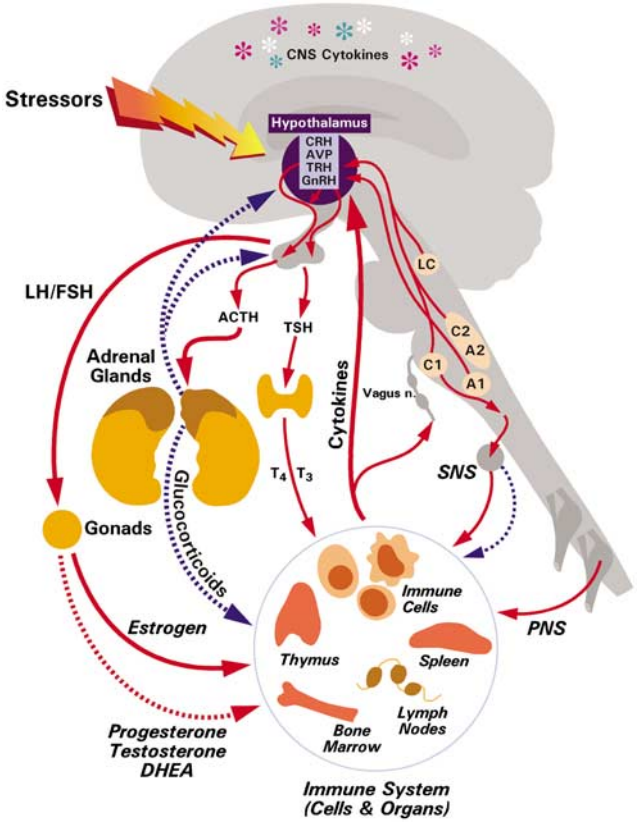

Figure 1 Schematic illustration of neural immune connections. The figure shows immune signaling of the CNS via systemic routes and the vagus nerve (Vagus n.) and CNS regulation of immunity via the hypothalamic–pituitary–adrenal (HPA), hypothalamic–pituitary–thyroid (HPT) and hypothalamic–pituitary–gonadal (HPG) axes, and the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). Cytokine expression within the CNS is represented by asterisks within the brain. Dotted lines represent negative regulatory pathways, and solid lines represent positive regulatory pathways. CRH, corticotrophin-releasing hormone; AVP, arginine vasopressin; TRH, thyrotropin-releasing hormone; GnRH, gonadotropin-releasing hormone; ACTH, adrenocorticotrophin hormone; TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine; LH, luteinizing hormone; FSH, follicle-stimulating hormone; SNS, sympathetic nervous system; PNS, parasympathetic nervous system; LC, locus ceruleus; A1, C1, A2, C2, brainstem adrenergic nuclei.

increased interleukin (IL)-1 and tumor necrosis factor (TNF)-α, to an anti-inflammatory cytokine pattern with increased IL-10 and IL-4.[26] Moreover, glucocorticoids regulate the expression of many proinflammatory genes encoding cytokines, adhesion molecules, chemoattractants, inflammatory mediators and other inflammatory molecules.[1,21,27] Although initially glucocorticoids, which were tested in pharmacological concentrations, were thought to be primarily immunosuppressive,[28,29] more recent studies using physiological concentrations and preparations show that glucocorticoids play an important physiological role in immunomodulation and immunoenhancement.[23,30] This dual dose-related effect of glucocorticoids has been shown in several assays of immune function, including: delayed-type hypersensitivity (DTH) reactions;[23] immunoglobulin synthesis and secretion by human peripheral lymphocytes;[31] thymocyte proliferation and apoptosis;[32] T-cell mitogenes,[33] macrophage phagocytosis;[34] and cytokine production and receptor expression.[35]

HPT axis

The HPT axis also modulates many immune functions. Hormones of the HPT axis, including thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4) have been shown to have direct stimulatory effects on immune cells.[36–38] The effect of thyroid hormones on the immune system can also result from the interaction between the HPT and HPA axes. In rats, hypothyroid states have been shown to reduce the HPA axis responses, while hyperthyroidism increases HPA axis responses.[39]

HPG axis

The HPG axis modulates the immune system both directly through sex hormone effects on immune cells and indirectly through interactions with the HPA axis. In general, physiological concentrations of estrogen enhance immune responses,[40,41] whereas physiological concentrations of progesterone and of androgens, such as testosterone and dehydroepiandrosterone (DHEA), suppress the immune response.[41,42] Estrogen can also trigger different responses in the immune system depending on its concentration. Thus, physiological low doses of estrogens enhance Th1 cytokines, while high doses of estrogen enhance Th2 cytokines.[42]

This pattern of sex steroid action on the immune system is consistent with epidemiological data showing that women have a greater risk of developing many autoimmune/inflammatory diseases, such as multiple sclerosis, rheumatoid arthritis (RA) and systemic lupus erythematosus.[43] It has also been shown that young women exposed to intensive stress situations, with low plasma of dehydroepiandrosterone sulfate (DHEA-S), and a recent use of contraceptive pills are most at risk for onset of autoimmune disease.[42,44,45]

DHEA and its metabolite DHEA-S are the most plentiful adrenal corticosteroids in humans, yet their physiological roles remain uncertain.[46] Animals studies in rodents have generally found memory-enhancing effects,[47] antidepressant-like effects,[48] antianxiety effect,[49] and neurotrophic effects.[50,51] In humans, levels in circulation decline with age,[52] with chronic stress and medical illness.[53] DHEA and DHEA-S may physiologically buffer the effects of excessive glucocorticoid exposure.[46] Thus, decreasing ratios of DHEA and DHEA-S to cortisol, especially in hypercortisolemic states such as aging, depression and others conditions, may enhance cortisol effects.[53]

Animal models have also shown the importance of estrogen in *in vivo* modulation of the immune system.[54,55] Estrogen receptors (ERs) (α and β) are important for thymus development and atrophy in a gender-specific manner in knockout mouse models.[56] An intriguing explanation for the peripubertal increase in incidence of autoimmune disease in females is suggested by studies in mice showing a gradual change during development in ratios of GRs to ERs in immune cells.[55] Thus, from birth to immediately prepuberty, murine B cells primarily express GRs, while after puberty ERs are expressed in greater amounts. The shift from a preponderance of receptors for immunosuppressive glucocorticoids prior to puberty to a preponderance of receptors for generally immunoenhancing estrogen postpuberty could hypothetically contribute to a shift to greater postpubertal autoimmunity and inflammation in females of child-bearing years.

The HPG axis is also regulated by the HPA axis, which inhibits reproduction in men and women. Glucocorticoids inhibit hypothalamic luteinizing hormone releasing hormone (LHRH), anterior pituitary gonadotrophic hormones (luteinizing hormone and follicle stimulating hormone), ovarian estradiol and testicular testosterone. Moreover, corticosteroids enhance resistance to estradiol and testosterone.[57] The LHRH neurons of the arcurate nucleus are also directly inhibited by CRH[58,59] or by β-endorphin.[60] Thus, interactions between the HPA and HPG axis, as might occur during stress, could also contribute to alterations in autoimmune/inflammatory susceptibility or disease expression.

Neuroendocrine dysregulations in patients with MDD

HPA axis, glucocorticoids, GR

For many years HPA axis dysfunction was considered a core feature of MDD, as determined by a number of measures including basal cortisol, dexamethasone suppression test (DST), basal and stimulated plasma cortisol and ACTH responses, and dexamethasone-CRH stimulation test.[61–68] Elevations of plasma cortisol in depression are consistent with, although not proportional to, increases in ACTH levels.[65] The DST and the dexamethasone-CRH stimulation test have shown impaired glucocorticoid responsiveness in patients with MDD. Nonsuppression of cortisol on the DST or dexamethasone-CRH stimulation test vary from approximately 25 to 80% in MDD patients, with high rates found in melancholic subtype of depression and older patients.[69,70] Many other HPA axis alterations have been reported in patients with MDD, including disturbances in the temporal pattern of cortisol secretion,[65,67,71–75] elevated levels of CRH in cerebrospinal fluid (CSF),[76–79] enlarged pituitary glands,[80,81] and enlarged adrenal glands.[82–84] Some *post-mortem* studies in depressive patients have also reported increased numbers of paraventricular nucleus CRH neurons and CRH mRNA expression in post-mortem hypothalamic tissue,[85,86] and decreased density of CRH receptors in the prefrontal cortex.[87] After clinical remission of depression, some studies have reported normalization in the DST test,[88,89] of CSF CRH levels,[90–92] of the CRH stimulation test,[93] and in adrenal gland size.[84] Some alterations in the HPA axis in a subset of patients with MDD seem to be state dependent, since HPA axis responses return to normality after remission of the depressive symptoms. However, in a subset of patients with MDD, cortisol alterations persist and may constitute a biological risk for relapse.[94,95]

Divergent results in HPA axis measures in mood disorders may be due to some variability of clinical characteristics such as subtypes of depression (endogenous *vs* psychoses *vs* atypical),[75,96,97] chronicity of illness,[98] the presence of anxiety symptoms,[68,99] recurrence of depressive episodes,[100] severity of symptoms,[96,101] age-dependent[102] and sampling factors (in-patients *vs* outpatients).[67,75,103–106]

HPA axis hyperactivity may play an important role in the pathogenesis of major depression. This hyperactivity is believed to be secondary to hypersecretion of CRH. Increased levels of CRH in the hypothalamus are thought to be related, in part, to altered feedback inhibition by circulating glucocorticoid hormones.[107] Glucocorticoid hormones potently negatively regulate the HPA axis activity, including synthesis and release of CRH, through binding to their receptors.[108] There are two receptors for glucocorticoids, the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR).[1] At low levels, endogenous corticosteroids bind preferentially to MR, and only at high levels, that is, during stress, is GR occupied.[109] GR has also a high affinity to dexamethasone. Since patients with depression have impaired HPA negative feedback in the context of elevated levels of cortisol, several studies have examined the number and or function of GR in patients with MDD.[107,110] In general, studies have found a lack of alteration in number of GR (using whole cell assay), but studies have also found decreased GR numbers in the cellular cystolic fraction.[111–113] These studies suggest that the GR changes in depression are likely secondary to nuclear compartmentalization of the GR, or nonassociation of the GR with the chaperon protein complex.[107] *In vitro* studies examined the GR function in patients with MDD and controls have found that lymphocytes from DEX nonsupressor subjects were more resistant to the inhibitory effect of DEX administered *in vitro*.[107] An inverse correlation between plasma cortisol concentration and DEX-induced inhibition of the proliferative response has also been shown, suggesting a link between hypercortisolemia and resistance to *in vitro* GR-mediated responses.[114] Conversely, GR resistance in the absence of elevated cortisol has also been demonstrated in patients with depression.[115] Some other *in vivo* studies provide evidence of glucocorticoid resistance in MDD, showing a reduced vasoconstrictor response to topical application of beclomethasone[116] and decreased sensitivity of

plasma sialytransferase levels to cortisol.[113] A possible molecular mechanism of GR resistance in MDD is via ligand-independent mechanisms.[107] GR functions can be influenced by many nonsteroid molecules including proinflammatory cytokines, such as IL-1[4,117] and proteins in the cAMP cascade including protein kinase A (PKA).[118] It has been recently shown *in vitro* that proinflammatory cytokines reduce the function of the GR by inhibiting the activation and translocation of the GR from the cytoplasm to the nucleus of cells.[4,117] Other possible mechanisms implicated in acquired steroid resistance are the rate of GRα/GRβ,[119] and changes in the GR transduction system (eg alteredAP-1 and NF-κB expression, heat shock protein.[120] In summary, patients with MDD exhibit impaired HPA negative feedback in the context of elevated circulating levels of cortisol. Indeed, altered GR signaling has been proposed as one possible major factor in the pathogenesis of the disorder.[70,107]

HPT axis, thyroid hormones

Thyroid dysfunction is an important secondary cause of depression. Hypothyroidism is considered a potentially reversible cause of depression, and both disorders have overlap symptoms that may complicate studies attempting to clarify the relationship between them.[121] The prevalence of depressive symptoms in hypothyroidism is near to 50% whereas in hyperthyroidism it reaches up to 28% of cases.[122] Clinical depression occurs in more than 40% of patients with hypothyroidism.[123]

Although some alterations in the HPT axis have been found in patients with MDD,[124–128] most depressed patients appear to have no alterations of HPT hormones[129–134] and overt thyroid disease is rare among depressed in patients.[134] Taken together, studies of the HPT in MDD show evidence of altered activity of the HPT axis in some cases of depression, including (1) increased total and/or free T4, without T3 alterations;[128] (2) reduction in serum T4 concentration during a wide range of somatic treatments;[128,135] (3) increased TSH in 2–2.6% of patients;[125,129] (4) excessive response of TSH to the TRH challenge test in 10% and a blunted response in 25% of the patients;[135–137] and (5) high levels of antithyroid antibodies.[124,128,138,139]

Some speculate that the mechanism of T4 increase with blunted TSH response to TRH reflects glucocorticoid activation of hypothalamic neurons. Bruhn *et al*[140] found that exposure of hypothalamic cultured fetal rats to glucocorticoids increased the genetic expression of TRH. However, some patients with depression show evidence of thyroid insufficiency with evidence of autoimmune thyroid disease without the presence of systemic hypothyroidism. This could be secondary to decreased conversion of T4 into T3 in the brain due to cortisol inhibition of type II deiodinase, and/or decreased T4 transport across the blood–brain barrier.[141] Another hypothesis for the HPT axis alterations in patients with depression suggest that changes could be related to alterations in serotonin and/or noradrenalin in the brain.[141,142]

Neuroendocrine dysregulations in autoimmune diseases

Evidence for the involvement of the HPA axis in autoimmune and inflammatory disease has been reported in many animal models, across species, strains and diseases, in rats, chickens as well as in human studies.[25] A blunted HPA axis has been associated with susceptibility to autoimmune and inflammatory disease in chickens (a model for autoimmune thyroiditis),[143] certain mouse lupus models,[144,145] and in the inbred rat strains[146,147] (Table 1).

The association between blunted HPA axis and autoimmune, inflammatory and allergic diseases has been reported in human illness including RA,[148–153] Sjogren's syndrome,[154] systemic lupus erythematosus,[155] multiple sclerosis,[156,157] allergic asthma and atopic skin disease.[158–160] (Table 1). In addition, although there is debate regarding the precise pathophysiological classification of these syndromes, a blunted HPA axis has also been show in fibromyalgia,[161–164] irritable bowel syndrome[165,166] and chronic fatigue syndrome.[163,167–171]

Disruption of the HPA axis or glucocorticoid response at different levels can predispose to enhanced susceptibility to autoimmune and inflammatory disease. Thus, low circulating glucocorticoids or abnormalities of GRs leading to glucocorticoid resistance can reduce glucocorticoid inhibition of immunity and increase inflammatory susceptibility.[172,173] Low circulating cortisol can result from alterations in

Table 1 Inflammatory/autoimmune diseases correlated with a dysfunctional HPA axis in humans and in some animal models

Species	*Inflammatory/autoimmune disease*	*Reference*
Chicken	Thyroiditis	143
Mouse	Systemic lupus erythematosus (SLE)	144, 145
Rat	Arthritis	147, 232–234
	Experimental allergic encephalomyelitis (EAE)	235
	Inflammation	236
Human	Rheumatoid arthritis	148, 149, 151-153, 162, 186 148, 149, 151–153, 162, 186
	Systemic lupus erythematosus (SLE)	155, 162
	Sjögren's syndrome	154, 162
	Dermatitis	158–160
	Multiple sclerosis	156, 157

Table 2 Glucocorticoid resistance, GR mutations and impaired signaling in autoimmune/inflammatory disease

Disease	*Molecular abnormality*	*References*
Rheumatoid arthritis	GRβ polymorphism	172
SLE	Increased MDR	237
	GR mutation	238
SLE nephritis	GR mutation, decreased GR number	239
Crohn's disease	Increased CBG	240
Asthma	Increased GRβ	241
	Decreased glucocorticoid sensitivity	242

the hypothalamus, pituitary or adrenals, with changes in the secretion of CRH, ACTH or cortisol, respectively. Changes in the levels of expression of cortisol binding globulin (CBG) and 11-β hydroxysteroid dehydrogenase can also influence available free cortisol.[25]

A growing number of reports indicate that relative glucocorticoid resistance from a variety of causes is also associated with enhanced inflammatory susceptibility and autoimmune disease (Table 2). Glucocorticoid resistance may be caused by mutations of the GR, which result in decreased GR number, stability or nuclear translocation of receptors or decreased affinity for the ligand. Other possible causes of glucocorticoid resistance include changes in ratio between activation of GRs and NFκB or AP-1 activity, higher expression of GRβ (an inactive dominant-negative GR), defects in nuclear hormone receptor cofactors, or alterations in concentration of intracellular glucocorticoid transporters.[25] Certain bacterial toxins (specifically the *Bacillus anthracis* lethal toxin) can sensitively and selectively repress the GR and other nuclear hormone receptors,[174] suggesting a mechanism by which glucocorticoid resistance may develop in the context of bacterial infection.

Rheumatoid arthritis

Studies in patients with RA have generally shown blunted cortisol secretion after HPA stimulation and also a loss of cortisol circadian rhythm.[150,153,175] Low levels of DHEA and DHEA-S have been reported in patients with RA and were correlated with early morning low cortisol and high levels of IL-6.[176] Hypersecretion of ACTH without corresponding increased adrenal cortisol production[175,177,178] has also been described in patients with RA. Associations have been reported between the cortisol diurnal cycle and diurnal variations in RA activity,[179] although it is still not clear whether this is a cause or effect of the illness.[180] It has also been shown that RA activity is exacerbated by inhibition of glucocorticoid synthesis by the 11-β hydroxylase inhibitor metyrapone.[181]

There is also some evidence for alterations in GR number and function in patients with RA. Both decreases and increases in GR number have been reported in patients with RA.[182,183] Some studies have shown a downregulation of GR during early RA[184,185] and others a higher expression of GR in untreated RA patients, but a decreased GR expression in glucocorticoid-treated RA patients.[186,187] Reduced glucocorticoid sensitivity due to GRβ overexpression,[149] and a polymorphism of the GRβ associated with the enhanced stability of the receptor, has also been described in patients with RA.[172]

Adrenal steroid secretion is also inadequately low in relation to inflammation (IL-6) in patients with RA,[177,188] suggesting a relative adrenal insufficiency in the setting of a sustained inflammatory process.[42] Cytokines and their receptors are thought to play an important role in the development and maintenance of the inflammatory process in RA.[189] Alterations in the Th1/Th2 balance with elevated Th1 and decreased Th2 cytokines have been reported in patients with RA,[190] and GR affinity is decreased by Th1 and proinflammatory cytokines.[117,191] Thus, the susceptibility and progression of RA are thought to be linked by the presence of host response genes that contribute to exaggerated immune responses, as well as by insufficient HPA axis restraint of cytokine secretion.[24,192,193]

Patients with RA also show abnormalities in other endocrine hormones. Low serum androgen and unchanged estrogen levels have been reported in patients with RA,[194–196] although high estradiol levels have been observed in premenopausal patients with RA with enhanced expression of anticardiolipin (aCL) antibodies.[197] An association between thyroid disorders and RA has also been described,[198] and a higher incidence of thyroid dysfunction has been reported in women with RA.[199,200] Increased levels of free T4 and lower levels of free T3 have also been shown[201] although other studies were unable to confirm low T3 levels in patients with RA.[202]

Association between MDD and RA

An association between RA and depressive symptomatology has long been recognized in the clinical literature,[203] and more recent reports indicate an association between allergy, pollen counts and suicide.[204] The underlying mechanisms for these associations are not fully understood. The relationship between MDD and RA is complex. Anxiety and depressive disorders occur in 20–25% of patients with RA.[205] In contrast with an increased incidence of MDD in RA, a decreased risk of schizophrenia has been reported in patients with RA.[206] The development of psychiatric symptoms in patients with RA may be, at least in part, the result of chronic physical symptoms such as pain and disability.[207,208] RA seems to be associated with clinically significant psychiatric syndromes in patients with the most severe disabling

RA, however, not in mild and moderate RA.[209] However, other psychological, biological and environment factors may be required for development of depressive symptoms in patients with RA. Social stress has been shown to be an important factor associated with depression in patients with RA, independent of the disease state.[207] Neuroendocrine and immunological factors are also important factors that account for the development of both illnesses. Indeed, both RA and depression are associated with alterations in HPA axis, immune function and cytokine production. Excessive secretion of IL-6, haptoglobin and PGE, an increased CD4/CD8 ratio, an overall leukocytosis with a relative neutrophilia, lymphopenia, reduction of NK-cell cytotoxicity and lymphocyte proliferative response to mitogen have all been reported in MDD.[210,211]

MDD and RA share some common dysregulations in both neuroendocrine and proinflammatory cytokine pathways. Moreover, interactions between these pathways could also account for their concurrent dysregulation in these diseases. Indeed, GR resistance can be induced by proinflammatory cytokines[117] and glucocorticoids can alter cytokines production.[117] Thus, MDD may not be simply correlated with or be a consequences of RA severity. Rather, depressive symptoms resulting from an inability to regulate negative affective responses to stress are also thought to contribute to neuroimmune dysregulation in RA.[192,203]

In light of the overlapping dysregulations of the HPA axis and other neuroendocrine axes and associated enhancement of immunity in both RA and MDD, it is possible that underlying neuroendocrine dysregulations may predispose to both these illnesses in the same individual. In this scenario, final disease expression would be dependent on a combination of specific environmental exposures and genetic predispositions.

Neuroendocrine dysregulations in osteoporosis

Osteoporosis is a condition characterized by bone fragility and increased risk of bone fracture.[212] Hypercortisolism, as occurs in Cushing's Syndrome or chronic steroid use, induces osteoporosis. Cortisol-related bone loss is primarily caused by decreased bone formation,[213] rather increased resorption. Hypercortisolism and CRH hypersecretion also lead to inhibition of the reproductive axis and hypogonadism, and decreased activity of GH-insulin-like growth factor 1 (IGF-1) axis.[214] Hypogonadism is considered a risk factor for bone loss in both sexes due to rise of osteoclastic activation triggering increased resorption.[215] The GH/IGF-1 axis is an important enhancer of bone formation.[216] Furthermore, hypercortisolism may affect calcium metabolism, which may trigger secondary hyperparathyroidism,[213] limit the conversion of vitamin D to its active metabolites and impair calcium absorption.[217] Alterations of the HPT axis can also lead to osteoporosis. Hyperthyroidism is accompanied by increased osteoblastic and osteoclastic activity resulting in predominance of bone resorption.[218,219] Raised levels of cytokines (IL-1, IL-6 and TNF) found in patients with hyperthyroidism[220–222] could be one possible factor mediating resorption of bone.[223] Some studies also show the effects of thyroid hormones on bone remodeling *in vitro*, including bone resorption and formation.[224,225] More recently, Abe *et al*[226] have shown that TSH directly inhibits both osteoblastic bone formation and osteoclastic bone resorption.

Association between MDD and osteoporosis

The association between MDD and osteoporosis has been extensively discussed in the literature. A recent review reported that decreased bone mineral density (BMD) is more frequently seen in depressed subjects than in the general population, suggesting that depression is a unrecognized risk factor for osteoporosis.[214] However, a casual link for the association between MDD and osteoporosis remains to be elucidated by prospective studies.

Alterations in endocrine and immunological system, such as hypercortisolism, increased levels of cytokines, particularly interleukin-6 (IL-6), and increased levels of leptin, are possible mechanisms of bone loss in patients with depression.[214] Cytokines including IL-6, IL-1, TNFα and leptin are important local factors that regulate the bone metabolism.[227] IL-6 is implicated in bone turnover and stimulates differentiation and proliferation of osteoclasts.[228] IL-1 and TNFα are also influence in resorption, particularly in high turnover states.[229] Leptin inhibits bone formation through a central mechanism involving a hypothalamic relay.[230,231]

Summary

Numerous neuroendocrine pathways have been shown to regulate immune responses that are dysregulated in autoimmune diseases. In turn immune molecules not only regulate neuroendocrine pathways that are dysregulated in depression but also induce mood alterations and behaviors characteristic of depression. In this review we focus on glucocorticoids, the HPA axis and the thyroid hormone axis in autoimmune disease and MDD. Dysregulations in these neuroendocrine axes at systemic, tissue and receptor levels have been reported in both autoimmune/inflammatory diseases and MDD. These hormonal dysregulations could contribute to disease expression and also could in part account for the association between autoimmune diseases and MDD. Disturbances in circulating glucocorticoids and thyroid hormones have been reported in these syndromes, as well as abnormalities at the receptor level. Thus, glucocorticoid resistance has been reported in both autoimmune diseases and MDD. However, while patients with RA show decreased glucocorticoid responses, patients with MDD exhibit elevated circulating cortisol levels in the context of GR resistance.

Glucocorticoid resistance may be acquired, and secondary to the presence of inflammatory mediators, or could be innate and related to polymorphisms or mutations. Alterations in number and function of GR in RA patients have also been shown. These hormonal disturbances could in part account for the clinical association between mood disorders and autoimmune/inflammatory disease, and could also contribute to the association between MDD and osteoporosis Finally, although not the topic of this chapter, dysregulation of immune responses could contribute to alterations in neuroendocrine responses and mood disorders seen in MDD, and could also account for the association between these conditions. Thus, disruptions of the bidirectional communication between the neuroendocrine and immune systems play a vital role in disease expression in both autoimmune disease and MDD.

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