Hyperprolactinemia and autoimmune diseases

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Abstract

The autoimmune diseases are more common in females. The sex hormones have an important role in this gender bias, mainly estrogen and prolactin (PRL) which modulate the immune response. PRL is secreted from the pituitary gland and other organs and cells mainly the lymphocytes. PRL has an immunostimulatory effect and promotes autoimmunity: PRL impairs the negative selection of autoreactive B lymphocytes occurring during B cell maturation into fully functional B cells. PRL has an anti-apoptotic effect, enhances proliferative response to antigens and mitogens and enhances the production of immunoglobulins and autoantibodies.

Hyperprolactinemia (HPRL) is observed in multi-organ and organ specific autoimmune diseases like systemic lupus erythematosus (SLE) rheumatoid arthritis (RA), Sjogren’s syndrome (SS), Hashimoto’s thyroiditis (HT) and multiple sclerosis (MS). There is no consistent correlation between PRL levels and disease activity. Murine models and small studies in SLE patients suggest some role of dopamine agonists in the therapy of those diseases. The genetic factor may have a role in humans as in animal models. The PRL isoform has an important effect on the bioactivity on prolactin receptors (PRL-Rs).

Keywords: Prolactin; Autoimmune; Immunostimulation; SLE; Bromocriptine; B-lymphocytes

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The high incidence of autoimmune diseases among females suggests that gender may be a risk factor in the development of autoimmune diseases. Sex hormones, mainly estrogen and prolactin, are implicated in modulating the immune response [1].

Prolactin is a peptide hormone secreted from the anterior pituitary gland under tonic inhibition of the hypothalamus, via dopamine. The cytokines IL-1, IL-2 and IL-6 stimulate PRL secretion, while interferon γ and endothelin-3 are inhibitory [2]. Pituitary secretion of PRL is stimulated by suckling and stress. PRL stimulates mammary growth and differentiation and is critical in lactation. PRL is secreted in a circadian rhythm with a peak at about 0200. PRL has multiple immunostimulatory effects and promotes autoimmunity. It has a role in reproduction, calcium metabolism, osmoregulation and behavior [2].

Pituitary monomeric free PRL consists of 199 amino acids and has a molecular weight of 23 kDa, but a portion undergoes dimerization or polymerization or binds to proteins [3]. The other isoforms of PRL include big (56 kDa) PRL and big big (macro) PRL (150–160 kDa) [2]. The macro PRL is mostly constituted by IgG-23 kDa (monomeric) PRL complex. PRL exists in several isoforms, due to variation in posttranslational modifications. The variants have different receptor binding and bioactivity [2,3].

PRL is produced also in extrapituitary sites including neurons, mammary epithelium, prostate, endothelium, skin and cells in the immune system: thymocytes and peripheral blood mononuclear cells, mainly lymphocytes. The extrapituitary PRLs have different molecular weight and biologic activity [3].

PRL is a cytokine. The PRL receptors consist of a ligand-binding extra-cellular transmembrane and cytoplasmic domains. They are included as members of the type I cytokine/hematopoietic receptor super-family and distributed throughout the immune system. Several isoforms of PRL-Rs have been described based on the differences in the amino acid sequence and size of the cytoplasmic domain [3]. PRL-Rs are expressed on monocytes, macrophages, T and mainly B lymphocytes, natural killer (NK) cells, granulocytes and thymic epithelial cells [3]. PRL-Rs signal through the Jak/Stat pathway [3].

1. The role of PRL in immune modulation

PRL regulates the maturation of CD4<sup>-</sup> CD8<sup>-</sup> thymocytes to CD4<sup>+</sup>CD8<sup>-</sup> T cells via IL-2 receptor expression and leads to the enhancement of pro-B cell generation. There is a correlation between PRL levels and the number of B and CD4<sup>+</sup> T lymphocytes, but PRL is not essential for lymphopoiesis [3].

Murine studies show that doubling of serum PRL levels alters B lymphocyte development in the spleen. This effect is genetically determined and found only in BALB/c mice but not in C57B16 mice. PRL impairs the negative selection of autoreactive B lymphocytes occurring during B cell maturation into fully functional B cells with a follicular phenotype [4].

The anti-apoptotic effect of PRL reflects its effect on activation of multiple signaling pathways leading to enhanced expression of survival proteins [5]. PRL induced a decrease in apoptosis of transitional B cells mediated by anti-IgM and may be important in the breakdown of B cell tolerance to self and the development of autoimmunity.

PRL enhances the proliferative response to specific antigens and mitogens [6].

PRL enhances the development of antigen presenting cells expressing MHC class II and co-stimulatory molecules CD40, CD80, and CD86 [7]. The effect of PRL on antigen presentation and on the interaction between B and T cells enhances response to MHC presented auto-antigens, promoting loss of self tolerance. The interaction of CD40 on B cells and CD40L on T cells up-regulates the expression of the anti-apoptotic molecule Bcl-2. This effect rescues autoreactive B cells from negative selection and reduces tolerance to self [4].

PRL enhances immunoglobulin production [8], which may contribute to increased autoreactivity. A variety of autoantibodies was observed in patients with hyperprolactinemia including antibodies to PRL, endothelial cells, cardiolipin, β<sub>2</sub>GPI [9], Ro and La. In SLE patients PRL may have effect on autoantibody production.

PRL up-regulates Th1 type cytokines. PRL triggers IL-12, IL-1, IL-6 and interferon γ (INFγ) production [3] and increase the effect of IL-2 on lymphocytes [10].
Some of the cytokines affect B cell function and may contribute to the development of autoimmunity.

2. Hyperprolactinemia (HPRL) and autoimmune diseases

The expected rate of HPRL in normal population is up to 3% [11]. The highest levels of PRL occur in association with prolactinoma. Women with prolactinoma present, usually, with clinical manifestations of galactorrhea, primary or secondary amenorrhea delayed menarch or a change in the menses either in the amount or in the regularity. HPRL has been demonstrated in multi-organ diseases as SLE, RA, systemic sclerosis (SSc), SS, and reactive arthritis. The organ specific autoimmune diseases associated with HPRL are diabetes mellitus (DM) type I, Graves’ disease (GD), HT, Addison’s disease (AD) lymphocytic hypophysitis (LH), Celiac disease (CD) multiple sclerosis (MS), uveitis and rejection of heart transplantation (Table 1) [12,2]. In a number of autoimmune diseases the level of cortisol is subnormal. The reduced corticosteroid tone has a permissive effect in development of autoimmune disease. Increased PRL level may accelerate immune response in patients with low cortisol level. Corticosteroids antagonize the stimulatory effect of PRL [2].

3. Genetic factor

In humans the PRL gene is located on the short arm of chromosome 6, close to the HLA-DRB1 region. Mutations in these genes could be associated with the pathogenesis of autoimmune diseases. Linkage disequilibrium between HLA-DRB1 alleles and microsatellite marker alleles close to the prolactin gene was demonstrated in RA and SLE patients in comparison with healthy controls, suggesting the possibility of extended haplotypes encoding for HLA-DRB1 and high prolactin production, which contribute to susceptibility to RA and SLE [13].

4. Systemic lupus erythematosus (SLE)

SLE is more common in women of the reproductive age with a 9:1 ratio when compared to men. Mild to moderate HPRL is demonstrated in 15%–33% of SLE patients of both genders [14,15]. In murine models of lupus there is clear evidence of the association between HPRL and disease activity [16]. In some of the clinical reports the relationship between HPRL and lupus activity was demonstrated [10], while refuted by others [14]. The discrepancies may be implicated by genetic factors. Possibly only subsets of SLE patients have a prolactin-responsive disease [3].

Recently, the little PRL (23 kDa) was demonstrated to be related with lupus activity while macroprolactinemia or low levels of little PRL were negatively related to the SLEDAI score [15]. The immune complexes of PRL-anti-PRL (which are the macroprolactins) are not biologically active, since the large size disturbs the cross through the capillary walls to reach the target tissues. SLE patients with these complexes may have less PRL-induced effect on disease activity. The free HPRL is related to neurological, renal, and hematological involvement, serositis, anti-double stranded DNA (dsDNA) and hypocomplementemia [15]. HPRL and induced HPRL in SLE patients were in correlation in one small study with disease activity and elevated titers of anti-dsDNA, anti-SSA, anti-SSB, anti-Sm and anti-RNP [17]. HPRL is implicated in lupus nephritis, central nervous system, cutaneous and articular involvement with association with increased level of IL-6 in lupus nephritis and neuropsychiatric lupus [18]. The presence of anti-PRL antibodies in the serum of lupus patients was found to correlate with decreased disease activity. This effect is explained by attenuation of the biological activity of PRL, by interfering with binding to the PRL-Rs on lymphocytes. The anti-PRL antibodies may deregulate PRL secretion and induce HPRL [19].

Prolactinomas are rare in SLE patients with no consistency of the clinical manifestations of HPRL or in the coincidence of HPRL with flares of SLE disease activity [20].

Studies of the therapeutic effect of the dopaminergic agonist bromocriptine, which selectively inhibit pituitary prolactin secretion, on animal models and in humans in SLE, provide evidence on the role of PRL in the pathogenesis of SLE. Inhibition of PRL secretion by bromocriptine decreased serum anti-dsDNA antibody titers and improved the survival of lupus-prone mice [21,22]. In order to find whether estrogen’s effect in SLE is PRL mediated, transgenic mice were treated by

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estradiol and bromocriptine. Bromocriptine blocked the lupus phenotype normally induced by estradiol. Estradiol-induced breakdown in B cell tolerance was abrogated by bromocriptine [16]. Injection of CD8+ T cells from bromocriptine-treated mice that had SLE or primary anti phospholipid syndrome (PAPS), abolished the disease development, suggesting that the effect of bromocriptine was through induction of natural nonspecific CD8+ suppressor cells [21].

In two studies bromocriptine therapy for SLE patients suffering from mild to moderate active disease was beneficial with significant improvement in activity scores [23,24]. Bromocriptine reduced the flare rate [24] and discontinuation of bromocriptine was followed by a flare of disease activity in all patients [23].

5. Multiple sclerosis (MS)

MS is twice as common in women as in men. In studies in experimental allergic encephalomyelitis, the animal model of MS, PRL levels were higher before disease onset and bromocriptine attenuated the attacks [25]. Mild to moderate HPRL was found in 30% of MS patients and was speculated to be related to hypothalamic lesions [26]. The role of bromocriptine in therapy for MS was suggested, however, an open-label pilot study did not show therapeutic effects on MS activity [27]. A study of intravenous methylprednisolone therapy 500 mg monthly caused a reduction of T2 lesion volume with a parallel decline in plasma prolactin in 9 relapsing remitting MS patients [28]. However these findings could not be confirmed by others. No correlation was found between disease activity and HPRL [29].

6. Rheumatoid arthritis (RA)

In RA, subnormal cortisol and excessive PRL secretion in response to inflammation, contribute to the development of the disease [30]. Increased PRL level was reported in patients suffering from RA [31]. Higher free serum PRL levels are reported in women with RA, compared with controls. Other studies did not confirm the HPRL in the serum of RA patients [32]. Breastfeeding might exacerbate RA through the effect of PRL [33]. Dopamine agonists may be a useful adjunct to the treatment for RA, even though bromocriptine does not affect lymphocyte-derived PRL secretion [34]. The risk to develop RA is increased postpartum and in breastfeeding women [35]. PRL may have a role in modulation of disease activity in RA, but the data is still contradictory.

7. Systemic sclerosis (SSc)

SSc is at least five times more common in women in childbearing age than in men.

PRL serum levels have been shown to be significantly elevated in patients with SSc [36,37]. A recent study demonstrated that peripheral blood mononuclear cells (PBMC) supernatants of SSc patients contain significantly increased amounts of prolactin as compared to healthy donors PBMC. These results show that lymphocytes in SSc patients are active producers of extrapituitary PRL and probably the immune activation in SSc may significantly contribute to HPRL in these patients. PRL stimulated lymphocytes produced increased amount of soluble IL-2 receptor (CD25). The same cells besides producing PRL are also sensitive to PRL stimulation [37].

8. Sjogren’s syndrome (SS)

Several studies demonstrated that PRL level in SS patients is 1.3–2.4 times higher than controls [11,38,39]. The rate of HPRL in the same studies among primary SS patients is variable between 3.6%–45.5%. Haga and Rygh found that PRL level did not correlate with disease duration, immunoglobulin levels autoantibodies, focus score in biopsies, but did correlate to score of internal organ disease [39]. The other studies did not find correlation between systemic manifestations and PRL level [11,38]. HPRL is assumed to reflect a disease pathology rather than being present in a subset of patients [11].

9. Autoimmune thyroid diseases

Hashimoto’s thyroiditis patients exhibit significantly higher PRL and lower cortisol levels than healthy controls. Nineteen percent of patients with chronic thyroiditis had HPRL. In primary hypothyroid group the prevalence of HPRL is much higher (42.4%) than in euthyroid patients [40]. Hyperprolactinemia is common in autoimmune diseases mainly SLE, autoimmune thyroiditis and multiple sclerosis. The data on the correlation between prolactin level and disease activity is controversial. Prolactin has immunostimmulatory effects by inhibition of the negative selection of autoreactive B lymphocytes, inhibition of apoptosis and increased antibody production.

The role of dopamine agonists in treatment of autoimmune diseases is yet to be determined. Further studies are needed to clarify the genetic factor and the role of the different PRL isoforms in the pathogenesis and activity of autoimmune diseases.
Take-home messages

- Most of autoimmune diseases are more common in women.
- Hyperprolactinemia is observed in various autoimmune diseases mainly SLE.
- Prolactin has an immunostimulatory effect mainly inhibition of negative selection of autoreactive B lymphocytes.
- There is no clear correlation between prolactin levels and disease activity.
- The monomeric PRL is the most prevalent isoform with high bioactivity.
- Dopamine agonists might have a role in therapy of autoimmune diseases.

References

Autoantibodies against tumor suppressor protein p53 in pleural effusions of patients with tuberculosis pleurisy.

Autoantibodies against the p53 proteins (p53Abs) can be detected in the serum, ascites, saliva and pleural effusions of various malignant patients. It is suggested that p53 Abs in pleural effusions might have some value for tumor diagnosis, prognosis or monitoring. The present study, Wang L. et. al. (Ann Clin Biochem 2007; 44: 57-62) investigated the prevalence of p53 Abs in the pleural effusions of 90 patients with various diseases. Patients with suspicious pleural effusions in chest film received thoracocentasis and their pleural effusions were collected. The presence of p53 Abs in effusion was detected by immunoblotting. Differences of p53 Abs with respect to the patient's age, gender, white blood cell count, lactate dehydrogenase, total proteins and adenosine deaminase scores were calculated by chi(2)-test. p53 Abs were detected in 14.4% (13/90) of our patients, with prevalences of 10.5% (6/57) and 21.2% (7/33) among patients with benign and malignant diseases, respectively. Notably, 16.1% (5/31) of patients with tuberculosis pleurisy were positive for p53 Abs. These five patients had no history of cancer or any related tumorigenesis. This is the first report regarding the detection of p53 Abs in pleural effusions from patients with tuberculosis pleurisy.

Detection of anti-Nogo receptor autoantibody in the serum of multiple sclerosis and controls.

A myelin-associated neurite outgrowth inhibitor Nogo-A plays a key role in inhibition of axonal regeneration. Axonal damage beginning at the early stage of multiple sclerosis (MS) is responsible for permanent neurological deficits, although its molecular mechanism remains unknown. In this study, Onoue H. et. al. (Acta Neurol Scand 2007; 115: 153-60) studied the prevalence of autoantibodies against Nogo-A and Nogo receptor (NgR) in the serum of MS. The antibodies were identified in the serum of 30 MS patients, 22 patients with non-MS other neurological diseases(OND), and 22 healthy control (HC) subjects by Western blot using recombinant human Nogo-A-specific segment (NAS), the shared segment of Nogo-A and –B (NAB), Nogo-66 (N66), the non-glycosylated form of NgR, the glycosylated NgR (NgR-Fc), and myelin oligodendrocyte glycoprotein (MOG). None showed immunoglobulin G (IgG) antibodies against NAS or NAB. In contrast, 30% of MS, 23% of OND and 32% of HC subjects exhibited anti-N66 IgG, while 27% of OND and 18% of HC showed anti-MOG IgG. None of HC but 33% of MS and 14% of OND showed anti-non-glycosylated NgR IgG. Furthermore, 60% of MS, 18% of OND and 14% of HC showed anti-NgR-Fc IgG. Because IgG autoantibodies against N66, NgR and MOG are often detected in the serum of MS and controls, they do not serve as an MS-specific marker.