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Prolactin and autoimmunity: The hormone as an inflammatory cytokine

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Nowadays, more than 80 autoimmune disorders are recognized, in which an aberrant immune response against different organs and tissues plays a crucial role. Hormonal homeostasis has great influence in achieving competent and healthy immune system function. Prolactin has a bioactive function acting as a hormone and a cytokine. It influences the immune system modulation, mainly inhibiting the negative selection of autoreactive B lymphocytes. Hyperprolactinemia has been detected in many patients with different autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, multiple sclerosis, autoimmune thyroid disease, systemic sclerosis, among others, and its believed to play a crucial role in disease pathogenesis. A direct correlation between prolactin levels and disease

Abbreviations list: DHEA, dehydroepiandrosterone; DMARDs, disease-modifying anti-rheumatic drugs; Ig, immunoglobulin; IL, interleukin; JAK/STAT, Janus kinase/signal transducer and activator of transcription; MAPK, phosphoinositide 3-kinase and the mitogen-activated protein kinase; NOD, Non-obese diabetic; SLE, systemic lupus erythematosus; TNF, Tumor necrosis factor.

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activity was not clear. Genetic factors may have a role in humans as in animal models. Dopamine agonists have proven to offer clinical benefits among autoimmune patients and represent a promising therapy to be explored. In this review, the authors attempt to provide a critical overview on the role of prolactin in the immune system, exploring its contribution to the development of autoimmune diseases.

Introduction

Nowadays, more than 80 autoimmune disorders are recognized, in which an aberrant immune response against different organs and tissues plays a crucial role [1]. The immune and neuroendocrine system are intimately connected, partaking of dynamic bidirectional communication. Hormonal homeostasis has a great influence in achieving a competent and healthy immune system function [2]. Prolactin is a polypeptide hormone and was firstly described as a pituitary factor stimulating lactation in rabbit models. Since then, a great variety of actions have been attributed to prolactin, although one of the most enigmatic and controversial aspects is related with its capability of regulating immune responses and autoimmune inflammation [3,4]. Hyperprolactinemia has been detected in many patients with different autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, multiple sclerosis, autoimmune thyroid disease, systemic sclerosis and others [5,6]. Although the mechanisms involving this interaction are not completely understood, it has been documented that prolactin can influence the communication and regulation of immune cells [7]. In this review, the authors attempt to provide a critical overview on the role of prolactin in the immune system, exploring its contribution to the development of autoimmune diseases.

Prolactin and the immune system

Prolactin is a 23 kDa polypeptide hormone, mainly secreted by the lactotrophic cells of the pituitary gland, under tonic inhibition of the hypothalamus via dopamine [4]. This hormone can also be secreted in several extra-pituitary locations, including mammary epithelium, ovary, placenta, neurons, endothelium, skin cells, adipose tissue, prostate, spleen, bone marrow and immune cells, although with a different molecular weight and biologic activity [8]. Serum prolactin levels may be influenced by the circadian rhythm (peak at 2AM) [9], exercise, emotional or physical stress, high-protein meals, breast stimulation and pathologic conditions such as prolactinoma, hypothyroidism and adrenal insufficiency [10]. Likewise, cytokines interleukin (IL)-1, IL-2 and IL-6 stimulate its secretion, while endothelin-3 and interferon-γ play an inhibitory influence [11]. Due to its variations by posttranslational modifications (such as phosphorylation and glycosylation), prolactin exists in several isoforms, each one with different receptor binding and bioactivity [12]. The prolactin receptor (PRLR) belongs to the cytokine/hematopoietic receptor super-family and is the only receptor known for prolactin. It also exists in assorted isoforms, based on amino-acid sequences and sizes of cytoplasmic domain. Prolactin is a cytokine which appears to stimulate both cell and humoral immunity [13]. Its receptors are expressed in a great variety of immune cells, including macrophages, monocytes, lymphocytes, granulocytes, natural killer cells and thymic epithelial cells (Fig. 1). The binding of prolactin to its receptor activates downstream signaling cascades, influencing several cell functions [14].

Prolactin and immunogenetics

Humans express a single prolactin gene, located on the short arm of chromosome 6, near the HLA-DRB1 region. Its expression is not restricted to the pituitary gland, since occurs in a variety of extra-pituitary sites. Estrogens are involved in the regulation of the prolactin gene [15,16]. Adamson et al.

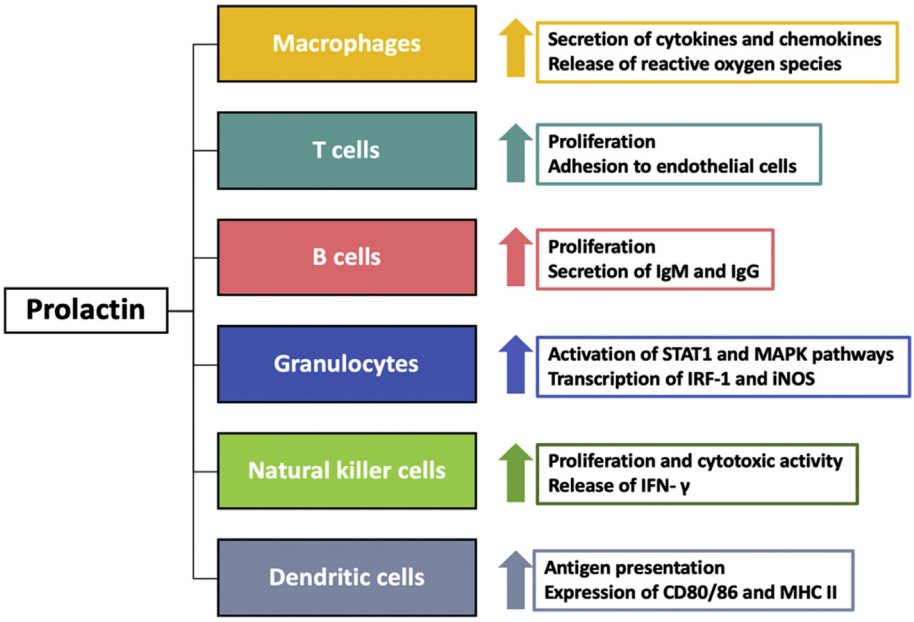

Fig. 1. Influence of prolactin on the immune cells. IFN, interferon; Ig, immunoglobulin; IL, interleukin; iNOS, inducible nitric oxide synthase; MAPK, phosphoinositide 3-kinase and the mitogen-activated protein kinase; STAT, signal transducer and activator of transcription.

successfully demonstrated a novel promoter-specific signaling interaction between estrogen and TNF-α signaling for prolactin regulation [17]. Furthermore, mutations in these genes have been associated with the development of autoimmune diseases. A relationship between HLA-DRB1 alleles and the microsatellite markers alleles near the prolactin gene were seen in women with rheumatoid arthritis and systemic lupus erythematosus, suggesting the possibility of extended haplotypes encoding for HLA-DRB1 susceptibility and hyperprolactinemia [18]. Recently, a meta-analysis investigated the association between prolactin-1149G/T polymorphism and the susceptibility to develop autoimmune disorders. The authors successfully demonstrated an association for rheumatoid arthritis but not for systemic lupus erythematosus [19]. In addition, another study examined the prolactin-1149G/T in women with systemic lupus erythematosus. The findings revealed that prolactin-1149TT genotype was correlated with prolactin gene expression, hyperprolactinemia and low levels of dehydroepiandrosterone (DHEA), hypothesizing that prolactin-1149TT genotype could represent a risk factor for systemic lupus erythematosus patients [20].

Immune modulation properties of prolactin

The prolactin receptor belongs to the cytokine/hematopoietic receptor super-family, which also includes receptors for leptin, IL-2, IL-3, IL-4, IL-6, IL-7, growth hormone, erythropoietin and leukemia inhibiting factor. The binding of prolactin to its receptor, triggers different reaction pathways, namely P13K/Akt, MAPK and JAK/STAT [14]. The activation of these cascades has the ability to influence immune cells secretion, differentiation, proliferation and survival [21]. Prolactin enhances cytokine production and the expression of human T-cell markers on mitogen-stimulated normal CD8+ T-cells [22]. Recent data supports a pleiotropic effect of prolactin in the thymus gland. When thymus dendritic cells were treated with prolactin, there was an increased responsiveness in allogenic mixed leukocyte reactions and enhanced cytokine production was observed [23]. Likewise, prolactin was shown to impair B cell receptor-mediated clonal deletion, deregulate receptor editing, decrease the threshold for

activation of anergic B cells and finally interfere with B cell tolerance induction [24]. In lupus murine models, prolactin decreased apoptosis of transitional B cells and promoted a breakdown of B cell tolerance to self [25]. These anti-apoptotic properties activate multiple signaling pathways and lead to a higher expression of survival proteins [26]. Furthermore, prolactin regulates Th1 type cytokines, boosting the production of IL-1, IL-2, IL-6, interferon-γ and enhances the expression of IL-2 receptor [2,27]. A correlation between prolactin levels and the number of B and CD4+ T lymphocytes was found. Indeed, prolactin was able to influence the maturation of CD4-and CD8-thymocytes, via IL-2 receptor, leading to the enhancement of pro-B cell generation [28]. In addition, it's influence on immunoglobulin production, development of antigen presenting cells and interaction between B and T cells can also induce auto-reactivity [29]. Several studies successfully demonstrated a variety of auto-antibodies in patients with hyperprolactinemia, including antibodies against prolactin, cardiolipin, β-2-glycoprotein I, endothelial cells, Ro and La [30–35]. Induced moderate hyperprolactinemia, was shown to break tolerance and induce lupus-like disease in non-spontaneously autoimmune mice with genetic susceptibility [36]. A low-dose of prolactin can provoke pro-inflammatory responses and antibody production, whereas high-doses suppress these responses. These controversial effects may involve modulation of a key transcription factor directing Th1 inflammatory responses, T-bet [37]. Another strategy to determine the prolactin influence in the immune system was made by reducing its serum levels with a dopamine D2 agonist (bromocriptine). Although the pharmacological specificity of this drug was questioned, based on studies that demonstrated a direct suppressive effect of the drug in lymphocyte function [38,39], the obliteration of prolactin secretion with bromocriptine shows beneficial effects both in human and animal models [40–42].

Prolactin and the “mosaic of autoimmunity”

More than 25 years ago, the concept of the “mosaic of autoimmunity” was introduced to the scientific community by *Shoenfeld* et al. [43]. Since then, new pieces have been regularly added, turning the mosaic into a more complex network each day [44]. Prolactin is an integral member of the immune-neuro-endocrinology chain and has long been related with autoimmune diseases [2,5,45]. High levels of serum prolactin have been described in the history of several autoimmune diseases, both organ and non-organ specific (Table 1) [46]. The interactions among prolactin, cytokines, antibodies and organ involvement propose an active influence of prolactin in inflammatory and immune processes, acting as a link between the neuroendocrine and immune system [47,48].

Non-organ specific autoimmune diseases

Prolactin and systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a complex and debilitating autoimmune disease, attributed to the development of antinuclear or anti-double strained DNA antibodies (anti-dsDNA) [49]. The

Table 1
Hyperprolactinemia and autoimmune diseases.

Systemic diseases	Organ-specific diseases
Systemic lupus erythematosus	Type 1 diabetes
Anti-phospholipid syndrome	Multiple sclerosis
Rheumatoid arthritis	Myasthenia gravis
Psoriatic arthritis	Pemphigus vulgaris
Sjögren syndrome	Psoriasis vulgaris
Systemic sclerosis	Celiac disease
Behçet's disease	Autoimmune thyroid disease
Reactive arthritis	Autoimmune uveitis
	Addison's disease
	Lymphocytic hypophysitis
	Peripartum cardiomyopathy
	Rejection of heart transplantation

higher incidence of SLE is among women at reproductive age when compared to men (ratio 9:1) suggesting a crucial role of sex hormones on the disease pathogenesis [50–52]. Despite all, serum levels of prolactin above the normal range have been described in patients with SLE irrespective to gender (15–45%) [45,53–56]. In animal models, prolactin receptor was found to be expressed in early bone marrow B cells, emphasizing the influence of this hormone in B cell development [57]. Furthermore, hyperprolactinemia was associated with higher IgG levels, anti-DNA antibodies, immune complexes, glomerulonephritis and premature death [58]. The prolactin effect appears to be accentuated by estrogen stimulation of prolactin secretion [59]. *Peeva* et al. performed a study with transgenic mice and successfully demonstrated that treatment with estrogen and bromocriptine led to a reduction of anti-DNA antibodies levels and IgG complex deposition in the kidneys, when compared to treatment using only estrogens. These results propose that estrogen-induced breakdown in B-cell tolerance can be neutralized by bromocriptine, which induces anergy in DNA-reactive B cells [36]. Indeed, both hormones promote the survival and activation of autoreactive B cells in SLE models, offering new targets for novel treatments [28]. In humans, hyperprolactinemia has been largely associated with SLE patients specially, those with active disease. Independent studies were able to find significant correlations between hyperprolactinemia and anti-dsDNA, anti-cardiolipin, low C3, erythrocyte sedimentation, anemia and all types of serositis [60,61]. Furthermore, clinical observations hypothesize that prolactin might be produced in damaged organs from SLE by accumulation and promotion of lymphocyte infiltration. Patients following an immunosuppressive therapy show lower prolactin levels in relation to disease remission [62]. The link between hyperprolactinemia and SLE activity might be explained by the decreased suppressive function of T-regulatory cells, promoting an inflammatory state. Despite all, results regarding prolactin and SLE disease severity remain controversial, probably due to altered bioactivity of the prolactin variants, genetic factors, methodologies and others [55,56,60,63]. Patients with active SLE have an enhanced production of a prolactin-like immunereactive substance with different molecular weight [64]. Besides, low levels of homovanilic acid, a dopamine metabolite, was found in SLE, suggesting a dopamine defect among these patients [65]. The exact source of hyperprolactinemia in SLE patients remains unclear, although several studies suggest an extra-pituitary production from lymphocytes. *Diamond* et al. discovered that some anti-DNA antibodies were capable of interaction with the N-Methyl-D-aspartate receptor in the brain and promoted the secretion of prolactin, introducing a novel idea for the development of new treatments that could disrupt the vicious cycle of lupus antibodies increasing prolactin levels and promoting disease severity [66,67]. A few controlled studies treating SLE patients with dopamine agonists have been conducted so far. Data strongly supports the benefits of bromocriptine on the reduction of flares and disease activity, even when compared to hydroxychloroquine [68]. Interestingly, the injection of CD8 cells from SLE-mice treated with bromocriptine, abolished disease development in experimental models. These results suggest that bromocriptine might downregulate autoimmune events through the induction of natural non-specific CD8 suppressor cells [40].

Prolactin and the primary anti-phospholipid syndrome

Anti-phospholipid syndrome is a systemic autoimmune condition, characterized by the presence of anti-phospholipid antibodies, recurrent thrombosis and miscarriages [69,70]. A large cohort performed by *Praprotnik* et al. unveiled for the first time significantly higher levels of prolactin among 12% of patients with anti-phospholipid syndrome (primary and secondary), for both genders, when compared to healthy subjects [71]. Curiously, typical clinical signs of hyperprolactinemia, such as galactorrhea, male gynecomastia and amenorrhea were not observed. In contrast, high levels of prolactin were associated with obstetric complications and the presence of lupus anticoagulants, although no significant association was found with thrombosis events. For a long time, prolactin was believed to be a potent coactivator of platelet aggregation and potential promoter of thromboembolic events, although recent studies reported controversial results [72,73]. Interestingly, the presence of hyperprolactinemia was negatively correlated with arthralgia, suggesting a possible protective role and alternative marker for some diseases manifestations [71]. In anti-phospholipid syndrome experimental models, bromocriptine was shown to downregulate autoimmune phenomena [40,74,75].

Prolactin and systemic sclerosis

Systemic sclerosis is a connective tissue disorder characterized by diffuse vascular lesions and fibrotic changes affecting skin and major organs. Its pathogenesis is extremely complex and still poorly understood [76,77]. Systemic sclerosis was found to be five times more common among women at reproductive age when compared to men [78]. *Fojtíková* et al. described the 1149 TT genotype of the extra-pituitary prolactin promoter as being specific for systemic sclerosis and that it was also associated with decreased risk of developing the disease in older age [79]. Studies have reported high levels of prolactin among a wide range of patients suffering from systemic sclerosis (3–81%), probably in relation with an aberrant circadian rhythm [46,53,80–83]. *La Montagna* et al. performed a study to evaluate the basal and dynamic levels of pituitary gonadotropin release in females with systemic sclerosis on childbearing and post-menopausal age. After stimulation with thyroid releasing hormone, prolactin levels were higher in fertile women but not in post-menopausal patients when compared to the healthy controls, suggesting an influence of the hormone on the decreased fertility among these women. Besides, prolactin levels were also associated with skin sclerosis, peripheral vascular and lung involvement [84]. Interestingly, in another study almost 80% of the patients with systemic sclerosis were diagnosed with asymptomatic microadenoma. After the metochlopramide test, prolactin levels were found dramatically increased in systemic sclerosis patients, maybe due to a higher dopaminergic tone [85]. Likewise, hyperprolactinemia was correlated with more aggressive skin involvement (mainly in early disease), diastolic dysfunction of the left ventricle and disease duration [82]. In accordance, patients with severe disease manifestations had significantly higher levels of prolactin and lower levels of dehydroepiandrosterone, probably due to enhanced soluble IL-2 receptor and vascular cell adhesion molecule [20]. As described in other autoimmune diseases, peripheral blood mononuclear cells were found to contain increased amounts of prolactin and to be more sensitive to prolactin stimulation [83]. These results suggest that the etiology of hyperprolactinemia in systemic sclerosis patients could be due to an increased dopaminergic tone and/or lymphocytic secretion.

Prolactin and rheumatoid arthritis

Rheumatoid arthritis is a chronic, autoimmune inflammatory disease affecting the synovial membrane, cartilage and bone [86]. A large study found a possible correlation between decreased risk of developing rheumatoid arthritis and the prolactin-1149T polymorphism, which has been associated with reduced prolactin production by lymphocytes [87,88]. Studies relating rheumatoid arthritis and hyperprolactinemia have been controversial, although serum prolactin and monomeric prolactin were significantly increased in rheumatoid arthritis patients [89]. Besides, male patients were also proved to have higher titers [90]. Prolactin is thought to have a crucial role in initiating and/or sustaining inflammation in rheumatoid arthritis. It is known that rheumatoid arthritis usually improves during pregnancy and exacerbates during postpartum, probably due to growing levels of prolactin and decreased cortisol and estrogen serum titers [91]. After the corticotropine releasing hormone test, upregulation of prolactin secretion in women under 40 years old was shown [92,93]. Higher levels of prolactin and prolactin/cortisol ratio at 2AM were demonstrated in postmenopausal women with active disease [94]. Furthermore, prolactin response to induced hypoglycemia was found to have controversial results [95,96]. *Kullich* et al. reported a positive influence of prolactin on pro-inflamatory cytokine production by macrophages [97]. Likewise, prolactin was found to be produced by fibroblast-like synovial cells and by T lymphocytes in rheumatoid joints, increasing the synthesis of matrix metalloproteinase-3, IL-6 and IL-8. In addition, serum prolactin has been associated with duration, activity of the disease, severe radiographic damage and worse functional stage [98]. *Figueroa* et al. successfully demonstrated clinical improvement and reduced immune activity following bromocriptine treatment in patients who discontinued DMARDs [99], while other studies failed to demonstrate clinical benefits of bromocriptine [100]. Regarding cabergolide, there is only one case report revealing disease improvement in a patient with prolactinoma [101]. In conclusion, dopamine is known to be inappropriate for downregulating prolactin production in extrapituitary tissues, therefore alternative therapeutic approaches have been developed to block prolactin receptor-mediated signaling instead of extra-pituitary prolactin production.

Prolactin and Sjögren syndrome

Primary Sjögren syndrome is a chronic autoimmune disease characterized by exocrine glandular insufficiency secondary to lymphocytic and plasmacell infiltration [102]. The spectrum of the disease extends from an organ specific autoimmune disease to systemic involvement [103,104]. Hyperprolactinemia has also been associated with Sjögren syndrome especially in patients diagnosed at a young age with active immunological disease [105]. Studies report levels of prolactin approximately 1.3–2.4 times higher than the healthy population and it was associated with internal organ disease score [105–107]. Despite all, the levels of the hormone were not correlated with the disease duration, systemic manifestations, antibodies or immunoglobulin levels. Prolactin is thought to reflect disease pathology rather than its presence in a subset of patients [108].

Prolactin and psoriatic arthritis

Psoriatic arthritis is an auto-inflammatory disease in which the prolactin receptor is expressed on macrophages [109]. Prolactin was found to be locally expressed in the synovial fluid of patients with psoriatic arthritis, by confirmed measuring of synovial micro-RNA expression [110] and its positively correlated with several clinical disease parameters, including erythrocyte sedimentation rate, swollen joint count of 28 joints, visual analog scale of global disease activity and disease activity score [111]. Through the years, studies have demonstrated benefits of bromocriptine treatment by modulating the disease [112–114]. Recently, *Kokot* et al. showed that regardless of serum prolactin levels, administration of bromocriptine improves joint and skin symptoms, which indicates a decrease in disease activity and might be a promising way of alternative therapy for psoriatic arthritis [115].

Prolactin and Behçet's disease

Behcet's disease is a chronic relapsing multi-systemic inflammatory disorder characterized by orogenital ulcerations, skin lesions, intraocular inflammation and less commonly arthritic, vascular, gastrointestinal and neurologic manifestations. The presence of hyperprolactinemia in patients with Behçet disease has been proposed in several studies [116]. *Atasoy* et al. demonstrated high levels of prolactin in patients with active disease in comparison to inactive Behçet disease patients [117]. The elevated levels of prolactin may contribute to disease activity by augmenting immune processes [118,119].

Organ-specific autoimmune diseases

Prolactin and type 1 diabetes

Type 1 diabetes is an insulin-deficient condition resulting from the autoimmune destruction of pancreatic beta cells. Although hyperprolactinemia has been detected in patients with type 1 diabetes, the possible influence of this hormone in disease development is poorly understood [53]. Hypothesis involving interactions between prolactin receptor and toll-like receptors during infections or inflammation processes triggering the disease have been postulated [120]. Recent studies have found a linkage disequilibrium between the prolactin gene and the major histocompatibility complex gene, known to be associated with type 1 diabetes [121]. Interestingly, in animal models, prolactin has shown an important role in the upregulation of islet cell function in the fetus, promoting increased β-cell proliferation, islet cell mass, insulin synthesis and secretion [122,123]. Likewise, prolactin was capable of regulating β-cell apoptosis and survival [124]. Recently, *Hyslop* et al. reported that prolactin was able to improve β-cell proliferation, pancreatic insulin content, and insulin secretory capacity above a threshold required to maintain normal glycemic levels in NOD mice [125]. Despite the wide correlation between hyperprolactinemia and autoimmune diseases in humans, the molecular mechanisms of prolactin influence in pancreatic islet cells has only been addressed on animal models.

Prolactin and multiple sclerosis

Multiple sclerosis is a chronic inflammatory disorder of the central nervous system characterized by the presence of multifocal areas of immune cell infiltration, demyelination and axonal damage mainly located in the white matter [126]. In animal models, this disease is represented by experimental autoimmune encephalomyelitis, believed to be an inflammatory response against oligodendrocytes

that form the myelin sheath surrounding neuronal axons driven by myelin-reactive CD4+ Th1/Th17 cells [127]. Almost 35 years ago, *Nagy* et al. reported a clinical improvement of experimental autoimmune encephalomyelitis following bromocriptine treatment, suggesting a potential negative influence for prolactin [128]. Since then, emerging data support the benefits of bromocriptine on animal models [129–131]. In addition, controversial results have been obtained while exploring hyperprolactinemia and multiple sclerosis [6]. Several studies demonstrate a positive correlation between hyperprolactinemia and disease onset, recurrence [132] and with the number of anti-myelin oligodendrocyte glycoprotein antibody secreting cells [133]. There was no difference in prolactin levels between the relapsing-remitting and the progressive type of multiple sclerosis [134]. Recently, *Da Costa* et al. documented hyperprolactinemia in 6.7% of patients with multiple sclerosis. Among female patients, prolactin was related to the secondary progressive type of the disease [135]. In accordance, a case report described multiple sclerosis onset during a developing prolactinoma, followed by disease relapse during adenoma recurrence, suggesting the pro-inflammatory role of prolactin on the disease [136]. Studies evaluating treatment with bromocriptine showed no efficacy in reducing disease activity [137].

Prolactin and myasthenia gravis

Myasthenia gravis is an archetypal autoimmune disease, characterized by autoantibodies against the acetylcholine receptor, muscle-specific tyrosine kinase or against a growing variety of postsynaptic proteins in smaller subsets [138]. Prolactin and its receptor are located on chromosome 6, near the HLA A1-B8 extended haplotype which is associated with myasthenia gravis in women with thymic hyperplasia [139,140]. Despite the limited data available, a few case reports of myasthenia gravis in association with prolactinomas have been published [141]. In accordance with early studies reporting high levels of prolactin among these patients, some of them in relation with prolactinomas, the suggestion that prolactin might be implied in the pathophysiology of the disease is inferred [142,143]. This hormone has been found on thymic epithelial cells and influences T cell function, thymulin production and thymic epithelial cell growth, which in the other hand can be modulated by anti-prolactin receptor antibodies with agonistic function. However, the possible roles of thymus derived prolactin and the functional involvement in thymic disorders remain unknown. No available data was found regarding dopamine agonist treatment in patients with myasthenia gravis.

Prolactin and pemphigus vulgaris

Pemphigus vulgaris is an autoimmune bullous disease involving both the skin and mucosal areas, which is characterized by intraepithelial flaccid blisters and erosions [144,145]. It is known that autoantibodies against desmosomal glycoproteins including desmoglein-1 and desmoglein-3 play a role in the pathogenesis of the disease, although the specific molecular steps in initiation and perpetuation of this abnormality remain unknown [146,147]. A cross-sectional study demonstrated that prolactin serum levels were correlated with the extent of body involvement ($P = 0.01$) [148]. Recently, *Yousefi* et al. demonstrated that patients with pemphigus had higher total and free prolactin and lower dehydroepiandrosterone concentrations. Besides, patients with more severe disease were found to have higher levels of total serum prolactin, suggesting an active role of this hormone in the pathogenesis of the disease [149]. Unfortunately, the available data relating these two entities is remote, therefore future studies are needed to clarify the influence of prolactin in pemphigus vulgaris.

Prolactin and celiac disease

Celiac disease is a gluten-sensitive autoimmune enteropathy where both adaptive and innate immunity are involved in its development [150]. In celiac patients, the production of inflammatory cytokines is increased by the consumption of gliadin. Serum levels of prolactin were shown to have a close relationship with celiac disease activity [151]. Besides, prolactin levels were positively correlated with the degree of mucosal atrophy and with the serum concentration of anti-endomysial antibodies. *Kapur* et al. reported a positive correlation between prolactin levels and disease activity, duration of symptoms and age at diagnosis [152]. A recent longitudinal study performed by *Delvecchio* et al. revealed high levels of prolactin among celiac patients when compared to healthy subjects. In addition, levels diminish after 6 months following a gluten-free diet. The evidence of decreasing prolactin

simultaneously with the decline of anti-transglutaminase antibodies, suggests that compliance with a gluten-free diet correlates with prolactin levels [153].

Prolactin and autoimmune thyroid disease

Autoimmune thyroid diseases comprise mainly two disorders, Grave's disease and Hashimoto thyroiditis. The etiology is multifactorial, involving genetic and environmental factors, with a great preponderance in females [154]. High levels of prolactin were found in 20% of patients with autoimmune thyroid disease and were twice more frequently among autoimmune hypothyroidism. Around 90% of Hashimoto's thyroiditis patients presented significantly higher prolactin levels in association with decreased cortisol titers [155]. Interestingly, schizophrenic patients under anti-psychotic drugs were found to exhibit hyperprolactinemia and anti-thyroid antibodies [156]. The laboratory follow up including prolactin levels for patients with autoimmune thyroiditis has been proposed specially, for those with impaired thyroid function [157]. The role of dopamine agonists in treatment of autoimmune diseases is yet to be determined.

Prolactin and psoriasis vulgaris

Psoriasis vulgaris is an inflammatory, immune-mediated skin disease, characterized by type 1 T cell infiltration. Human skin is also a source of prolactin. Likewise, prolactin acts as a neuroendocrine modulator of both skin epithelial growth and the skin immune system [158]. *Rathika* et al. found significantly higher levels of prolactin in patients with psoriasis in comparison to healthy subjects, with a positive correlation with disease severity. Besides, levels of prolactin decreased after psoriasis treatment [159]. Hyperprolactinemia might play a role in the proliferation of keratinocytes in psoriasis vulgaris, promoting T cell infiltration via CCL20 [160,161]. Treatment of this disease with bromocriptine has been proposed in the past, displaying evident benefits and mild side effects [162,163].

Prolactin and autoimmune uveitis

Autoimmune uveitis is an organ-specific disorder characterized by irreversible lesions to the eye and is among the leading causes of visual deficit and blindness [164]. Hyperprolactinemia has been linked with anterior uveitis, although no significant correlation with disease activity was found. *Proença* et al. reported high serum levels of prolactin in HLA-B27 related uveitis patients [165]. Likewise, intra-ocular prolactin was elevated in patients with cataract and anterior uveitis, in comparison with patients carrying only cataract [166]. Bromocriptine was found to lower prolactin systemic levels and diminished the inflammatory response in experimental autoimmune uveitis models, in accordance with preliminary trials in humans [167,168].

Prolactin and lymphocytic hypophysitis

Lymphocytic hypophysitis is defined as an inflammatory condition of the pituitary gland of autoimmune etiology that leads to pituitary dysfunction [169]. Hyperprolactinemia has been frequently described in patients with lymphocytic hypophysitis accompanied by an enlargement of the pituitary gland. *De Bellis* et al. demonstrated high prolactin levels associated with anti-prolactin antibodies in patients with lymphocytic hypophysitis [170], suggesting that the hormone source could be both from the pituitary and immune cells [47]. Besides, anti-prolactin antibodies could be useful in identifying forms of subclinical autoimmune pituitary disease in patients with apparently idiopathic hyperprolactinemia [171].

Prolactin and peripartum cardiomyopathy

Peripartum cardiomyopathy is a rare but potentially fatal disease defined by heart failure towards the end of pregnancy or in the months following delivery, affecting previously healthy women [172]. The etiology of this disease remains unclear, although several underlying mechanisms have been proposed, including viral infections, low selenium level, stress-activated cytokines, inflammation and autoimmune reactions, and a pathological response to hemodynamic stress [173]. Prolactin has demonstrated an active role in the pathophysiology of peripartum cardiomyopathy. Increased oxidative stress and subsequent generation of 16 kDa prolactin impairs the cardiac vasculature and its metabolism, finally culminating in systolic heart failure [174–176]. *Haghikia* et al. identified the

presence of auto-antibodies against troponin I and sarcomeric myosin in the serum of patients with peripartum miocardiopathy. Furthermore, the presence of those antibodies was correlated with the severity of left ventricle dysfunction and lower rate of full cardiac recovery on follow-up [177]. In addition to the autoantibodies, these patients demonstrate a heightened level of fetal microchimerism, an abnormal cytokine profile (increased levels of TNF, IL-6 and soluble Fas receptors), decreased levels of CD4+ CD25lo regulatory T cells, and a significant reduction in the plasma levels of progesterone, estradiol and relaxin, contributing to an aberrant immunologic activity and inflammatory processes [178,179]. In the las years, several studies emerged using dopamine agonists in the treatment of this disease, with great results so far [180–183].

Conclusions

Prolactin has a bioactive function acting as a hormone and a cytokine. It exerts a great influence in the immune system modulation, mainly inhibiting the negative selection of autoreactive B lymphocytes. Hyperprolactinemia has been associated with several autoimmune diseases, and it's believed to play a crucial role in disease pathogenesis. In accordance, a direct correlation between prolactin levels and disease activity was founded in some disorders. Probably, it might be one of the hidden keys promoting pregnancy and postpartum exacerbations of autoimmune diseases. Dopamine agonists have proven to offer clinical benefits and represent a promising therapy to research.

Conflicts of interest

The authors have no potential conflicts of interest in authorship or publication.

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Practice points

- Autoimmune diseases are more common in women, mainly at a reproductive age.
- Prolactin interferes with the negative selection of auto-reactive B cells, enhances their proliferation, survival and increases antibody production.
- Hyperprolactinemia has been associated with several autoimmune disorders and is believed to play a crucial role in disease pathogenesis.

Research agenda

- A consistent correlation between prolactin levels and autoimmune disease activity is yet not clear, therefore investigations to delineate this association are lacking.
- Dopamine agonists have been used in the treatment of autoimmune diseases with great results, nevertheless future studies are needed to reinforce this benefits.

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