The Second International Conference on the Neuroendocrine Immune Basis of the Rheumatic Diseases

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At the Second International Conference on the Neuroendocrine Immune Basis of the Rheumatic Diseases, held in Genoa (Santa Margherita, Italy) on 21–23 September 2001, researchers from 20 different countries presented their latest works in this fascinating field of study. The conference took place 10 days after the Twin Towers disaster, and the New York victims were commemorated during the opening ceremony. More than 180 participants were registered; some U.S. speakers were unable to attend because of the disaster and some were substituted by other U.S. presenters.

General overview

Elenkov and Wilder (Bethesda, USA) introduced the state of art of neuroimmunoendocrinology. Substantial progress has been made in delineating molecular, cellular and systemic physiologic mechanisms that underlie the communication between components of the stress response and the immune and endocrine systems. Progress has also been made in defining how abnormalities involving hormones (i.e., estrogens, androgens, cortisol, catecholamines, etc.) may contribute to the initiation, progression and severity of autoimmune rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus. For RA, the available data support the view that inflammatory and immune system inhibitory mechanisms involving the hypothalamic-pituitary-adrenal axis and sympathetic nervous system are deficient. For SLE, accumulating recent data indicate that estrogens and androgens exert contrasting effects on B lymphocytes (i.e., estrogens enhance, testosterone suppresses). Elenkov and Sternberg (Bethesda, USA) reported on neural pathways that play a role in inflammatory disease regulation, including the sympathetic and peripheral nervous systems that modulate inflammation at regional or local levels. New therapeutic interventions currently being developed based on this research include the use of anti-inflammatory drugs in Alzheimer's disease, anti-stress hormone drugs in arthritis, neurotransmitter-related drugs for aging-associated immunosuppression, and cytokine antagonists and immune T cells for treatment of spinal cord injury, nerve trauma and stroke. A.T. Masi (Chicago, USA) discussed the adrenal steroid deficiencies in RA patients and the different expression of the hypoadrenal gland function in many subsets of patients. These conditions, among other risk factors, may permit modeling immunologic development or re-activity. The neuroendocrine aspects of the central nervous system involvement in the antiphospholipid syndrome were discussed by Y. Shoenfeld (Tel Hashomer, Israel).

Stress and rheumatic diseases

Stress is a well-known stimulator of the hypothalamic-autonomic nervous system axis and the HPA axis, and may – based on the above and other interactions – influence the immune response.

RA and SLE patients differ in their immunologic response to acute psychological stress: natural killer activity increased in healthy controls only, while there was an increase in interleukin-4-producing cells in SLE patients only. Phytohemagglutinin-stimulated peripheral blood morphonuclear cell cultures demonstrated increased interferon-gamma and IL-10 levels in healthy subjects but not in SLE or RA patients after stress exposure. Furthermore, the number of beta2-adrenoceptors on PBMC significantly increased only in healthy subjects after stress but not in SLE patients. RA patients showed an increased sensitivity to beta2-adrenoceptor stimulation, accompanied by a decrease in G-protein-coupled receptor kinase activity. This may be a potential pathway whereby inflammatory mediators may influence stress-associated mechanisms that can modulate outcome in inflammatory diseases (Schedlowski, Essen, Germany).

In a follow-up study of symptomatic Gulf War veterans, *in vitro* immune response tests showed no significant impairment (Everson, Birmingham, USA), indicating that the relation between stress and the immune system in these otherwise healthy people is not always straightforward. In an animal model of stress induced by chronic food restriction, adjuvant arthritis developed less frequently and was less severe in the stressed group of animals (Seres, Prague).

Role of the autonomic nervous system

The adrenal hormone epinephrine and the sympathetic neurotransmitters norepinephrine and adenosine (after conversion from ATP) play an immunomodulatory role due to their binding to different receptor subtypes on cells of the immune system. Epinephrine preferentially binds beta-adrenoceptors, and norepinephrine binds alpha-adrenoceptors (at high concentrations also beta-adrenoceptors). Studies in early rheumatoid arthritis indicate that the expression of beta2-adrenoceptors on lymphocytes is reduced, followed by a reduced cAMP production and an impaired auto-

RA = rheumatoid arthritis
SLE = systemic lupus erythematosus

HPA = hypothalamic-pituitary-adrenal
IL = interleukin

PBMC = peripheral blood morphonuclear cells

nomic nervous function. These beta2-adrenoceptors play an inhibitory role for production of pro-inflammatory cytokines such as tumor necrosis factor, IL-2, IL-12 and IFN-gamma, lymphocyte proliferation, energy metabolism, expression of adhesion molecules, and other aspects of the immune reaction. Therefore, reduced beta2-adrenergic action may contribute to the pathogenesis of RA. A negative correlation has been found between disease activity of RA and beta2-adrenoceptors (Wahle and Baerwald, Leipzig, Germany). It was also shown that catecholamines inhibit energy metabolism of immune cells within seconds; propranolol (beta-adrenoreceptor antagonist) but not phentolamine (alpha-adrenoreceptor antagonist) reversed the norepinephrine-induced inhibition in quiescent cells. Conversely, phentolamine but not propranolol was capable of blocking norepinephrine-mediated effects in activated cells (Buttgereit, Berlin). This indicates that depending on the activation state of immune cells differential alpha- and beta-adrenoceptors play a regulatory role.

In elegant experiments, Straub (Regensburg, Germany) demonstrated a decrease of sympathetic nerve fibers in synovial tissues of RA patients, accompanied by a marked norepinephrine release from tyrosine-hydroxylase positive cells in this tissue. This norepinephrine secretion is probably anti-inflammatory (reduces IL-6, IL-8 and TNF) to counteract local inflammation, but its exact role remains to be determined. Dendritic cells are potent antigen-presenting cells involved in inflammation and autoimmunity. Maestroni (Locarno, Switzerland) demonstrated that norepinephrine enhances these cells to migrate, while the alpha-adrenergic antagonist prazosin inhibits this migration.

Pain modulation

Inflammation causes peripheral and central sensitization, which is the basis of pain. Sensitization also facilitates the efferent arm of sensory neuronal pathways by releasing a local substance P, whereby the nervous system influences the inflammatory process. Peripheral sensitization is induced by inflammatory mediators such as bradykinin, prostaglandins, neuropeptides and cytokines. Hyperexcitability of spinal cord neurons is predominantly regulated by glutamate that activates N-methyl-D-aspartate (NMDA) and non-NMDA-receptors. Blockade of these receptors can prevent and reduce central sensitization. Substance P and CGRP, but also prostaglandin E2, facilitate this transmission; indomethacin is able to significantly attenuate the development of hyperexcitability (Schaible, Jena, Germany). During this sensitization the increase in intraneuronal cAMP concentration plays a pivotal role. Morphine inhibits this cAMP formation by inhibiting adenylate cyclase. Morphine may prevent not only the development of pain, but also the resulting inflammation, as shown in experimental and degenerative models of arthritis (Konttinen, Helsinki). This finding is in line with the detection of novel opioid peptides endomorphine-1 and 2 in inflamed synovial tissue (Jessop, Bristol, UK).

Corticotropin-releasing hormone

Corticotropin-releasing hormone is a key regulator of the HPA axis and coordinator of the stress response. Its crucial role was further confirmed by the identification of local up-regulation of CRH and the CRH receptor type 1alpha (CRH-R1) in inflamed synovial tissue. CRH receptor-mediated signaling, in part through the nuclear transcription factor NURR1, plays a role in both the vascular and pathologic changes associated with joint inflammation. NURR1 is up-regulated in inflamed synovial tissue; treatment with prostaglandin E2, IL-1 and TNF enhances NURR1 mRNA and protein levels. This up-regulation requires a proximal promoter region that contains a consensus nuclear factor kB (NFkB) DNA-binding motif and a direct cAMP response element binding protein-1 (CREB-1)-dependent regulation by PGE2 (McEvoy, Dublin).

CRH stimulation has been studied in different rheumatic diseases. Conflicting data have been observed in fibromyalgia patients. Neeck (Bad Nauheim, Germany) divided the cortisol response to CRH in fibromyalgia patients based on their scoring on a depressive mood scale; those who scored higher had a low cortisol response while those with low scores had a higher cortisol response.

Pro-inflammatory cytokines, especially IL-6 and IL-1, stimulate CRH, ACTH and cortisol. In the acute phase this stimulation is adequate while in the more chronic situation the increase in ACTH and cortisol is blunted. There is also an indirect pathway via the release of catecholamines, independent of the HPA axis (Bornstein, Düsseldorf). Furthermore, there is a hormone-independent way of stimulating adrenal steroid hormone secretion due to intra-adrenal cell-cell contacts, which may be an important regulatory element in inflammatory diseases (Bornstein, Düsseldorf).

Glucocorticoids

We have known for over 50 years that glucocorticoids play a pivotal role in the endocrine regulation of the immune response. Not only are glucocorticoids the most effective antiphlogistic and immune suppressive substances with instant effect, but low dose long-term treatment in patients with RA had clear antiproliferative effects on cartilage and bone (Neeck, Bad Nauheim).

The immune suppressive effects of glucocorticoids are related to inhibition of processes such as cytotoxicity, phagocytosis and synthesis of inflammatory cytokines such as TNF, IL-1, IL-2 and IL-8. Other anti-inflammatory actions have been ascribed to the synthesis of a protein termed lipocortin 1 or annexin 1, which inhibits phospholipase A2 activity with subsequent reduction in arachidonic acid release and eicosanoid production. Another relevant mechanism is the capacity of glucocorticoids to interfere with intercellular adhesion processes, which are instrumental in mediating leukocytes to endothelial cells and cell migration into peripheral tissues (Pitzalis, London). This regulation may be effected by the classical genomic pathways, but also by non-genomic pathways in cases of higher dosages of glucocorticoids. These actions occur rapidly (within seconds) and are related to physicochemical effects on membranes and putative membrane receptors. Clinically relevant glucocorticoid concentrations inhibit plasma membrane Ca2+ and Na+ uptake, RNA/DNA synthesis and substrate oxidation reactions, and stimulate the leak of protons across the mitochondrial inner membrane (Buttgereit, Berlin).

Glucocorticoid receptor concentrations have been studied in different groups of

IFN = inteferon
TNF = tumor necrosis factor

CRH = corticotropin-releasing hormone

patients with RA. Huisman (Utrecht, the Netherlands) found decreased levels in early diagnosed, disease-modifying anti-rheumatic drug-naive and prednisone-naive female patients, in combination with low cortisol levels. In patients with more long-standing and more active RA other researchers found increased levels, in combination with higher cortisol levels.

Glucocorticoid resistance is becoming a better understood clinical entity. Steroid-resistant RA patients have enhanced expression of glucocorticoid receptor beta isoform in their PBMC. The molecular mechanisms possibly involved are alterations in intracellular signaling, cytokine profile, dysregulation of GCR function, enhanced AP-1 expression and others (Chikanza, London).

The effects of glucocorticoids on bone are well established, but the underlying mechanisms are not yet fully elucidated. Glucocorticoids increase bone resorption due to a decrease in osteoprotegerin, and an increase in RANK ligand expression with an increase in osteoclastogenesis. Glucocorticoids have a direct inhibitory effect on osteoblast formation and function, possibly also by inducing their apoptosis. Glucocorticoids also enhance collagen degradation by inducing collagenase 3 expression in osteoblasts. Glucocorticoids also reduce the synthesis of insulin-like growth factor, which stimulates bone formation (Canalis, Hartford, USA).

The clinical value of glucocorticoids in the treatment of patients with RA was further confirmed by a new study investigating the effect of prednisone versus placebo in DMARD-naïve early RA patients. Symptomatic relief was seen in the first months; after 2 years a significant reduction in (progression of) erosions occurred, combined with a decrease in the use of non-steroidal ant-inflammatory drugs and other interventions such as physical therapy and intraarticular injections (Bijlsma, Utrecht). Four different very recent studies reported a reduction in (progression of) erosions during treatment with low dose glucocorticoids, but the effect of the combination of DMARD plus glucocorticoids was better than that of glucocorticoids alone. This suggests that the anti-inflammatory properties of glucocorticoids are different from their disease-modifying effects.

Gonadal hormones

Generally, estrogens are implicated as enhancers of the immune response, and androgens as natural suppressors. In synovial tissue of patients with RA, receptors for estrogens as well as androgens were found on macrophages and B and T lymphocytes. Estrogens may stimulate macrophages to produce TNF-alpha, IL-1 and IL-6, B lymphocytes to produce immunoglobulins and inhibit T lymphocytes to produce IL-4, IL-2 and IFN-gamma. Androgens may (to a lesser degree) have the opposite effects. Concentrations of estrogens at the level of the inflammatory area are increased due to increased aromatase activity (Cutolo, Genoa, Italy).

Levels of expression of cytokines and cytokine inhibitors are ruled by hormones: estrogens increase the expression of IL-1 mRNA on monocytes, while androgens inhibit the production of IL-1 and TNF by monocytes/macrophages. Estrogens tend to inhibit TH1 cytokines, while androgens tend to inhibit TH2 cytokines (Dayer, Geneva).

The important role of the vascular endothelium in inflammation has become increasingly more apparent. Estrogens enhance a number of endothelial cell biologic activities, such as proliferation, adhesion to matrix proteins, migration, and cell differentiation, which promote inflammation and angiogenesis (Cid, Barcelona).

An interesting aspect of gonadal hormones is its interaction with glucocorticoids. Estrogens influence the secretion of CRH by the hypothalamus and the expression of glucocorticoid receptors, thus affecting the negative feedback to the hypothalamus. When the response of ACTH and cortisol to IL-6 was measured in healthy adult males and females, maximum cortisol levels correlated with IL-6 dosage in males but not in females. The opposite was found for a correlation between ACTH and cortisol. This suggests that the adrenals of males and females may have different sensitivity to ACTH and IL-6 (da Silva, Coimbra, Portugal).

Data were submitted by Sullivan (Boston) on the influence of gonadal hormones on the dry eye in Sjogren's syndrome. Androgen deficiency and estrogens (and progesterone) promote the development of the dry eye syndrome as demonstrated in animal models and epidemiologic studies.

Melatonin

The pineal hormone melatonin has a variety of effects on the immune system. Melatonin enhances IL-1, IL-6, IL-12, TNF and IFN-gamma production. It has been suggested that melatonin counteracts immunosuppression and thymus atrophy induced by stress or glucocorticoids (Maestroni, Locarno). Also an indirect effect via modulation of androgens has been suggested. Melatonin receptors are present on synovial macrophages of RA patients. Melatonin serum levels are higher in RA patients, but have the same nocturnal rhythm, with the peak level early in the morning. It has been suggested that symptoms such as morning gelling, stiffness and swelling might be related to the neuroimmunomodulatory effect of melatonin (Cutolo, Genoa).

Aging and rheumatic diseases

Aging has a clear influence on our endocrine, nervous and immune status. During aging many changes occur in cytokines, hormones and neurotransmitters, depending on oxidative damage, non-enzymatic glycosylation, mitochondrial mutations, defects in cell cycle control, genome instability, telomere shortening, and other pathologies. To mention a few: during aging IL-6 levels increase, DHEA levels decrease, the ratio cortisol/ACTH decreases (more evident in women then in men), and a shift in TH1/TH2 in favor of TH2 is observed. These changes may be relevant for the occurrence of neuroendocrine immune-mediated diseases in different age groups (Straub, Regensburg).

The Third International Conference on Neuroendocrine Immune Basis of the Rheumatic Diseases is scheduled to be held in Genoa in 2004. In 2004 Genoa will celebrate its official position as "2004 Cultural MainTown" in Europe and important events are planned.

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DMARD = disease-modifying anti-rheumatic drug