



Editorial

Neuroimmunoendocrine interaction in autoimmune rheumatic diseases: a new challenge for the rheumatologist

La interacción inmuno-neuro-endocrina en enfermedades reumáticas autoinmunes: un nuevo desafío para el reumatólogo

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A lot of evidence gathered over the last 3 decades indicates that there is bidirectional communication between the central nervous system (CNS), endocrine system and immune system starting during embryonic and neonatal development to the final stages of life. This “neuro-immuno-endocrine” communication is constantly seen in situations of stress as occurs in infections, inflammatory/autoimmune diseases or trauma, which trigger a series of reactions that activate the neuro-immuno-endocrine system. This system is composed of the following areas: 1. hypothalamic-pituitary-adrenal (HPA) that includes the cortisol, corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH); 2. hypothalamic-pituitary-gonadal (HPG), that includes luteinizing hormone (LH), follicle stimulating hormone (FSH), gonadotropin-releasing hormone (GnRH), oestrogen, progesterone and androgen; 3. Hypothalamic-pituitary-thyroid (HHT) composed of thyroid hormones (T3 and T4) and 4. prolactin/growth hormone (PRL/GH) system. The messengers of this bidirectional communication are the abovementioned hormones, neuropeptides, “pro-inflammatory” and “anti-inflammatory” cytokines as well as neurotransmitters that are synthesised by the cells of the 3 systems. These messengers act via receptors, producing activation or inhibition of the innate and adaptive immune response, from the nervous system and endocrine system. The autonomic nervous system together with the synthesis and release of catecholamines also participate in this communication. The breakdown of this homeostatic-molecular balance shares in the pathogenesis of various inflammatory, autoimmune, neoplastic, infectious, cardiovascular, metabolic and psychiatric processes.¹⁻³

The synthesis and release of messengers has 24 hour action cycles when referring to the physiological processes. These variations are called circadian rhythm, and they influence the clinical manifestations

of various diseases. This circadian rhythm is generated and controlled by the CNS through the hypothalamus.⁴

The synthesis and secretion of hormones and cytokines is a dynamic process that is undertaken in a cellular microenvironment. The cells have receptors for hormones, cytokines and pathogen-associated molecular patterns (PAMPs). They are all activated to physiologically respond to pathogens.⁵

When there is a local or systemic inflammatory/immune process, the immune systems cells release proinflammatory cytokines: interleukin 1 beta (IL-1 β), tumour necrosis factor (TNF) and interleukin 6 (IL-6), which cross the blood-brain barrier and reach the CNS. The blood-brain barrier breakdown is mediated by lipopolysaccharides and cytokines that activate the CNS functions and produce behavioural and cognitive changes, arthritis, fever and activate systems to respond to stress.⁶ We have seen that an IL-1 injection in mice produces activation of the HPA axis releasing ACTH and cortisol, since tests were carried out in the eighties of the last century. This is a hypothesis that was later confirmed by the demonstration that IL-1 activates neurons in the paraventricular nucleus of the hypothalamus that contain CRH.⁷

A characteristic of autoimmune rheumatic diseases is the loss of immunological tolerance. The tolerance occurs when antigen-presenting cells process and present to it in the context of a reduced expression of the major histocompatibility complex (MHC) class II in a microenvironment that contains cytokines and anti-inflammatory hormones (IL-4, IL-10, cortisol, progesterone, androgens). If the microenvironment is made up from cytokines and pro-inflammatory hormones (IL-1, TNF- α , IL-6, oestrogen, PRL), the immune response will be exacerbated and will lead to a loss of tolerance and the development of an autoimmune disease.⁸

Therefore, disturbances in these physiological regulatory processes could become a potential risk factor in the development of autoimmune rheumatic diseases. In fact, an abnormal neuro-immuno-endocrine response has been found in patients with rheumatoid arthritis (RA), lupus erythematosus (SLE), Sjögren's syndrome,

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systemic sclerosis, fibromyalgia, etc. These alterations could be the cause or consequence of inflammatory and immunological abnormalities observed in these entities.^{9,10}

Many studies on animals and humans have shown the effect of stress on the immune system, which is considered a risk factor in the development of autoimmune diseases. Furthermore, retrospective studies have found that a high proportion of patients (80%) referred to a situation of stress before their illness started. Additionally, the disease itself causes stress, creating a vicious circle. Psychological stress, infections, physical trauma, etc. act as triggers to neuro-immuno-endocrine activity releasing cytokines and hormones.¹¹ A recent study analysed the response systems to stress of RA and SLE patients. They were submitted to short term experimental stress (psychological, cognitive, exercises and pain induction) and changes were found in the immune response when compared to the controls. However the results were inconsistent regarding the autonomic nervous system response and HPA axis.¹² These changes can contribute to the maintenance or exacerbation of inflammatory response in patients with these autoimmune diseases. Other studies have analysed the role of stress factors in infancy and their relationship with the risk of diseases, and found that individuals that reported 2 or more traumatic events during this stage in their life had an increased risk of up to 100% in developing a rheumatic diseases when compared to those that did not report it.¹³ The mechanisms implicated in these associations probably include changes in the function of the neuro-immuno-endocrine system.

Neuro-immuno-endocrine changes before an autoimmune disease develops have not been greatly investigated. A subgroup of premenopausal women that developed RA before they were 50 years old had decreased serum levels of dehydroepiandrosterone (DHEA), cortisol and testosterone elevation of IL-1, TNF and IL-6, for up to 12 years before developing the disease. Risk has also been related to lactation, which causes an increase of PRL and immune activation and with other environmental factors such as smoking in pregnancy and the positivity of anti-citrullinated antibodies and rheumatoid factor, amongst others. Although somewhat controversial, these findings suggest a change in the neuro-immuno-endocrine system in a pre-symptomatic phase of RA.^{14–17} Some patients have presented hyperprolactinemia before developing an autoimmune disease such as Graves disease, dermatomyositis, Sjögren syndrome and SLE.¹⁸ In accordance with the above a subgroup of patients with SLE who presented prolactinomas has been described. Nearly 50% of these patients presented hyperprolactinemia up to 5 years before the SLE diagnosis and developed clinical manifestations of SLE when the PRL levels were between 20–40 ng/ml.¹⁹

The neuro-immuno-endocrine system changes in RA and SLE have been a reason for research during the last decades. Serum cortisol levels similar to control subjects have been found in patients with RA, although with the presence of high levels of pro-inflammatory cytokines, which represent an inefficient response to this proinflammatory medium, even in the initial stages of the disease. These alterations are measured by hypothalamic hormones, pituitaries and some pro-inflammatory cytokines, such as IL6 and TNF- α .^{20,21} In fact it has been demonstrated that anti-TNF α therapy restores the HPA axis alterations in patients with RA and reduces tiredness, which clearly indicates that the pro-inflammatory cytokines alter the CNS function.^{22–24} A recent study showed that patients that had a good response to anti-TNF- α treatment also presented an increase in serum cortisol levels in contrast to patients with a poor response. The study indicates that inflammation induced by TNF- α interferes with the integrity of the HPA axis and correlates to treatment response. The determination of plasma cortisol can be a sensitive marker to predict the response to anti-TNF- α treatment.²⁵

There are low serum concentrations of androgens and their metabolites in RA patients, while the estrogen levels remain normal or even high.²⁶ An altered hormone metabolism with raised

16 α -hydroxiestrona/4-hydroxiestradiol metabolites has been reported in the synovial liquid of RA patients, which plays a role in the in synovial hyperplasia and interacts with pro-inflammatory cytokines (TNF- α , IL-1, eIL-6) and with estrogen receptors present in the synovial cells.^{27–30} Therapeutic blockade of TNF- α has shown beneficial effects on these alterations, increasing the dehydroepiandrosterone sulfate (DHEAS) levels, improving HPG axis.³¹

The activation of the sympathetic and parasympathetic nervous system in RA occurs parallel to the HPG axis activation and to the expression of cytokines, hormones and neurotransmitters. This hypothesis is based on experimental models of arthritis induced by type II collagen and studies on humans.^{32–35}

There is a clear female predominance in the autoimmune/inflammatory disease where SLE is a prototype, which indicates an immunomodulatory role of oestrogens and PRL. There is evidence in Murine SLE and humans of changes in the HPG axis characterised by adrenal insufficiency and normal pituitary functioning.³⁶ There has been evidence of abnormalities in androgen and estrogen metabolism with relation to the HPG axis since the eighties of the last century.³⁷ These changes are characterised by a hyperestrogenism state, with a reduction of androgens and their metabolites that participate in T cell activation and contribute to SLE pathogenesis.³⁸ Oestrogens also take part in the development and maturing process of the B lymphocytes.³⁹

The relationship between PRL and the immune system has been demonstrated over the last 3 decades. PRL is secreted not only by the anterior pituitary but also by many cells, including those of the immune system. PRL has an important role in innate and adaptive immune response as well as regulating the growth differentiation of the mammary gland and ovary. Hyperprolactinemia has been described in SLE, RA, systemic sclerosis, and psoriatic arthropathy amongst others. PRL increases the IFN- γ and IL-2 synthesis by lymphocytes and takes part in antibody production. Experimental studies and a few studies in humans support the efficacy potential of Dopamine agonists in LES, even during pregnancy and postpartum.⁴⁰

To conclude: A great amount of clinical and experimental evidence indicates that stress and changes in the neuro-immuno-endocrine system are a risk factor for the development of RA, SLE and other autoimmune diseases, and that they participate in the pathogenesis and clinical expression of these diseases. However, we still have along way to go. It is necessary to confirm these findings, investigate how these systems interact as a response to stress with the autoimmune system and propose new therapeutic alternatives that are able to restore the delicate balance of the neuro-immuno-endocrine system in autoimmune rheumatic diseases. This represents a real challenge for the rheumatologist over the next few years.

References

- Besedovsky HO, Del Rey A. Immune-neuro-endocrine interactions: facts and hypotheses. *Endocr Rev.* 1996;17:64–102.
- Jara LJ, Navarro C, Medina G, Vera-Lastra O, Blanco F. Immune-neuroendocrine interactions and autoimmune diseases. *Clin Dev Immunol.* 2006;13:109–23.
- Tait AS, Butts CL, Sternberg EM. The role of glucocorticoids and progestins in inflammatory, autoimmune, and infectious disease. *J Leukoc Biol.* 2008;84:924–31.
- Lakatos P, Blumsohn A, Eastell R, Tarjan G, Shinoda H, Stern PH. Circadian rhythm of in vitro bone-resorbing activity in human serum. *J Clin Endocrinol Metab.* 1995;80:3185–90.
- O'Connor JC, McCusker RH, Strle K, Johnson RW, Dantzer R, Kelley KW. Regulation of IGF-I function by proinflammatory cytokines: at the interface of immunology and endocrinology. *Cell Immunol.* 2008;252:91–110.
- Banks WA, Erickson MA. The blood-brain barrier and immune function and dysfunction. *Neurobiol Dis.* 2010;37:26–32.
- Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun.* 2007;21:153–60.
- Straub RH, Besedovsky HO. Integrated evolutionary immunological neuroendocrine framework for the pathogenesis of chronic disabling inflammatory F diseases. *FASEB J.* 2003;17:2176–83.
- Jafarian-Tehrani M, Sternberg EM. Neuroendocrine-immune modulation of autoimmune/inflammatory diseases. *Front Horm Res.* 2002;29:69–82.

10. Vera-Lastra O, Jara LJ, Medina G, Rojas JL, Velázquez F, Ariza R, et al. Functional hyperprolactinemia and hypophyseal microadenoma in systemic sclerosis. *J Rheumatol.* 2006;33:1108-12.
11. Stojanovich L, Marisavljevic D. Stress as a trigger of autoimmune disease. *Autoimmun Rev.* 2008;7:209-13.
12. De Brouwer SJ, Kraaijmaat FW, Sweep FC, Creemers MC, Radstake TR, Van Laarhoven AI, et al. Experimental stress in inflammatory rheumatic diseases: a review of psychophysiological stress responses. *Arthritis Res Ther.* 2010 May 17;12: R89 Epub.
13. Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, Croft JB. Cumulative childhood stress and autoimmune diseases in adults. *Psychosom Med.* 2009;71:243-50.
14. Masi AT, Aldag JC, Chatterton RT. Sex hormones and risks of rheumatoid arthritis and developmental or environmental influences. *Ann N Y Acad Sci.* 2006;1069:223-35.
15. Brennan P, Silman A. Breast-feeding and the onset of rheumatoid arthritis. *Arthritis Rheum.* 1994;37:808-13.
16. Berglin E, Kokkonen H, Einarsdottir E, Agren A, Rantapää Dahlqvist S. Influence of female hormonal factors, in relation to autoantibodies and genetic markers, on the development of rheumatoid arthritis in northern Sweden: a case-control study. *Scand J Rheumatol.* 2010;39:454-60.
17. Colebatch AN, Edwards CJ. The influence of early life factors on the risk of developing rheumatoid arthritis. *Clin Exp Immunol.* 2011;163:11-6.
18. Walker SE, Jacobson JD. Roles of prolactin and gonadotropin-releasing hormone in rheumatic diseases. *Rheum Dis Clin North Am.* 2000;26:713-36.
19. Jara Quezada LJ, Saavedra Salinas MA, Vera Lastra O, Alcalá Marquez. Enfermedades endocrinológicas y metabólicas. In: Alarcón Segovia D, Molina J, editors. *Tratado Hispanoamericano de Reumatología.* 1st ed. Volume II. Bogotá, Colombia: Schering-Plough; 2007. p. 1285-99.
20. Cutolo M, Sulli A, Pizzorni C, Cravioito C, Straub RH. Hypothalamic-pituitary-adrenocortical and gonadal functions in rheumatoid arthritis. *Ann NY Acad Sci.* 2003;992:107-17.
21. Straub RH, Paimela L, Peltomaa R, Schölmerich J, Leirisalo-Repo M. Inadequately low serum levels of steroid hormones in relation to IL-6 and TNF in untreated patients with early rheumatoid arthritis and reactive arthritis. *Arthritis Rheum.* 2002;46:654-62.
22. Herrmann M, Schölmerich J, Straub RH. Influence of cytokines and growth factors on distinct steroidogenic enzymes in vitro: a short tubular data collection. *Ann NY Acad Sci.* 2002;966:166-86.
23. Straub RH, Pongratz G, Schölmerich J, Kees F, Schaible TF, Antoni C, et al. Long-term anti-tumor necrosis factor antibody therapy in rheumatoid arthritis patients sensitizes the pituitary gland and favors adrenal androgen secretion. *Arthritis Rheum.* 2003;48:1504-12.
24. Daza L, Martín-Jiménez R, de la Torre P, Hernández E, Murillo B. Improvement of ACTH response to insulin tolerance test in female patients with rheumatoid arthritis due to tumor necrosis factor inhibition. *Eur J Endocrinol.* 2007;157:47-51.
25. Straub RH, Pongratz G, Cutolo M, Wjibrandts CA, Baeten D, Fleck M, et al. Increased cortisol relative to adrenocorticotropic hormone predicts improvement during anti-tumor necrosis factor therapy in rheumatoid arthritis. *Arthritis Rheum.* 2008;58:976-84.
26. Cutolo M, Capellino S, Montagna P, Villaggio B, Sulli A, Seriolo B, et al. New roles for estrogens in rheumatoid arthritis. *Clin Exp Rheumatol.* 2003;21:687-9.
27. Castagnetta L, Carruba G, Cutolo M, Stefano R, Miele M, Schmidt M, et al. Increased estrogen formation and estrogen to androgen ratio in the synovial fluid of patients with rheumatoid arthritis. *J Rheumatol.* 2003;30:2597-605.
28. Capellino S, Montagna P, Villaggio B, Soldano S, Straub RH, Cutolo M. Hydroxylated estrogen metabolites influence the proliferation of cultured human monocytes: possible role in synovial tissue hyperplasia. *Clin Exp Rheumatol.* 2008;26:903-9.
29. Cutolo M, Capellino S, Straub RH. Sex hormones, the immune system and autoimmune diseases. In: Walker SE, Jara LJ, editors. *Endocrine manifestations of systemic autoimmune diseases. Handbook of Systemic Autoimmune Diseases.* 1st ed. Volume 9. Elsevier B V; D 2008. p. 13-9.
30. Capellino S, Riepl B, Raucn L, Angele P, Cutolo M, Straub RH. Quantitative determination of steroid hormone receptor positive cells in synovium of RA and OA patients: is there a link to inflammation. *Ann Rheum Dis.* 2007;66:53-68.
31. Ernestam S, Hafström I, Werner S, Carlström K, Tengstrand B. Increased DHEAS levels in patients with rheumatoid arthritis after treatment with tumor necrosis factor antagonists: evidence for improved adrenal function. *J Rheumatol.* 2007;34:1451-8.
32. Del Rey A, Wolff C, Wildmann J, Randolph A, Hahnel A, Besedovsky HO, Straub RH. Disrupted brain-immune system-joint communication during experimental arthritis. *Arthritis Rheum.* 2008;58:3090-9.
33. Kuis W, de Jong-de Vos van Steenwijk CE, Sinnema G, Kavelaars A, Prakken B, Helders PJ, et al. The autonomic nervous system and the immune system in juvenile rheumatoid arthritis. *Brain Behav Immune.* 1996;10:387-98.
34. Dekkers JC, Geenen R, Godaert GL, Bijlsma JW, Van Doornen LJ. Elevated sympathetic nervous system activity in patients with recently diagnosed rheumatoid arthritis with active disease. *Clin Exp Rheumatol.* 2004;22:63-70.
35. Capellino S, Straub RH. Neuroendocrine immune control mechanisms, their influence on autoimmune diseases. In: Walker SE, Jara LJ, editors. *Endocrine manifestations of systemic autoimmune diseases. Handbook of Systemic Autoimmune Diseases.* 1st ed. Volumen 9. Elsevier B V; 2008. p. 3-12.
36. Zietz B, Reber T, Oertel M, Glück T, Schölmerich J, Straub RH. Altered function of the hypothalamic stress axes in patients with moderately active systemic lupus erythematosus II Dissociation between androstenedione, cortisol, or dehydroepiandrosterone and interleukin 6 or tumor necrosis factor. *J Rheumatol.* 2000;27:911-8.
37. Lahita RG, Bradlow HL, Kunkel HG, Fishman J. Increased 16 alpha-hydroxylation of estradiol in systemic lupus erythematosus. *J Clin Endocrinol Metab.* 1981;53:174-8.
38. Walters E, Rider V, Abdou NI, Greenwell C, Svojanovsky S, Smith P, et al. Estradiol targets T cell signaling pathways in human systemic lupus. *Clin Immunol.* 2009;133:428-36.
39. Venkatesh J, Peeva E, Xu X, Diamond B. Cutting Edge: Hormonal milieu, not antigenic specificity, determines the mature phenotype of autoreactive B cells. *J Immunol.* 2006;176:3311-4.
40. Jara LJ, Medina G, Saavedra MA, Vera-Lastra O, Navarro C. Prolactin and autoimmunity. *Clin Rev Allergy Immunol.* 2011;40:50-9.