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Lecture

Prolactin and autoimmune diseases in humans

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Abstract. Prolactin has been shown to have immunomodulatory as well as lactogenic effects. Generally less well known is that prolactin may also play a role in the activity of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. Studies have shown decreasing prolactin production to be beneficial in animal models of autoimmune disease. Thus far, double-blinded, placebo-controlled studies of dopamine agonist treatment in humans with autoimmune disease have been done only in lupus patients, and support the potential efficacy of such agents. Small, open-label trials have also suggested potential benefit in patients with rheumatoid arthritis, Reiter's syndrome, and psoriasis. More studies are required to further delineate the mechanisms by which prolactin affects autoimmune disease activity, to determine in which specific diseases prolactin plays a significant role, and to test the efficacy of prolactin-lowering agents as therapy for such diseases. (www.actabiomedica.it)

Key words: Prolactin, hyperprolactinemia, autoimmune disease, rheumatoid arthritis, systemic lupus erythematosus

Introduction

Prolactin (PRL) is produced by lactotroph cells in the anterior pituitary gland and is commonly known for its lactogenic and mammotrophic effects. However, from as early as 1930 evidence has supported an additional role for PRL in stimulation and modulation of immune function (1). Evidence also supports an association between prolactin levels and the activity of human autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In this review we will briefly summarize currently published data regarding prolactin and autoimmunity, and discuss the therapeutic ramifications.

The PRL receptor has been classified as a member of the cytokine receptor superfamily (which includes the IL-2, IL-3 and interferon receptors) and is found on lymphocytes, monocytes, neutrophils, natural killer (NK) cells, and thymic epithelial cells (2, 3). PRL appears to be necessary for IL-2 receptor expression and T-cell proliferation (4), and may also modulate B-cell expansion (5). Other findings in animal and *in vitro* studies regarding the immunomodulatory role of PRL are summarized below.

Two issues regarding the production and measurement of PRL should be introduced at this point, as they will be relevant later in the discussion. First of all, it is known that PRL is also made in extrapituitary tissue including T-lymphocytes, B-lymphocytes, and human chorion. So-called lymphocyte PRL produced by T-lypmphocytes is under the control of an alternative upstream promoter (6), and is believed to have autocrine and paracrine functions (7, 8). Whether lymphocyte PRL is physiologically significant, particularly in individuals with autoimmune disease, has been debated. Also relevant is the fact that while bromocriptine has been shown *in vitro* to suppress lymphocyte prolactin, to date no such data have been published for any of the other currently available dopamine agonists, such as cabergoline and quinagolide (9).

It is also known that macroprolactin (or big, big PRL) is in fact a PRL-IgG complex due to anti-PRL

autoantibodies. This complex is generally thought to be biologically inactive or less active than PRL but cross-reacts with some PRL assays, in some studies occurring in 4-5% of cases of hyperprolactinemia (10, 11). These issues have been investigated in patients with autoimmune disease and will be discussed below.

Animal and *in vitro* studies

Hypophysectomized rats evince thymic involution and decreased cell-mediated immune function, both of which are reversed by the administration of ovine PRL (12, 13). Similarly, hypoprolactinemia induced in animals by bromocriptine or anti-PRL antibodies has been shown to lead to impaired lymphocyte proliferation and macrophage-activating factor production, again reversed by ovine PRL (14). Rats with the immune-mediated disease adjuvant arthritis show elevated levels of PRL; in hypophysectomized rats, development of the disease is inhibited, but restored with either pituitary implants or ovine PRL (15). NZB/NZQ F1 lupus rats also have high PRL levels; treatment with bromocriptine leads to improvement in disease symptoms and delayed lupus-related death (16). In the murine model of SLE, bromocriptine was shown to suppress immunoglobulin levels, autoantibodies, and immune-complex glomerulonephritis, and to improve survival rates (17). Interestingly, however, PRL and PRL-receptor knockout animals have shown that prolactin is not essential for normal immunity, as they have normal development, distribution, and function of T-lymphocytes, B-lymphocytes, and NK cells. It has been suggested that other cytokines may be compensating for the lack of prolactin in these knockout models (18), or that prolactin has significant effects on the immune system only under conditions of stress (19).

As previously discussed, PRL receptors are found on multiple cells of the immune system, and PRL appears necessary for certain immune functions. Conversely, PRL production is stimulated *in vitro* by the cytokines IL-2 and IL-6 and inhibited by IL-1 (20-22). A number of *in vitro* and *in vivo* studies of humans with hyperprolactinemia have demonstrated abnormalities in T-cell function and phenotype which corrected with bromocriptine treatment (23); abnormal T-cell proliferation (24); inhibition of NK cells which was corrected and in fact made more efficient by bromocriptine administration (25); decreased neutrophil chemotaxis (26); and increased activity of antigen-presenting cells (27).

PRL and human autoimmune diseases

Studies of patients with hyperprolactinemia of various etiologies have suggested an increased rate of autoantibodies (including antithyroid, anti-dsDNA, anti-ro, anticardiolipin, and antinuclear antibodies (ANA)) without clinical evidence of autoimmune disease (28-30). Conversely, elevated levels of prolactin have been found in patients with SLE, RA, psoriatic arthritis, multiple sclerosis, Reiter's syndrome, primary Sjögren's syndrome, psoriasis, and uveitis (18, 30-33), leading to hypothesized causal relationships and a possible therapeutic target.

Systemic lupus erythematosus (SLE)

Currently, the best evidence for the association between prolactin and human autoimmune disease exists for SLE. SLE patients have demonstrated in a number of studies an increased frequency of hyperprolactinemia (as high as 40%), and these elevated PRL levels do appear to correlate with clinical disease activity as well as ANA and anti-dsDNA titers (34-37). Investigation has shown that a subset (30-40%) of SLE patients with idiopathic hyperprolactinemia has detectable anti-PRL antibody (38, 39). These patients evinced fewer clinical and serological manifestations of SLE than those without the antibody, leading to the hypothesis that anti-PRL antibodies attenuate the biological activity of PRL, possibly by the formation of macroprolactin. However, *in vitro* studies demonstrated that macroprolactin from SLE patients is fully active (40).

Other *in vitro* studies support the association of PRL and SLE. On the one hand, it has been shown that lymphocyte-derived PRL is increased in patients with SLE compared with normal subjects (41). On the other hand, prolactin has been demonstrated to

enhance *in vitro* production of IgG in peripheral blood mononuclear cells (PBMC) from subjects with SLE but not in those from healthy controls (42).

Conventional immunosuppressive therapy in SLE patients, including glucocorticoids and hydroxychloroquine, has been shown to reduce prolactin levels in direct correlation with decreased SLE activity (43). Several studies support the efficacy of dopamine agonists in the treatment of SLE. Walker et al. treated 7 SLE patients in an open-label trial, utilizing 3.75 to 7.5 mg/day of bromocriptine for 6 months. Serum prolactin levels were suppressed in all 7 subjects, and clinical measurements of disease activity improved in 6 of the 7 subjects; following cessation of bromocriptine therapy, all patients had increased disease activity and prolactin levels. All were on concurrent prednisone therapy, the dose of which could be reduced in many of the subjects during the period of the trial (44). Quinagolide given to 20 SLE patients and 17 healthy subjects for up to 6 months was associated with reduction in disease activity and IL-6 levels, although the correlation with the reduction in PRL levels was weak (45). A double-blind, placebo-controlled study of low-dose bromocriptine therapy (2.5 mg/day) in 36 patients (*vs* 30 SLE patients on placebo) treated for a mean of 12.5 months again showed a significant decrease in PRL levels with treatment, associated with a significant decrease in disease activity indices (46). The patients were permitted to take prednisone and immunosuppressive drugs during the study. Walker et al. showed in another double-blinded study that bromocriptine is as efficacious as hydroxychloroquinone for the treatment of active SLE (47). Interestingly, in reviewing these studies, there appeared to be a beneficial effect of the drug even in patients with initial PRL levels within the normal range.

Rheumatoid arthritis (RA)

Studies of prolactin levels in patients with RA have not consistently demonstrated elevated levels (48-51), although Halko et al. demonstrated a correlation between rising prolactin levels and disease activity as measured by joint swelling (52). Ram et al. showed that both total and free prolactin levels were higher in RA patients compared with healthy controls; no subjects had either hyperprolactinemia or macroprolactinemia (53). In a study of 22 RA patients, 5 did have hyperprolactinemia and 2 of these had macroprolactin values >15% of the total PRL. There was no difference in clinical variables based on percentage of macroprolactin in another study (48). T-lymphocytes infiltrating the synovium produce PRL and have been shown to induce excessive synovial cell function in RA patients; bromocriptine treatment *in vitro* suppressed lymphocyte PRL as well as IL-6 and lymphocyte proliferation (9).

There have been four open-label trials of bromocriptine treatment in small numbers of patients. Dougados et al. treated 6 RA patients with cylosporine in addition to bromocriptine in doses up to 6.25 mg/day and found no difference in clinical and laboratory measures of disease activity (54). Marguerie et al. compared bromocriptine with penicillamine therapy in 30 patients with active RA; bromocriptine did show clinical improvements comparable to penicillamine, but failed to significantly improve laboratory parameters, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complement levels (55). Mader treated 5 patients with refractory RA with 5 mg bromocriptine daily. Three showed improvement clinically at 12 weeks of treatment, although the improvement was maintained in only 2 by the 6-month mark. No correlation was found between serum PRL levels and disease activity (56). Figueroa et al. demonstrated a correlation between improvement in clinical indices and reduction in *in vitro* levels of immune activity, including PBMC response to antigen and production of IL-2, in 9 RA patients treated with bromocriptine for 3 months (57).

Eijsbouts et al. treated 9 RA patients already on non-steroidal anti-inflammatory drugs and prednisone with quinagolide for 6 months. No patient had baseline hyperprolactinemia; PRL levels were suppressed below detection levels within 4 weeks of treatment initiation. There was no significant improvement in either clinical or laboratory disease activity measurements (58). There is also a single case report of a patient treated with cabergoline for her microprolactinoma and noted to have incidental improvement in her RA (59). No randomized double-blind placebo-controlled trials have been published to date.

Other autoimmune diseases

In one study, 36% of patients with Reiter's syndrome had hyperprolactinemia, compared with only 2.9% of those with ankylosing spondylitis (31). Four male patients with Reiter's syndrome refractory to treatment with NSAIDs and sulfasalazine were treated with bromocriptine (2.5-5 mg/day), resulting in improvement in all patients, two within 24 hours of the first dose, the other two after four days of treatment. All four patients remained asymptomatic for at least four months of bromocriptine therapy (60).

A study of patients with psoriasis demonstrated they had a higher mean PRL level than patients with atopic dermatitis; some of the psoriasis patients had levels within the normal range while others were hyperprolactinemic (33). Regaña and Millet reported 3 cases of women whose worsening in psoriasis correlated with development of hyperprolactinemia due to prolactinomas. All three were treated with bromocriptine and had normalization of PRL levels and concurrent improvement of psoriatic lesions. All three incurred relapses in psoriasis when they discontinued bromocriptine (61). Multiple case reports have also suggested the potential efficacy of bromocriptine in the treatment of psoriatic arthritis (62-66). In one open-label study, 35 patients with psoriatic arthritis refractory to conventional therapy were treated with bromocriptine (started at 2.5 mg and titrated up to 30 mg/day). Significant improvement was seen in 77%, with 34% showing complete remission and 43% with ~50% improvement in articular symptoms (67).

Uveitis is sometimes associated with the seronegative spondyloarthropathies. Bromocriptine has been shown to suppress uveal inflammation both as monotherapy and as combination therapy with cyclosporine (68-73). In one double-blind, placebo-controlled study of 13 patients with chronic recurrent anterior uveitis, bromocriptine was started during a period of remission and continued for 1 year at 2.5 mg twice a day. In the bromocriptine group, 2 of 7 patients had no recurrences during the entire study period. Two other patients had to discontinue therapy due to recurrences, but in contrast to earlier recurrences they responded well to topical corticosteroid therapy. Two other patients without recurrences had to discontinue therapy prior to 1 year due to side effects. In the placebo group, 5 of 6 patients had recurrences (68).

The mean PRL level in 55 patients with primary Sjögren's syndrome was found to be significantly higher than that of 110 matched controls; this difference was most pronounced in younger patients with active disease. PRL was also found to correlate to the index for internal organ disease (32). Others have also found an association between hyperprolactinemia and Sjögren's syndrome (74, 75). Hyperprolactinemia has been found in patients with scleroderma as well (76-78). To date there are no published studies of dopamine agonists used to treat either Sjögren's syndrome or scleroderma.

Conclusions

Despite being known primarily as a lactogenic hormone, PRL is in fact also an immunomodulatory hormone. There is a growing body of evidence demonstrating an intriguing link between PRL and autoimmune diseases in humans. At present, the best evidence for a relationship between PRL levels and disease activity exists for SLE, but it may also exist in RA, Reiter's syndrome, psoriasis, and other yet unstudied conditions.

Interestingly, it is possible that differences in peripheral or lymphocyte, rather than pituitary production of PRL may worsen disease activity in certain patients. Of the currently available prolactin-lowering drugs, bromocriptine at least has been shown to decrease both peripheral and pituitary PRL production and may represent a useful adjunctive therapy in certain patients, particularly those with refractory disease. More studies are warranted in order to examine the potential causal relationship between PRL and human autoimmune disease and to determine the usefulness of dopamine agonists as adjunctive therapy in the management of these often debilitating disorders.

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