Immunopathogenesis of Rheumatic Diseases in the Context of Neuro-Endocrine Interactions

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Abstract

Growing evidence supports the hypothesis that alterations of the stress response and interactions between the neuroendocrine and immune system contribute to the pathogenesis of rheumatic diseases like rheumatoid arthritis (RA). In particular the hypothalamus-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS) are of special interest. Polymorphisms of the corticotropin releasing hormone (CRH) regulating region have been described recently. These polymorphisms are differentially distributed in RA patients and healthy subjects of various ethnic origin, thus supporting the hypothesis that they represent a new genetic marker for RA susceptibility.

The decreased expression of beta2-adrenergic receptors (beta2-R) on lymphatic cells in rheumatic diseases like RA together with an impaired influence of catecholamines on immune function in these patients further underlines the concept of a dysfunction of the ANS in rheumatic diseases. Results from work in this field will gain more insight into the pathogenesis of RA and help to establish novel therapies for this chronic rheumatic disease.

Introduction

The adaptive response of organisms to stressors and inflammatory signals involves the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS). Products of both of these systems (e.g. corticosteroid hormones and catecholamines) are able to modulate the activity of various immune effector cells directly [1]. Behavioural, psychosocial, and neurobiological studies have revealed multiple channels of communication between the central nervous system and the immune system.

Noradrenergic (NA) and peptidergic innervation of primary and secondary lymphoid organs furnishes some of the necessary physical links for neural modulation of immunity [2-4]. The anatomical distribution of NA innervation in lymphoid organs suggests the existence of sympathetic neural interactions, via the

neurotransmitter norepinephrine (NE), with lymphoid and accessory cells of the immune system. Furthermore, circulating lymphocytes are exposed to catecholamines, mainly epinephrine (EPI), released from the adrenal gland into the blood stream. Further evidence for such interactions may be drawn from the discovery of the expression of beta2-adrenergic receptors (beta2-R) on T and B lymphocytes, macrophages, natural killer cells, and neutrophils [5-9]. In addition to beta2-R, ligand binding studies and functional experiments could demonstrate alpha1-adrenergic receptors on lymphocytes even though in humans the functional effect of signals mediated via these receptors seems to be of significance in chronic inflammatory disease states only [10-12]. Growing evidence indicates that the ANS influences the immune response via activation and modulation of adrenergic receptors while, in turn, cytokines can interact with central neurones and modulate their activity [1].

The second pathway involved in the stress response of the organism is the hypothalamic-pituitary-adrenal (HPA). The response of the HPA axis to inflammatory stimuli involves the activation of the hypothalamus and pituitary gland by cytokines like interleukin-1beta or tumor necrosis factor-alpha. The concomitant increase in corticotropin releasing hormone (CRH) production augments the production of adrenocorticotropic hormone (ACTH), thereby stimulating the synthesis of corticosteroids by the adrenal gland [13]. CRH is a 41-amino acid peptide which has been functionally implicated in the regulation of many endocrine and immune responses in various organs of the body [14]. In particular, it mediates the interaction of stress events and inflammatory signals on the HPA axis. This report will discuss recent studies demonstrating the first CRH promoter polymorphisms in RA patients of various ethnic origin and will focus on the altered interactions of the ANS and the immune system observed in patients with chronic rheumatic diseases.

The Hypothalamic-pituitary-adrenal axis in rheumatoid arthritis

The disease activity pattern in RA is dependent on a diurnal rhythm of cortisol secretion. However, the amount of cortisol secreted is below normal [15-17]. Therefore, the HPA axis is assumed to be defective in patients with chronic rheumatic diseases like RA as well as in rat models for autoimmune diseases. In particular an impaired modulation of the central regulator of the HPA axis, CRH, seems to be crucial for the onset of the disease [18, 19]. Based on previous investigations the view emerged that genetic variance at the CRH locus might contribute to the susceptibility of RA. The human CRH gene, and its regulatory region, has been localized to chromosome 8q13 [20]. Early on in the disease course of RA a subtle dysfunction of the HPA axis could be demonstrated [21, 22]. Animal studies suggested that the defect might reside in the 5' regulatory region of the CRH. Therefore the hypothesis was tested that genetic variance at the CRH locus might contribute to the susceptibility of RA. Sequencing this region revealed the first polymorphisms in this highly conserved part of the genome [23, 24]. Subsequent population studies resulted in a remarkable difference of the allele distribution between an indigenous south African population and white Caucasian [25]. Furthermore, despite these differences in the allele frequencies there was a distortion in the distribution of the alleles between RA patients and ethnically matched controls in both population studied [26]. Even though the polymorphisms were not present in every RA patient it points to a contribution to the genetic component of the disease. This finding was further strengthened by a recent family study demonstrating a linkage to the CRH region on chromosome 8 [27].

Interactions between the autonomic nervous system and the immune system in rheumatoid arthritis

Numerous investigations have revealed a dysfunction of the ANS in RA patients [28, 29]. In particular cardiovascular reflex tests showed pathological results in 15

to 50 % of RA patients even though a correlation neither to disease duration nor to various disease activity parameters was described [28-30]. Interestingly, in patients with RA of recent onset a diminished ANS responsiveness could be shown, most clearly in patients with severe pain [28]. The pathogenesis of the altered ANS function in RA is still enigmatic. A primary disturbance of ANS function contributing to the onset and perpetuation of RA can as well be the case as a secondary lesion of the ANS by the inflammatory process of RA: In the latter case, ANS disturbance may in part be attributable to autoantibodies directed against autonomic nervous system structures [30]. Taken together all these studies point to a role of the ANS in the pathogenic process of RA since an altered ANS responsiveness can be observed in early disease states already.

Further evidence for a role of interactions between the ANS and the immune system in the pathogenesis of chronic inflammatory diseases is provided from animal models of experimental allergic encephalomyelitis or streptococcal cell wall arthritis. In Lewis rats the activation of beta2-R on peripheral blood mononuclear cells (PBMC) led to a decrease in disease activity [2, 31]. Based on investigations by Levine and colleagues the sympathetic nervous system has been implicated in the pathogenesis of experimental arthritis in susceptible rats, in which denervation of NA nerve fibres diminished the inflammatory response and arthritic changes [32]. These findings are consistent with clinical observations that propranolol, a beta-adrenergic receptor antagonist, and regional sympathetic blockade with guanethidine reduces the inflammatory activity and pain in patients with RA [33, 34] indicating an enhancing effect of beta2-adrenergic stimulation on the inflammatory process in RA in humans. On the other hand, denervation of NA nerve fibres from lymph nodes which drain the affected joints led to an earlier onset of inflammatory changes in experimental arthritis of the rat [2]. Furthermore a beneficial effect by the application of beta2-R agonists or cAMP analogues into the joint of patients with inflammatory arthritis and the administration of the beta2-R agonist salbutamol in collagen induced arthritis has been reported [35, 36].

These conflicting results suggest that manipulation of NA nerve fibres in secondary lymphoid organs and joints may have different effects on the inflammatory process depending on the stimulating antigen, the type of cells that are primarily involved in the immune response (B-cells, CD4+ or CD8+ T-cells) and the activation status of the cells responding to sympathetic stimulation [37]. In any event, all these studies give strong evidence for the close interplay between the sympathetic nervous system and the immune response.

Neurotransmitters of the ANS such as EPI and NE bind to adrenergic receptors on the cell surface. It has been demonstrated that lymphocytes constitutively express beta2-R but may also express alpha1-R under certain conditions like in active inflammatory joint diseases [38]. Moreover, alpha1-adrenergic receptor subtypes are differentially upregulated by neuroendocrine mediators on monocytes [39]. Since the detection of beta2-R on cells of the immune system an abundance of experiments have focussed on their role in immune reactivity. Stimulation of beta2-R on lymphocytes initiates the accumulation of the second messenger cAMP after a conformational change of G-proteins and activation of adenylate cyclase (AC). This in turn activates the protein kinase A (PKA) [40]. Activated PKA translocates into the nucleus and binds to the transcription factor cAMP response element binding protein (CREB). CREB in turn builds a complex with another protein which binds to DNA via ”zinc fingers” eventually exerting the effects on gene transcription [41, 42]. This results in a modulation of the function of various immune effector cells [43].

Reasoning along these lines the density of beta2-R on PBMC in RA patients was investigated. We could demonstrate a significant decrease in beta2-R density on PBMC from RA patients negatively correlated to the systemic disease activity [44]. Further studies revealed that this downregulation is not a disease specific process but might be due to the inflammatory process in various chronic disease states, i.e. systemic lupus erythematosus (SLE) and Crohn’s disease [45, 46]. This finding was further strengthened by the observation that proinflammatory cytokines are

able to modulate beta2-R expression [47-49] and by the negative correlation between beta2-R density on PBMC and soluble Interleukin-2 receptors, an activation marker for PBMC, being increased in patients with chronic inflammatory diseases [46]. Interestingly, for beta2-R densities in patients with SLE and RA there was neither an association to systemic catecholamine concentrations nor a protection from the loss of beta2-R binding sites under medication with low dose corticosteroids [45]. Further investigations by our group revealed an even more pronounced decrease of beta2-R on synovial fluid mononuclear cells (SFMC) in RA patients indicating a local modulation of beta2-R characteristics [50]. However, the factors modulating beta2-R in the joints have not been identified yet. It may be speculated that the beta2-R status is influenced by NE originating from macrophages [51] or sympathetic nerve fibres innervating the synovial membrane [52]. This assumption is underlined by the negative correlation we found between beta2-R densities on SFMC and the levels of synovial fluid NE. Alternatively, the beta2-R decrease may simply be due to the altered state of activation of SFL in RA patients or may be attributable to the influence of locally released cytokines which are able to modulate beta2-R expression [47, 53].

Different densities of beta2-R on various lymphocyte subsets have been described [8, 54, 55]. Interestingly, we found a differential regulation of beta2-R expression on T lymphocyte subsets in RA patients with a significant decrease of beta2-R on CD8+ cells but no difference for beta2-R on CD4+ cells [50]. These results demonstrate that the decrease of beta2-R on PBMC in patients with RA is not explained by a simple down regulation of the receptors in response to a stress induced elevation of systemic catecholamines, but can be at least partly contributed to a selective down regulation of beta2-R on lymphocyte subsets including CD8+ cells [53].

To further elucidate the functional relevance of reduced beta2-R binding sites on PBMC observed in RA patients, the influence of catecholamines on lymphocyte proliferation was studied ex vivo. Since PBMC from RA patients show a reduced

responsiveness to the stimuli used [56] we compared the percentage of the changes in the 3H-thymidine uptake by catecholamines for statistical analysis. In concordance with previous studies catecholamines exert stimulatory or inhibitory effects on PBMC reactivity due to the stimuli used [57]. In RA patients exhibiting decreased beta2-R density on PBMC the catecholamine induced modulation of PBMC reactivity was significantly diminished in particular the beta2-R mediated signals [58]. This conclusion is further strengthened by a recent study demonstrating a similar reduced catecholamine effect in healthy individuals with terbutaline induced down-regulation of beta2-R on PBMC [59]. In particular activation of T cells via monoclonal anti-CD3 antibodies (OKT3) is a suitable model to investigate the effects of catecholamines on lymphocyte activation. It could be demonstrated that the catecholamine induced cAMP increase inhibits intracellular actin polymerisation and pseudopodia formation which are early events following binding of monoclonal anti-CD3 antibodies to the TCR/CD3 complex [60]. This effect could partly be reversed by adding beta2-R antagonists suggesting that catecholamines elicit their inhibitory effects via beta2-R on PBMC as well as an alternative pathway.

In addition to these beta2-R mediated effects, in various experimental settings catecholamine effects were also mediated via alpha1-adrenergic receptors (alpha1-R). However, alpha1-R responses depended on the disease activity in RA patients [12]. Since in healthy controls catecholamines mediate their signal via beta2-R the expression of alpha-adrenergic receptors on PBMC seems to ensue the chronic inflammatory process. It could be shown that under physiologic conditions only lymphocytes in lymphoid tissues posses alpha1-R while circulating lymphocytes do not express alpha1-R. In contrast, in inflammatory states like in children with active juvenile chronic polyarthritis alpha1-R may be induced in lymphocytes. Since we could demonstrate a decreased responsiveness of the beta2-R second messenger system, i.e. cAMP, in RA patients [12], in chronic rheumatic diseases the physiologic beta2-R mediated interplay between the ANS

and the immune system is shifted to an alpha-adrenergic response which might contribute to the perpetuation of the ongoing immune response [12, 61].

Not only the cellular arm but also the humoral arm of the immune response is modulated by catecholamines. Several studies could demonstrate profound effects of catecholamines on B cell functions [57]. Intriguingly, in a recent study Sanders et al. could demonstrate differential expression of beta2-R on Th1 and Th2 lymphocytes elucidating the importance of the autonomic nervous system for cytokine production and B cell help [62]. In this respect it is interesting that data of our laboratory show a significant decrease of beta2-R on B lymphocytes in RA patients as well as in patients with other rheumatic diseases [63, 64].

Summary and Conclusion

In general it is assumed that the two pathways (i.e. hypothalamic-pituitary-adrenal axis and the sympathetic nervous system) probably act co-operatively to maintain homeostasis. The above mentioned studies clearly point to a disturbance in the interaction between the ANS, the HPA axis and the immune system in chronic rheumatic diseases. Even early on in the disease course of RA these changes can be observed. Along with the results obtained in animal models an important role of neuroendocrine interactions in the pathogenesis of RA is proposed. However, further studies are pending in order to establish the exact contribution of the autonomic nervous system both in the initiation and perpetuation of RA.

In the future, it may be possible to interfere with the inflammatory process in RA by an exactly timed neuroendocrine intervention right at or even before the onset of the disease. Furthermore, therapy with steroids in RA might be better planned based on the genetically determined reactivity of an individual's HPA axis. Based on the current literature on the disturbances in the neuroendocrine, immune, and microvascular systems found in early RA it may be speculated that in genetically predisposed individuals an imbalance in the interactive homeostasis of these

systems develops during a long preclinical phase and eventually leads to the outbrake of the disease. This interesting hypothesis includes the perspective that individuals prone to develop RA may be identified in a preclinical phase and be treated prophylactically.

In any event, results from all these studies are promising in two ways: to gain more insight in the pathogenic process of RA as well as to establish novel therapies to help the patients bear their burden of a chronic rheumatic disease.

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