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Review

Autoimmune diseases and their relation with immunological, neurological and endocrinological axes

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ABSTRACT

The immune response is complex, multifactorial, individualized and often unpredictable. There are multiple interconnected systems that allow a balance between physiological autoreactive processes and pathological autoimmunity with consequent organ-specific or systemic autoimmune disease. Based on the concept of the autoimmunity mosaic, up to 50% of autoimmune disorders do not have a clear etiological factor. In order to achieve a clear understanding of the different systems that influence the development of autoimmune diseases, the clinical auto–immunologist needs a dynamic and comprehensive vision of all interconnected pathways that maintain a precise balance in the organism. This has been and will remain a challenge. Understanding the different pathophysiological processes of these diseases will be the basis for predicting different clinical spectra and has the potential to offer innovative therapeutic approaches. This paper offers a practical overview of the bidirectional communication between the immune and endocrine system and the influence this has on the development of autoimmune diseases.

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1. Introduction

In order to maintain the balance between effective immunity and tolerance position against autoantigens, living beings have undergone a large number of molecular and biochemical processes of high complexity. In practical terms, the functions of the immune system can be summarized as follows: *1) recognize and respect 'own'*. Having the ability to recognize cell products such as hormones, cell receptors, metabolites, organelles and structures, interleukins and growth factors, among others, without mounting an immune response against them; *2) recognize non-self and be able to destroy it and debug it*. Non-self molecules, such as viruses, bacteria, toxins, and foreign tissue like grafts or transfusions and foreign proteins; *3) finally, the immune system also has the ability to recognize the self that has been modified and destroy it*. As in the case of tumor cells (expression of tumor antigens), virus infected cells or bacteria (co-expression of viral antigens presented by HLA molecules of class I), cells with mutations or aberrant expression of antigens.

In 1901, Paul Erlich, a German immunologist and hematologist, issued the first descriptions of these findings, coining the term known as *Horror autotoxicus*, a concept that, in clinical immunology, means homeostasis. After a century this theory remains in force. Erlich did not know elements of the immune system, however, he imagined the horror or tolerance as a regulatory mechanism to prevent self-poisoning

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or autoimmunity. In other words, he inferred the ability to recognize self and non-self. Erlich emphatically said that autoimmunity is a potentially active mechanism that under normal conditions it is kept under control. At the time, the medical community did not accept this hypothesis and believed that autoimmunity had to be intrinsically impossible. They considered that, in evolutionary terms, it was utopian to believe that living things could have the possibility of being subjected to "horrendous" self-destruction. Little by little, however, they associated various mysterious illnesses to the "autotoxicus horror". With the use of highly sensitive technologies, it was found that the autoimmunity is normally present in healthy individuals and plays an important role in the regulation of various biological processes, particularly in regards to avoiding the development of degenerative diseases. This slight degree of physiological activity to maintain immune homeostasis has been called self-reactivity. Conversely, when circulating antibodies are developed and even infiltrated tissue is present but with no association to clinical consequences, we face a process of incipient autoimmunity, which precedes pathological autoimmunity that is characterized with dysfunction and immune-mediated organ damage [1,2]. Depending on the interaction between common genes and/or genes specific to different environmental factors, autoimmune disease is expressed with different phenotypes (organ specific vs. non-organ specific). Thus, we conclude that autoimmune diseases are a complex group of chronic diseases resulting from the interaction between genetic, epigenetic, hormonal and environmental factors [3]. This multifactorial origin means that the exact cause of autoimmune diseases is unknown and in 1989, the term 'mosaic of autoimmunity' was coined, referring to the complex interplay between the immune system and the various stimuli that influence its control mechanisms [4]. As a group, autoimmune diseases share many signs and symptoms, pathophysiological mechanisms and even genetic, hormonal and environmental factors that allows them to be considered as a single disease with a single common origin, a term that has been named the 'tautology of autoimmunity' [5]. Collectively, they affect approximately 3.5% to 5% of the general population, with an estimated prevalence of 20% according to the NIH in 2001. Epidemiological data have shown that many autoimmune diseases are more frequent in some susceptible populations. This susceptibility is due to a common genetic background, but it is also associated with environmental factors, as already mentioned. This increased susceptibility is also important in the prediction context. Interestingly, 80% of the reported cases of autoimmune diseases are found in women of reproductive age, indicating that hormones have a predominant role in the development of autoimmunity [3,6].

This paper aims to review the impact of hormonal influences as potential triggers of autoimmune diseases.

1.1. Importance of the neuro-immune-endocrine axis in controlling immune homeostasis

When faced with an autoimmune disease, this should be evaluated from the perspective of the pathophysiological explanation for the loss of immune tolerance. Categorically, hormones are classified as pro-inflammatory (i.e., estrogens and prolactin (PRL)) and anti-inflammatory (i.e., cortisol, progesterone, androgens). It is likely that a pro-inflammatory environment or loss of physiological anti-inflammatory properties provides the breakdown of immune tolerance. From preclinical stages, it seems that this hormonal imbalance already exists [7]. It is thus likely that, based on this hormonal microenvironment, immunological tolerance occurs when antigen-presenting cells process and present autoantigens in the context of a decreased expression of class II major histocompatibility complex (MHC) under the influence of anti-inflammatory cytokines and hormones (IL-4, IL-10, cortisol, progesterone, androgens). If this microenvironment is based on pro-inflammatory cytokines and hormones (IL-1, TNF-alpha IL-6, estrogens, PRL), an exacerbated immune response will lead to the loss of tolerance and the development of an autoimmune disease [5,8,9].

From the initial activation of innate immunity, through the interaction of antigen presenting cells (APC), with the damage-associated molecular patterns and/or pathogenic (DAMPs and/or PAMPs) through to toll-like (TLRs) receptors, the activation of the endocrine system begins. Products of the binding of PAMPs or DAMPs with TLRs, a series of intracellular processes are generated, including activation of nuclear factor KB (NF-kB) and the mitogen activating protein kinase (MAPK). This generates transcription signals to the cell nucleus to produce pro-inflammatory cytokines such as interleukin-1α/β (IL-1α/β), and interleukin-6 (IL-6). These cytokines will not only generate a trigger of the same immune system to perpetuate the inflammatory response but they also will reach the central nervous system (CNS) to exert additional functions on local and systemic inflammatory control. As part of the innate immune system, the complement cascade also maintains a connection with the endocrine system. The presence of receptors for C3a has been demonstrated in the adrenal glands, pituitary gland, glial cells and neurons. For example, Francis and colleagues [10], hypothesized a new channel of communication between the immune system and the endocrine system, noting that C3a moiety, acting as a derived cytokine complement, is able to activate the hypothalamus-pituitary-adrenal axis, in order to control inflammation in stressful situations. Also, it seems that C3adesArg (a non-inflammatory metabolite) in cultured pituitary cells stimulates production of prolactin, growth hormone and adrenocorticotropin.

Besides control of cellular activation of the innate immune response to glucocorticoids inhibiting the production of pro-inflammatory cytokines and metalloproteinases (see below), anti-inflammatory cytokines are also produced diverting Th1 response to a Th2 response. The Th2 phenotype is a purely humoral response, in which cytokines are angiostatic and maintain the integrity of the systems while preserving microvascular permeability and inhibiting the expression of adhesion molecules, limiting endothelial activation and cell migration to inflammatory foci [11].

It should be noted that the synthesis and secretion of hormones and cytokines is a dynamic process that takes place in the cellular microenvironment. The cells have receptors for hormones, cytokines, PAMPs and/or DAMPs, all of which are activated to respond in a physiological manner to pathogens. Thus, the neuroendocrine system can, directly or indirectly, influence the development and function of the immune system; alternatively, the same immune system can contribute to the regulation of endocrine activity. The observed changes in hormone levels in the various autoimmune diseases may be reflective of coordinated bidirectional communication between the neuroendocrine and the immune systems. For many years, the CNS was considered a privileged organ, thanks to the inability of it to initiate an immune response against different antigens. Scientific information has, however, been accumulated, indicating that there is a bidirectional interaction between the CNS, endocrine and the immune system [12]. These interactions are maintained through embryonic and neonatal development to the final stages of life due to the interrelationship between neural pathways, hormonal circuits, cytokines, neuropeptides and chemokines. Activation of this network of systems is constantly influenced by stress processes such as infectious disease, autoinflammatory and/or autoimmune diseases or trauma. Different hormones and neuropeptides are not only secreted by endocrine glands but also by the same immune cells generating a paracrine effect on its function [13].

The neuroendocrine system is composed of the following axis: *1) hypothalamic-pituitary-adrenal (HPA) including cortisol, corticotropin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH)*; *2) hypothalamic-pituitary gonadal (HPG), including luteinizing hormone (LH), follicle stimulating hormone (FSH), gonadotropin releasing hormone (GnRH), estrogen, progesterone and androgens*; *3) hypothalamic pituitary-thyroid (HPT) consisting of thyroid hormones (T3 and T4), thyroid stimulating hormone (TSH) and thyrotropin releasing hormone (TRH)* and *4) system prolactin/growth hormone (PRL/GH)*. The messengers of this two-way communication are hormones, neuropeptides, the "pro-