THE ROLE OF NEUROENDOCRINE SYSTEM IN THE PATHOGENESIS OF RHEUMATIC DISEASES (MINIREVIEW)

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Interactions between the neuroendocrine and immune system play an important role in maintaining and restoring homeostasis. In susceptible individuals a dysfunction of the neuroendocrine system may be one of the risk factors involved in the pathogenesis of rheumatic diseases. Specific causes of altered neuroendocrine function are still not fully elucidated. Accumulation of genetical, environmental, behavioral and other risk factors during long preclinical period may result in chronic imbalances in homeostatic mechanisms maintained by neuroendocrine, microvascular and immune systems. Chronic inflammatory stress mediated by humoral and neural signals during active stages of the disease and autoantibodies against the structures of the neuroendocrine system may further participate in the neuroendocrine dysfunction. In a subset of patients with rheumatoid arthritis (RA), an assumed defect of the hypothalamic-pituitary-adrenocortical axis may be implicated in the pathogenesis. Results of some studies support the concept of adrenal dysfunction in women with premenopausal onset of the RA. Significantly lower levels of dehydroepiandrosterone sulfate (DHEAS) plasma levels of women who subsequently developed RA indicate that neuroendocrine dysfunction may be present already in preclinical period and thus are not only secondary due to ongoing inflammatory process. These findings are sketching the new prospects of possible primary prevention of RA in the future. The role of some other hormones including prolactin, growth hormone, sex hormones and involvement of autonomic nervous system in relation with the rheumatic diseases is also reviewed in the paper. Further research concerning their role in the pathogenesis of other rheumatic diseases will possibly provide new prospects in optimizing their therapy.

Keywords: Rheumatoid arthritis – Systemic lupus erythematosus – Sjoegren's syndrome – HPA axis – Prolactin – Growth hormone – Autonomic nervous system – HPG axis

Bidirectional neuroendocrine-immune relations provide an adequate modulation of the immune system response and thus appropriate adaptation to many endo- and exogenous stimuli. Adaptive reactions are complex and their effectiveness depends on the state of health, age, gender and other behavioral and genetic factors (CHIKANZA and GROSSMAN 2000). Understanding relations between the neuroendocrine and immune systems can contribute to elucidation of pathogenesis of autoimmune disorders, including rheumatic diseases.

An up-to-date model of rheumatic disease pathogenesis proposes that multiple genetic and environmental factors must accumulate and operate in the individual for the disease to become manifest. During a long preclinical interval risk factors are believed to induce the physiologic perturbations of homeostatic processes. If in susceptible persons homeostatic imbalances may no longer be controlled, the clinical expression of inflammatory and other pathological symptoms become manifest (MASI et al 1999, MASI 2000).

Physiological imbalances may be normalized when possible risk factors are identified and reduced during long premorbid phase. In the future such an approach may help to delay the onset or abate the disease activity (MASI et al 1999).

Inflammation and neuroendocrine system

The inflammatory response of the organism induced by infectious disease, autoimmune processes or trauma is associated with a complex of interactions between the immune and neuroendocrine systems. With the aim to maintain the homeostasis of the organism coordination of these processes is assured by a number of factors (Chikanza and Grossman 1996). The cells of the immune and neuroendocrine systems share common signal molecules and their receptors. Hormones and neuropeptides can modulate the activity of immune cells (Table 1). Noradrenergic sympathetic and peptidergic fibres innervate lymphoid organs. By way of its mediators (e.g. cytokines) the immune system can modulate the function of the neural and endocrine systems (Chikanza and Grossman 2000).

Local inflammatory response is orchestrated by a network of substances, which includes cytokines, prostaglandins, free radicals and locally produced hormones. Interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α) induce the production of chemotactic factors, enzymes, second wave cytokines (IL-8, IL-12, IL-15, IL-17, IL-18, interferon-α, interferon -β, etc.), as well as the expression of adhesive molecules and selectines in endothelial cells (Mackay, Imhof 1993, Ferencik et al 1999). Many locally produced proinflammatory neuropeptides like prolactin (PRL), corticotrophin releasing hormone (CRH), arginine vasopressin (AVP) and substance P, are involved in the coordination of the immune response (Weinstock and Elliott 1998, Chikanza and Grossman 1996). Counterregulation of processes maintained by antiinflammatory cytokines (e.g. IL-4, IL-10, IL-11, IL-13) and neuropeptides (corticotrophin (ACTH), β-endorphin, somatostatin and α-melanocyte-stimulating hormone (α-MSH)) is important in tuning the inflammatory response (Chikanza and Grossman 2000).

The cytokine pattern and neuropeptides produced in the central nervous system and locally are closely involved in the process of T-lymphocytes differentiation to subtype T helper1 (Th1) or Th2. Phenotype Th1, responsible for cellular immunity, comes into play predominantly in response to inflammatory stimuli (Romagnani 1991). The shift to phenotype Th2 which downregulates the cellular inflammatory reactions, may serve as one of the mechanism controlling the inflammatory response (Rook et al 1994).

Release of IL-1β, IL-6 and TNF-α from the inflammatory site into the systemic circulation and signaling via the vagus nerve initiate a cascade of reactions in the central nervous system (Akira et al 1990, Bluthe et al 1994). The temperature set point in the hypothalamus becomes altered in order to generate fever response. The activity of the sympathetic nervous system is increased. Initiation of adaptive behavior occurs and the neuroendocrine response is triggered. Inflammatory cytokines also induce alteration of hepatic metabolism and gene expression, leading to the synthesis of acute-phase proteins (Chikanza and Grossman 2000).

Neuroendocrine system response to inflammatory stress

In the hypothalamus, IL-1β, TNF-α and IL-6 activate the production of α–MSH, CRH and AVP, which are stimulatory factors for ACTH release in the pituitary gland and consequent cortisol production in the adrenal cortex (Eijsbouts and Murphy 1999). CRH stimulates the production of macrophage migration inhibitory factor (MIF) in the pituitary, which counteracts the effect of corticosteroids on T-cells and macrophage production of IL-1β, TNF-α and IL-6 (Calandra and Bucala 1997). Corticosteroids themselves inhibit the production of CRH and AVP in the hypothalamus and of ACTH in the pituitary (Chikanza and Grossman 2000).

IL-1β, TNF-α and IL-6 induce nitric oxide-synthase and hemoxygenase activity in the hypothalamus. Nitric oxide and carbon monoxide suppress directly CRH and AVP production or their effect may also be mediated by increased substance P and PRL release. This provides a further counterreugulatory mechanism of hypothalamic-pituitary-adrenal (HPA) axis stimulation by inflammatory mediators (Kostoglou – Athanassiou et al 1998).

Corticosteroids have a strong antiinflammatory effect. They suppress cell-mediated immunity. The production of many proinflammatory cytokines (e.g. IL-1β, IL-2, IL-6, IL-8) is inhibited and that of antiinflammatory cytokines (e.g. IL-4, IL-5, IL-10, IL-13, TGF-β) is upregulated by corticosteroids. They are also angiostatic and are able to influence the in-

tegrity of the microvascular system. The increased release of corticosteroids during inflammation completes an important regulatory circuit for immune and inflammatory reactions (Masi et al 1999).

IL-6 may stimulate the AVP secretion and thus can be involved in the pathogenesis of inappropriate AVP secretion syndrome in patients undergoing major surgery or affected with infectious diseases (Mastorakos et al 1994). AVP released from the hypothalamus has a synergistic effect with CRH on ACTH production in the pituitary. Moreover, its stimulation of V1 receptors in the adrenal cortex increases cortisol release in parallel with ACTH (Perraudin et al 1993). However, in patients with rheumatoid arthritis (RA), increased AVP plasma concentrations were not associated with ACTH and cortisol levels. Increased AVP levels in RA patients may be due to increased local production or maybe secondary, as a response to inappropriately low cortisol level during inflammation (Chikanza 1996, Chikanza and Petrou 2000).

The production of dehydroepiandrosterone (DHEA), a weak adrenal androgen, is under ACTH control. Decrease of adrenal androgens observed in many autoimmune disorders may be caused by acute or chronic HPA axis stimulation (Cutolo 1995a).

PRL and β-endorphin production is increased while that of thyrotropin hormone (TSH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) is decreased by inflammatory cytokines.

The integrity of the neuroendocrine-immune loop is essential for proper modulation of the immune response. A defect of this loop may contribute to the pathogenesis of rheumatic diseases (Chikanza and Grossman 2000).

Dysfunction of hypothalamic-pituitary-adrenal axis

During the last decade, a great effort was made in searching for evidence of improper HPA axis function in patients with rheumatic diseases as had been demonstrated in animal models (Sternberg et al 1989). Defective HPA axis response can be one of the factors responsible for a shift from the acute phase of inflammation to the chronic one. HPA axis dysfunction has been suggested to be present in some patients during the preclinical phase. A defect of the HPA axis should not be only the consequence of chronic inflammatory process (Chikanza 1996).

No conclusive differences were reported in urinary corticosteroid metabolites or in corticosteroids secretion in response to ACTH stimulation between RA patients and healthy controls (Kanik and Wilder 2000). Neither did circadian secretion of cortisol and ACTH show any differences (Harkness et al 1982). Elevated cortisol levels were reported in premenopausal female patients with RA previously not treated with glucocorticoids (Mirone et al 1996). On the other hand, another study showed normal serum and normal 24-hour cortisol and elevated ACTH concentrations indicating defective adrenal glands, function in untreated RA patients (Gudbjornsson et al 1996). In a group of 15 patients with clinical symptoms of, less than one-year duration, elevated C-reactive protein and erythrocyte sedimentation rate, normal cortisol, ACTH, DHEA and dehydroepiandrosterone-sulfate (DHEAS) was observed compared with age- and sex- matched controls (Kanik et al 2000). This observation also supports the suggestion that in RA patients, the HPA axis is functionally defective already in early stages of the disease, as evidenced by the inappropriately low cortisol levels regarding the ongoing inflammation.

The evaluation of HPA axis response to various stimuli yielded to controversial results. Chikanza et al (1992) showed lower diurnal cortisol levels in RA patients and their lower cortisol response to surgical stress as compared with control patients with osteomyelitis and osteoarthritis. Normal results of CRH stimulation test in these patients indicated normal pituitary and adrenal function. Based on these results the authors suggested impaired hypothalamic function. They also proposed that impaired HPA axis together with observed elevated PRL levels before and after surgery in RA patients might lead to proinflammatory hormonal status with possible involvement in RA pathogenesis (Chikanza et al 1992, 1993). Similar study, however, did not detect differences in ACTH, cortisol and PRL levels before and after surgery in RA and osteoarthritis patients (Eijsbouts et al 1998).

Insulin-induced hypoglycemia resulted in slightly lower cortisol response in RA patients not treated with corticoids (Gutierrez et al 1999). Evaluation of basal levels of ACTH, cortisol, TSH, PRL, FSH, LH and subsequent response to CRH, thyrotropin releasing hormone TRH, growth hormone-releasing hormone

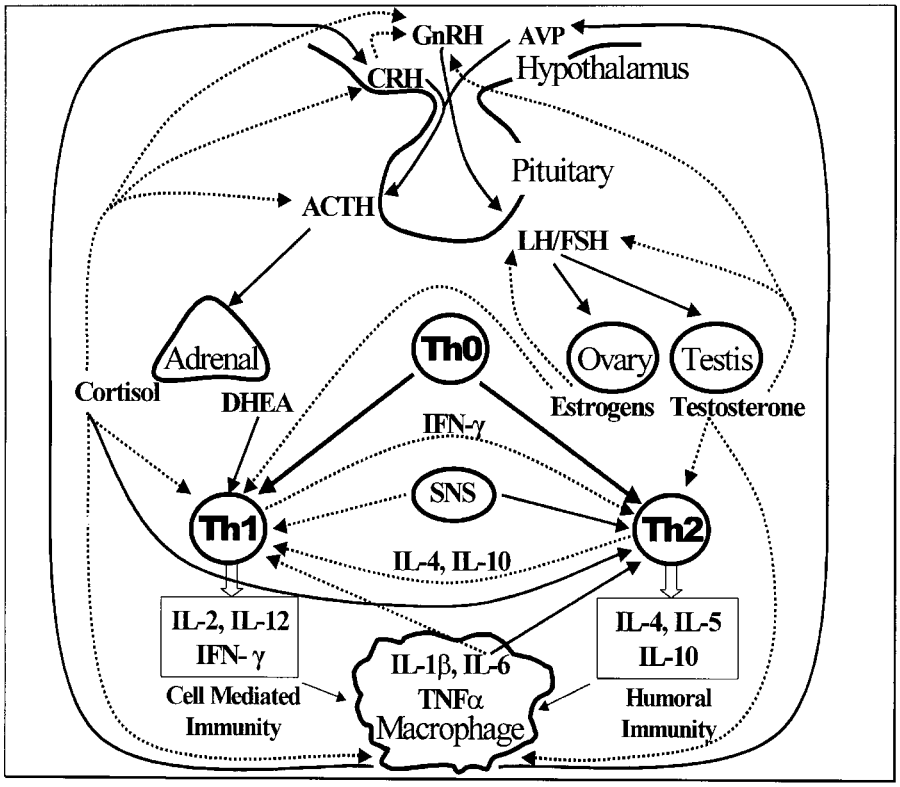

Fig 1 Proinflammatory cytokines (e.g. IL-1β, TNF-α and IL-6) released during acute phase of inflammation stimulate HPA axis to produce cortisol. In turn, increased cortisol modulates inflammatory response and favors T helper 2 (Th2) humoral immune reactivity over a T helper 1 (Th1) cell mediated immune patern. The major sex hormones (e.g. estrogens an testosterone) also modulate immune response and contribute to gender dimorphism. Estrogens, sympathetic nervous system (SNS) enhance humoral immunity and favors Th2 cytokine pattern, whereas dehydroepiandrosterone (DHEA) may favor Th1 immune responsivness. Testosterone tends to be immunosuppressive. Solid arrow = stimulation, dashed arrow = inhibition. (Modified from MASI AT: Neuroendocrine immune mechanisms in rheumatic diseases. An overview and future implications. Rheum Dis Clin North Am 26,1004-1005, 2000)

(GHRH), gonadotrophin-realising hormone (GnRH) stimulation in newly diagnosed RA patients did not detect significant differences compared with healthy controls (TEMPL et al 1996). Decreased response of DHEA and DHEAS to low dose ACTH and ovine CRH stimulation in untreated RA females in the follicular phase of the cycle supports the concept that adrenal rather than pituitary function is impaired (CUTOLO and FOPPIANI 1999).

Defects in HPA axis and elevated IL-1 and IL-6 levels were also reported in patients with Sjögren's syndrome (JOHNSON et al 2000).

Dysfunction of autonomous nervous system

Adaptive response to various stress stimuli, including inflammatory stress involves activation of the HPA axis and autonomic nervous system. Noradrenergic and peptidergic innervation of lymphoid organs provides a physical link to neural modulation of the immune response (FELTEN 1993). Immune system cells in lymphoid organs are modulated by norepinephrine (NE) released from sympathetic nerve endings, while immune cells in the circulation are exposed to epinephrine (EPI) released by the adrenal medulla (BAERWALD et al 2000). Neutrophils, macrophages, NK cells, T- and B-lymphocytes express on their surface β2 adrenergic receptors (LANDMANN et al 1984). Under physiologic circumstances the presence of α1 receptors was reported only on lymphocytes in lymphoid organs. In patients with juvenile rheumatoid arthritis expression of α1 receptors was detected on circulated lymphocytes (HEIJNEN et al 1996). A decreased number of β2 receptors was

Table 1.
Effect of selected hormones and neuropeptides on immune parameters.

Hormone/Neuropeptide	Effect
ACTH	↓ Ig and IFN-γ synthesis
	↑ B cell proliferation
	↑ NK cells activity
Glucocorticoids	↓ overall cytokine synthesis
CRH	↑ T cell proliferation
	↑ IL-2 receptors expression
	↑ IL-1 , IL-6 in macrophages
Epinephrine	↑ NK cells activation
	↓ CD4+ lymphocytes
	↑ CD8+ lymphocytes
	↓ lymphocytes proliferation
α-endorphine	↓ antibody production
β-endorphine	↑ lymphocytes proliferation
χ-endorphine	↓ antibody production
	↑ NK cells activation
Prolactin	↑ IL-2 receptor expression
	↑ T cell proliferation
Growth hormone	↑ antibody production
	↑ NK cells activation
	↑ IL-1, IL-2, TNF-α production
TSH	↑ antibody production
	↑ T and B cells proliferation
α–MSH	↓ antibody production
	↓ IL-1 activity
	↓ monocytes secretion of IL-2
VIP	↓ NK cells activity
	↓ T cells activity
Somatostatin	↓ T cells proliferation
Estrogens	↑ lymphocytes function
Substance P	↑ mast cells mediators release
	↑ macrophage phagocytosis
Met-enkephalin	↑NK cells activity
	↑IFNγ synthesis
	↓ antibody production

found on mononuclears from peripheral blood of RA patients (Baerwald et al 1999). Administration of the β2-agonist terbutalin also reduced the number of receptors in healthy volunteers (Werner 1997).

Many studies revealed the involvement of catecholamines in T-lymphocytes differentiation towards the Th2 type probably due to different numbers of β2 receptors on Th1 and Th2 lymphocytes (Ramer-Quinn et al 1997). The effect of catecholamines on the immune system is mediated not only by direct action on immune cells but also by affecting various tissues, such as endothelium, connective tissue and smooth muscles, resulting in modulation of lymphocyte proliferation, differentiation, cell adhesion and migration associated with changes in a local blood flow (Baerwald et al 2000).

Clinical investigations of patients with RA revealed dysfunction of the autonomic nervous system (ANS). Cardiovascular reflex tests showed pathologic results in 15% to 50% of RA patients. However no correlation with disease activity or duration was observed. Diminished ANS responsiveness was observed in patients with recent onset of RA (Geenen et al 1996). Patients with juvenile chronic arthritis presented altered ANS function associated with increased noradrenergic outflow, which caused decreased response to orthostatic stressor (Kavelaars et al 1998). Patients with primary Sjögren's syndrome showed signs of both sympathetic and parasympathetic dysfunction in the finger skin blood flow test and deep-breathing test (Mandl et al 2001). Reduced sympathetic and increased sensory inervation in synovial tissue of RA patient's joints may also contribute to the maintenance of the disease (Miller et al 2001).

Pathogenetic factors involved in altered ANS function are still under debate. Possible causes include primary disturbance of the ANS present in the preclinical phase or a secondary response to the inflammatory process or to autoantibodies directed against ANS structures (Baerwald et al 2000).

Dysfunction of hypothalamic-pituitary-gonadal axis

Many experimental data support the suggestion that gonadal and adrenal androgens are involved in modulation of the immune response. DHEA, DHEAS, testosterone (T), dihydrotestosterone (DHT) suppress the activity of the human IL-6 gene promoter (Keller et al 1996). Direct exposure of T-lymphocytes, their clones and hybridomes to low DHEAS concentrations increases the secretion of cytokines associated with the Th1 phenotype (Cutolo 1997).

The strong female preponderance has been observed in many rheumatic diseases (Johnson et al 2000). RA incidence in men under the age of 45 years is lower than in women, but with increased age the incidence risk approaches that of similarly aged women (Kanik and Wilder 2000). In patients with Sjögren's syndrome a disease activity correlated with increased androgens

levels (Brennan et al 1999). Evaluation of androgen concentrations in RA patients displayed decreased DHEAS in premenopausal women and decreased testosterone levels in men (Masi 1995). A study of 50 human leukocyte antigen (HLA) identical postmenopausal RA discordant sibling pairs revealed significantly lower levels of DHEAS in the RA siblings and their DHEAS levels correlated with disease severity and duration (Deighton et al 1992). A prospective study in the USA showed decreased DHEAS levels in 35 women before disease development (Masi 1995). A similar study in Finland reported no significant differences between 116 patients and 329 controls (Heikkila et al 1998). The reasons for these discrepant results include differences in methodology or in genetic factors (Kanik and Wilder 2000).

The observed decreased plasma concentrations of adrenal androgens may be due to lower pooling, lower sensitivity to ACTH or an enzymatic defect of the adrenals. Patients previously not treated with glucocorticoids have changed steroidogenesis of DHEA a DHEAS (Cutolo and Foppiani 1999).

In patients with systemic lupus erythematodes SLE, decreased plasma androgens levels were also reported (Jungers et al 1982). The high incidence of RA onset in menopause indicates that estrogens and progesterone also play role in the pathogenesis of the disease. Estrogens are able to increase HPA axis activity by downregulating the number of glucocorticoid receptors in the hypothalamus. Estrogens are likely to be involved in the switch from Th1 to Th2 lymphocyte phenotype (Cutolo 1995b). Clinical observations demonstrate, that disease activity was affected by the menstrual cycle. Comparison of hormone concentrations in RA patients and healthy women showed decreased progesterone levels during the luteal phase and decreased testosterone and corticosteroid levels during the luteal and follicular phases in RA patients (Valentino et al 1993). The use of estrogens and progesterone as oral contraceptives and hormone replacement therapy did not present clear association with RA incidence (Kanik and Wilder 2000).

Pregnancy and rheumatic diseases

Clinical signs of RA are ameliorated in 75% of RA female patients during pregnancy followed by an increase of disease activity in the postpartum period. Increased onset incidence of RA was reported during the first 3 months after delivery. Women are about 10-times more likely to develop RA in the postpartum period compared with other time periods. Variations in hormonal levels and cytokine profiles are associated with shifts in Th1 and Th2 mediated immune responses (Kanik and Wilder 2000).

Increased activity of the HPA axis is partially due to increased production of placental CRH and gradual decrease of CRH-binding protein plasma levels. Hypothalamic CRH production is suppressed during the postpartum period while the levels of immunostimulatory PRL are increased in relation with breastfeeding (Eijsbouts 1999, Masi et al 1999).

In SLE patients, the reversed effect of pregnancy on disease activity was observed. This may be explained by increased progesterone and estrogens associated with Th2 cytokine profile responsible for the production of antibodies (Lahita 2000).

PRL and rheumatic diseases

PRL is a peptide hormone/cytokine produced by various tissues including lactotroph cells in the anterior pituitary gland, lymphocytes, endometrium, brain and skin. It has a similar structure, transduction pathways and receptor types with many cytokines. PRL receptor belongs to the growth and lactogenic family, which includes receptors for IL-2β, IL-3, IL-4, IL-6, IL-7, growth hormone (GH) and erythropoietin (Thoreau et al 1991).

Considerable amount of data suggests that PRL may participate in the clinical expression and pathogenesis of rheumatic diseases, but exact mechanism remains unknown. Hyperprolactinemia induced by the D2 receptor antagonist domperidon transiently increased the number of theophylline-sensitive T cells and decreased the number of CD4+ lymphocytes. The number of CD8+ lymphocytes was unchanged (Rovensky et al 1995). No significant effect of chronic elevation of plasma PRL on immune parameters was observed in patients with prolactinoma (Clodi et al 1992). Another study revealed increased CD4:CD8 lymphocyte ratio, increased number of CD4+ lymphocytes and decreased NK cells activity. PRL lowering therapy with the D2 receptor agonist bromocriptine led to normalization

in the number of CD4 cells and in the activity of NK cells (Gerli et al 1987). Based on the studies investigating many autoantibodies in hyperprolactinemic patients without signs of autoimmune disease, some authors suggested that elevated PRL levels may stimulate their production (Walker and Jacobson 2000). An *in vitro* study showed that physiological PRL concentrations (20 ng/ml) induced IgG production in lymphocytes from systemic lupus erythematodes (SLE) patients more effectively than did higher concentrations (100 ng/ml) (Jacobi et al 2001).

At least 7 cases of hyperprolactinemia preceding the onset of rheumatic diseases were reported (Walker and Jacobson 2000). Hyperprolactinemia was found in 40% of patients with RA, 20-30% of patients with SLE, 59% of patients with scleroderma, 46% of patients with Sjögren's syndrome. Some investigators have also found an association between increased circulating PRL and disease activity (Jara et al 1992, Walker and Jacobson 2000). Decreased response to therapy and increased demand for corticosteroids was found in hyperprolactinemic patients with SLE and RA (Rovensky 2001). However PRL lowering therapy with bromocrptine did not uniformly improve clinical symptoms in patients with SLE (Walker and Jacobson 2000).

Increased circadian PRL secretion and increased PRL levels was documented before and after surgery in RA patients compared with osteomyelitis patients (Chikanza et al 1992, 1993). PRL response to TRH stimulation was significantly increased in RA patients (Jorgensen et al 1995). Similar study showed prolonged PRL secretion during the TRH stimulation test (Gutierrez et al 1998). In contrast, SLE patients had similar PRL response to TRH stimulation (Rovensky et al 1998). Increased incidence of RA in association with elevated PRL plasma levels in the postpartum period was described elsewhere in this paper (Kanik and Wilder 2000).

Significant elevation of PRL plasma concentrations was observed in 9 pregnant women with SLE. On the other hand, 5 pregnant RA patients in the study had only slightly increased PRL levels compared with healthy pregnant women (Jara - Quezada et al 1991).

Several known causes of hyperprolactinemia, such as prolactinoma, hypothyrodism, renal failure or effect of drugs, may be identified in some patients with rheumatic diseases. Anti-PRL antibodies were identified in a subset of SLE patients with lower disease activity. These antibodies may also interfere with PRL feedback regulation in the pituitary (Walker and Jacobson 2000, Jara et al 2001). TNFα and IL-6 are able to stimulate PRL release in man, which provides another cause of hyperprolactinemia in patients with rheumatic diseases. Inflammatory cytokines are able to cross the blood-brain barrier (Banks and Kastin 1991). PRL and IL-6 were identified in cerebrospinal fluid of SLE patients with neurological symptoms (Jara et al 1998).

Regulation of PRL secretion in the pituitary is mainly under inhibitory control of dopamine. Some other compounds, such as serotonin and gama-aminobutyric acid (GABA), are also involved in regulation of PRL secretion. Altered function of regulatory pathways may be a further possible cause of hyperprolactinemia (Paradisi et al 1991, Jara et al 2001).

PRL produced by immune cells may also be involved in the pathogenesis of rheumatic diseases (Montgomery 2001). Lymphocytes from SLE patients had increased *in vitro* production of PRL. PRL gene expression in lymphocytes is under the control of different promoter gene than in the pituitary (Stevens et al 2001). It is not clear whether locally produced PRL may influence its plasma concentrations.

Growth hormone and IGF-1 in rheumatic diseases

Modulation of the immune system by GH and IGF-I has been shown in many studies. GH may be involved in the protection against bacterial infection by promoting the maturation of myeloid cells, stimulating phagocyte migration and enhancing opsonic activity (Saito et al 1996). Human GH deficiency was not found to be associated with clinically significant depression of host defense. A possible explanation is that independent production of mediators such as IGF-1 compensate for the lack of GH. Immunostimulatory PRL may also compensate GH deficit. GH is able to bind on PRL receptors, thus an action of PRL may be partially mediated by GH (Murphy et al 1992).

Studies on GH and IGF-1 deficient animals indicate that PRL, GH and IGF-1 are not obligate immunoregulators and they act as anabolic and stress-modulating hormones in most cells, including those of the immune system (Dorshkind et al 2000).

Implications of a chronic effect of inflammatory mediators on the somatotropic axis have not yet been fully demonstrated. IL-1β was shown to modulate release of GHRH and somatostatine but not TNF-α and IL-6 in rat hypothalamic cell culture (Honegger et al 1991). Increased IL-1 levels were found to stimulate GHRH and somatostatin release in hypothalamus of rats (Payne et al 1992). Chronic overproduction of IL-6 in patients with systemic juvenile idiopathic arthritis caused decreased IGF-binding protein 3 levels resulting in decreased association of IGF-1 (De Benedetti et al 2001). On the other hand, increased levels of IGF-binding protein were observed in RA patients. This may result in reduced availability of free IGF-1 (Neidel 2001).

Administration of GH for the growth retardation was associated with development of lupus flare in the patient with 11 years history of SLE (Bae et al 2001).

Basal levels of GH in RA and SLE patients are within physiological range. Significantly decreased response of GH to GHRH stimulation was observed in newly diagnosed RA patients (Templ et al). SLE patients did not display a different response of GH to hypoglycemia (Rovensky et al 1998).

Conclusions

Neuroendocrine dysfunction is very likely one of the important risk factors involved in the pathogenesis of rheumatic diseases. Results of some studies suggest that deficiency of adrenal androgens (DHEA, DHEAS) in female RA patients with premenopausal onset of disease may be one of the risk factors or risk markers. Causes of inappropriately normal plasma cortisol concentrations with regard to the ongoing inflammation observed in RA patients are open to discussion. Further studies are necessary to identify the reasons of this phenomenon (altered production, degradation, influence of cytokines or PRL).

Genetical heterogenity within each clinical unit must be taken into consideration. Identification of genetic markers and their correlation with other clinical and experimental data should shed more light on the primary or secondary causes of neuroendocrine alterations in rheumatic diseases.

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