

PREHLADNÝ REFERÁT

REVIEW

PROLACTIN AND AUTOIMMUNE DISEASES

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PROLAKTÍN A AUTOIMUNITNÉ CHOROBY

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Summary

Prolactin is capable of influencing immune responses and in all likelihood is a cytokine. Circulating prolactin has been reported to be elevated in a number of autoimmune diseases, and reports have detailed possible associations between prolactin and SLE. SLE is a chronic, incurable autoimmune disease that is hormone-sensitive. About 20 % of SLE patients are hyperprolactinemic. Some have prolactinomas, and others have secondary causes of hyperprolactinemia such as hypothyroidism, drug-induced hyperprolactinemia, or chronic renal failure. In some lupus patients, no secondary cause can be found for hyperprolactinemia. In NZB/NZW mice, an animal model of SLE, transplantation of syngeneic pituitary glands resulted in sustained high serum levels of prolactin. Mice that received the implanted pituitary glands had premature death from autoimmune renal disease. In contrast, treatment with the prolactin-suppressive drug, bromocriptine, was beneficial and resulted in significant prolongation of life in NZB/NZW mice. Bromocriptine therapy favorably modified disease and improved quality of life in humans with SLE. In a preliminary open label study, SLE patients treated with bromocriptine for 6 months had significant improvement in disease activity. These responses were corroborated by blinded therapeutic studies. Daily treatment with low-dose bromocriptine prevented lupus flares, and bromocriptine treatment was found to be as effective as hydroxychloroquine in treating active non organ-threatening disease.

Key words: prolactin, autoimmune diseases, autoimmunity.

Súhrn

Prolaktín dokáže ovplyvniť imunitnú odpoveď a je veľmi pravdepodobné, že je to cytokín. Pri mnohých autoimunitných chorobách sa opisuje zvýšenie hladín cirkulujúceho prolaktínu a podrobne sa uvádza súvislosť medzi prolaktínom a SLE. SLE je chronické nevyliciteľné autoimunitné ochorenie, ktoré je citlivé na hormóny. Hyperprolaktinémia sa udáva u približne 20 % pacientov so SLE. Niektorí majú prolaktinómy, u niektorých je hyperprolaktinémia sekundárna v dôsledku iných príčin, napríklad hypotyreoidizmus, hyperprolaktinémia vyvolaná liečivami, alebo chronickou obličkovou nedostatočnosťou. U niektorých pacientov so SLE nemožno zistiť primárnu príčinu hyperprolaktinémie. Implantácie syngénnych hypofýz myšiam NZB/NZW, ktoré predstavujú zvierací model SLE, vyvolala stále zvýšenie hladiny prolaktínu v sére. Myši, ktorým sa implantovala hypofýza, predčasne hynuli v dôsledku autoimunitného ochorenia obličiek. Na rozdiel od toho malo podávanie bromokriptínu — liečiva, ktoré porláča prolaktín, priaznivý účinok a viedlo k významne dlhšiemu prežívaniu myši NZB/NZW. Podávanie bromokriptínu priaznivo ovplyvnilo ochorenie a zvýšilo kvalitu života pacientov so SLE. V predbežnej otvorenej štúdií, v ktorej sa podával pacientom so SLE bromokriptín počas 6 mesiacov, sa zistila významná úprava aktivity ochorenia. Táto reakcia bola podporená slepými terapeutickými štúdiami. Denné podávanie bromokriptínu v nízkych dávkach zabránilo vzniku lupusových eflorescencií a v liečbe aktívneho ochorenia neohrožujúceho žiadne orgány malo podávanie bromokriptínu účinok ekvivalentný podávaniu hydroxychlorochínu.

Kľúčové slová: prolaktín, autoimunitné ochorenia, autoimunita.

INTRODUCTION

Prolactin, a peptide hormone, is produced in the anterior pituitary gland and stimulates mammary growth and differentiation. Pituitary secretion of prolactin is stimulated by suckling and stress, and restricted by hypo-

thalamic dopamine (1). It is now recognized that prolactin is produced in a number of sites outside the pituitary, including the brain and lymphocytes (2). Furthermore, prolactin has widespread influences on proliferation and differentiation of a variety of cells in the immune system. A number of reviews have emphasized the impor-

tance of prolactin in maintaining immune competency (3—18). Therefore, prolactin has the potential to affect immune responses and play a role in the pathogenesis of autoimmune illnesses.

PROLACTIN RECEPTORS

Prolactin is of interest to immunologists and rheumatologists because it shares many properties with well-recognized cytokines and hematopoietic growth factors. Prolactin has comparable structural motifs, is synthesized in multiple sites (including lymphocytes) (2), and has similar receptor structures and signal transduction pathways. Receptors for prolactin are distributed widely throughout the immune system, and are found on T-cells, B-cells, and monocytes (19, 20). Prolactin receptors are in the novel cytokine/growth hormone/prolactin receptor family, which includes receptors for interleukin (IL)-2 beta, IL-3, IL-4, IL-6, IL-7, growth hormone, and erythropoietin (21).

PROLACTIN AND THE IMMUNE SYSTEM — *IN VITRO* STUDIES

Prolactin can influence the immune system directly through the thymus. Thymic epithelial cells have high expression of prolactin receptors and appear to mediate some of the immunologic functions of prolactin. Dardenne and associates (22) reported that ovine prolactin increased secretion of thymulin, a T-cell differentiation factor, from the thymic epithelium of mice. Prolactin and growth hormone were found to enhance release of thymocytes from the thymus; this effect was partly mediated through surface adhesion molecules (23).

Prolactin induces IL-2 receptors on lymphocytes (24) and is an important lymphocyte growth factor. In most experimental systems, however, adding prolactin directly to cultures of lymphoid cells does not stimulate mitogenesis. The sensitivity of the cultures to specific concentrations of prolactin, the biphasic effect of prolactin on mitogenesis in culture systems, and the necessity for co-culturing cells with low concentrations of mitogen may help to explain the apparent insensitivity of many cell lines to exogenous prolactin. Spangelo and associates (25) showed that adding prolactin directly to unstimulated lymphocyte cultures did not increase uptake of tritiated thymidine. The hormone did, however, stimulate mitogenesis in mouse spleen cells that were co-cultured with the T-cell mitogen, concanavalin-A. Cell division was stimulated through a narrow range of prolactin concentrations (0.001—1.0 microM). A synergistic effect on cell division was present when prolactin was used in the presence of relatively low concentrations of mitogen, below the level that was expected to produce optimal stimulation.

The growth-stimulating property of prolactin has been demonstrated in systems employing mitogen-induced proliferation of unfractionated mouse spleen cells and human peripheral mononuclear cells, as well as interleukin (IL)-2-dependent cloned murine T-helper cells (26, 27). In these experiments, the addition of exogenous prolactin did not stimulate the cultured cells to divide. Adding anti-prolactin antibodies, however, inhibited responses of unfractionated lymphoid cells and IL-2-dependent T-cells to T-cell and B-cell mitogens. The inhibitory effect of the antibody did not depend upon neutralization of growth factors found in calf serum. Inhibition of cell division occurred in culture systems that were set up either with or without a serum supplement (26). These observations were in accord with other reports that lymphocytes synthesized and secreted prolactin, which acted as an autocrine and/or paracrine growth factor (2).

LYMPHOCYTE PRODUCTION OF PROLACTIN

Lymphocytes synthesize and release a biologically active form of prolactin (28) which is employed by the cells as an autocrine and paracrine growth factor. The mechanisms that control production of lymphocyte prolactin are not completely understood, and it is not known if lymphocyte prolactin is affected by concentrations of circulating pituitary prolactin. Dexamethasone does inhibit gene expression of both forms of prolactin (11). Likewise, it is not known if lymphocytes can produce enough prolactin to cause an increase in serum prolactin levels. It seems unlikely that lymphocyte prolactin is present in high enough concentrations to be assayed in serum. However, one patient with acute myeloid leukemia has been reported to have hyperprolactinemia. Her leukemic cells were isolated and processed in media that did not contain a serum supplement, and the cells contained immunoreactive prolactin by immunoblot examination. It was postulated that the leukemic myeloblasts were a source of excessive prolactin, and this prolactin was detected at high levels in the serum prolactin assay (29).

PROLACTIN AND THE IMMUNE SYSTEM — *IN VIVO* STUDIES

In experimental animals, elevated levels of prolactin have been shown to affect the immune system in newborns (30). Pituitary grafts, used to increase prolactin in one-day-old thymus-grafted nude mice, stimulated CD4-positive cell development. Furthermore, hyperprolactinemia stimulated development of functional CD4-positive cells in newborn mice and prolactin depletion was detrimental to cell viability and development of surface antibody-positive T-cells (31).

In adult rodents, prolactin affects the immune system at almost every level. Prolactin has been shown to influence T-cells, B-cells, macrophages, and natural killer cells. The pioneering experiments of Nagy and Berczi (32, 33) demonstrated the importance of prolactin in maintaining normal immune function and sustaining life. Hypophysectomized rats had reduced dinitrochlorobenzene-induced dermatitis and suppressed antibody responses to the T-cell antigen, sheep red blood cells. This suppression was abrogated by prolactin injections and by syngeneic pituitary grafts. Fischer 344 rats that were deprived completely of prolactin by hypophysectomy and anti-prolactin antibody treatment developed anergy and anemia and died within 8 weeks. Replacement injections of either prolactin or growth hormone stimulated expression of the *c-myc* growth promoting gene and reversed spleen and thymus involution (34).

High levels of circulating prolactin stimulate immune responses in mice. Hyperprolactinemia was created in female C57BL/6 mice by either implanting one or two syngeneic pituitary glands, or by injecting exogenous mouse prolactin. Both procedures increased primary humoral antibody responses to sheep red blood cells (35). In another study, mice injected with 100 or 200 micrograms of bovine prolactin had increased production of anti-sheep red blood cell antibodies. In contrast, there was no effect on antibody production in mice injected with a 400 microgram dose (36). Bryant and associates (37) treated C3H/HeN mice with cysteamine, a sulfhydryl reducing agent, to reduce serum prolactin. The mice developed atrophy of the thymus, and responses to T-cell mitogens and B-cell mitogens were suppressed. The doses of cysteamine that produced the greatest suppression of serum prolactin were those that suppressed the immune responses.

Prolactin is a potent stimulator of macrophages (38). In mice, prolactin increased production of macrophage interleukin (IL)-1 and nitric oxide (39) and stimulated phagocytic activity (40). In humans, physiologic doses of prolactin induced macrophages to produce interferons (IFN)-gamma (41). Hypoprolactinemia has been associated with tissue depletion of macrophages. When cycling rats were treated with the prolactin-suppressive agent, CB154, serum prolactin concentrations were lowered significantly and regressing corpora lutea were depleted of macrophages (42).

ROLE OF PROLACTIN IN AUTOIMMUNE DISEASES

The recognition that prolactin interacts with the immune system has promoted the theory that it has a role in the pathogenesis of autoimmune diseases. Studies in experimental animals suggest that prolactin is likely to be involved in the pathogenesis of induced autoimmune experimental allergic encephalitis and adjuvant arthritis in rats. Both of these

disorders responded to therapy with the prolactin-lowering drug, bromocriptine (43, 44).

THE NZB/NZW MOUSE MODEL OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

The F1 hybrid New Zealand Black (NZB) X New Zealand White (NZW) (NZB/NZW) mouse model of SLE was chosen for experiments designed to evaluate the effects of hyperprolactinemia and bromocriptine treatment on autoimmune disease. This lupus model spontaneously develops antibodies to double-stranded DNA (anti-ds DNA) and dies with renal disease caused by immune-mediated glomerulonephritis. Furthermore, disease in NZB/NZW mice is influenced strongly by gender. Females have accelerated disease that is stimulated estrogen and ameliorated by testosterone. The late-onset disease in males is related to the protective properties of testosterone (45).

INTERACTIONS OF CYTOKINES AND HORMONES IN NZB/NZW MICE

Autoimmunity in the NZB/NZW model is regulated through cytokines. The disease is interrupted if these mice are treated with antibodies to the Th1 cytokine, IFN-gamma (46), or with antibodies to the Th2 cytokines, IL-6 (47) or IL-10 (48). Th1 cytokines initiate development of experimental SLE in susceptible 16/6 Id.BALB(c and CH3.SW mice, and Th2 cytokines are produced later in the course of disease (49). In the NZB/NZW mouse, both Th1 and Th2 cytokines participate in development of the pathologic process (50). It is proposed that Th1 cytokines are involved in initiating autoimmunity and Th2 cytokines contribute to production of autoantibodies by B-cells.

Female hormones have the potential to stimulate high levels of IFN-gamma transcripts. Estrogen stimulates the IFN-gamma promoter, and 17beta-estradiol increases IFN-gamma mRNA expression in ConA-stimulated mouse spleen cells (51). Estrogen is also a potent stimulus for production of prolactin in the anterior pituitary, and high-dose estrogen treatment resulted in concentrations of serum prolactin that were 10X—91X greater than control values in female NZB/NZW mice (52).

Production of the Th1 cytokine, IL-2, is defective in lymphoid cells from NZB/NZW mice but is nevertheless detrimental in these autoimmune animals (45). In the past, it was not understood how this cytokine with low grade secretion could direct autoimmune processes. It is now recognized that the functions of IL-2 may be taken over by IL-15, a newly discovered cytokine from monocytes that shares receptor subunits with IL-2. IL-15 can bind to components of the IL-2 receptor and substitute for IL-2 under many conditions (53).

The transcription factor gene, interferon regulatory factor-1 (IRF-1), is an important regulator of T-cell and B-cell differentiation and maturation and is thought to have a role in T-cell activation. Prolactin, which is higher in females compared to males, is a potent stimulator of IRF-1 and IFN-gamma in T-cells (16, 54). Prolactin stimulates IRF-1, which in turn regulates expression of Th1 cytokines such as IFN-gamma and IL-15. The potential of IRF-1 to promote autoimmunity was demonstrated when type II collagen-induced arthritis was induced in mice that were either IRF-1 deficient (-/-) or IRF-1 positive (+/-). Disease was reduced in the IRF-1 -/- mice compared to the +/- mice (55). It was concluded that absence of IRF-1 gene activity was protective in a model with induced autoimmune disease.

THE ROLE OF PROLACTIN IN STIMULATING DISEASE IN A MOUSE MODEL OF SLE

In NZB/NZW mice, transplantation of syngeneic pituitary glands resulted in sustained high serum levels of prolactin. Mice that received the implanted pituitary glands had premature death from autoimmune renal disease. Female NZB/NZW mice were made chronically hyperprolactinemic (representative mean serum prolactin concentrations 127—182 ng/ml) by implantation of 2 syngeneic pituitary glands under the renal capsule of each mouse. This manipulation was followed by the development of premature renal disease and early mortality. In contrast, treatment with the prolactin-suppressive drug, bromocriptine, was beneficial and resulted in delayed appearance of anti-ds DNA and significant prolongation of life spans (56). In another group of NZB/NZW females, each animal received 4 transplanted pituitary glands. Serum prolactin concentrations were greater than the mice that had received 2 pituitary transplants; levels ranged from 743—1643 ng/ml. Twelve wks after the pituitary glands were implanted, 80 % of the mice had anti-ds DNA and striking hypergammaglobulinemia (57).

Another study designed to determine if naturally occurring hyperprolactinemia was detrimental. Groups of female NZB/NZW mice that whelped two litters and were allowed to either suckle their young had stimulation of anti-ds DNA. Other females had tubal ligations and were caged with males in order to induce the diurnal surges of hyperprolactinemia associated with pseudopregnancy. Pseudopregnant animals had the most pronounced evidence of accelerated disease in this study. Albuminuria and anti-DNA appeared early, but these mice did not die prematurely (58).

Male NZB/NZW mice have indolent, late-onset autoimmune disease. Autoimmunity in these males was accelerated by high serum prolactin levels. We implanted males with either 2 or 4 pituitary glands and observed that the recipients of 4 glands had prolactin levels that were twice as high as recipients

of 2 glands. The magnitude of increased serum prolactin did not, however, regulate progression of disease. Instead, both groups of male mice with chronically elevated serum prolactin had premature mortality with similar death curves (59).

Prolactin is therefore an important stimulator of disease in NZB/NZW mice. Elbourne et al. (60) found that prolactin was required in order for estrogen to stimulate autoimmune disease in NZB/NZW mice. Female NZB/NZW mice were manipulated so that they had either high or low circulating estrogen concentrations, in all possible combinations with high or low circulating prolactin concentrations. Hyperprolactinemic mice had accelerated autoimmune disease in the presence of either high estrogen levels (produced by estrogen injections) or low estrogen levels (produced by surgical castration).

AUTOANTIBODIES IN HYPERPROLACTINEMIC PATIENTS WHO DID NOT HAVE AUTOIMMUNE DISEASES

Because prolactin is associated with immune system activity, there has been interest in examining hyperprolactinemic patients for autoantibodies. Hyperprolactinemic men, many of whom had prolactinomas, had significantly more positive tests for fluorescent antinuclear antibodies compared to controls (61). Hyperprolactinemic subjects with no history of SLE were evaluated for anticardiolipin antibodies. These antibodies were found in 5/23 (22 %) of women and men with elevated serum prolactin (62). In another survey, multiple autoantibodies were detected in sera from hyperprolactinemic women but the subjects did not have clinical evidence of autoimmune disease (63). Krause and associates (64) reported low-level antibodies to DNA, anticardiolipin antibodies, and anti-endothelial antibodies in hyperprolactinemic sera.

HYPERPROLACTINEMIA IN AUTOIMMUNE DISEASES

A number of autoimmune diseases are associated with circulating prolactin levels that are higher than the levels established for normal populations. These include severe iridocyclitis (65), Addison's disease (66), and autoimmune thyroiditis (67). In two patients, elevated serum prolactin preceded the development of autoimmune diseases. Hyperprolactinemia was found on one patient 5 years before she developed signs and symptoms of Graves' disease. In a second individual, idiopathic hyperprolactinemia appeared 2 years before dermatomyositis was diagnosed (68). Surveys of patients with primary Sjögren's syndrome revealed that 46 % were hyperprolactinemic (69), and elevated serum

prolactin levels were identified in 59 % of patients with scleroderma (70). Serum prolactin concentrations were elevated in a group of girls with juvenile rheumatoid arthritis and positive antinuclear antibody tests, compared with seronegative girls with juvenile rheumatoid arthritis and age-matched controls (71). Another report suggested that hyperprolactinemia in juvenile chronic arthritis was associated with disease chronicity, rather than the presence of antinuclear antibodies (72).

HYPERPROLACTINEMIA IN SLE

There is currently great interest in the possibility that high prolactin levels are associated with SLE. Some surveys have produced positive results. Eight men with SLE had serum prolactin above the mean (73), and 5 pregnant lupus patients had serum prolactin levels above expected values for gestation (74). In 4 additional groups, 16—20 % of lupus patients had serum prolactin concentrations that were elevated above the population norm (75—78). Other reports stated that hyperprolactinemia was not increased in lupus patients (79, 80).

In some surveys, hyperprolactinemia was not associated with active SLE (76, 77). Jimena and associates (81) reported a case control study in which 28 % of SLE patients were hyperprolactinemic, but high prolactin was not a marker for active disease. Other surveys, however, showed that high prolactin levels correlated with active SLE (74, 75, 82). In some instances, hyperprolactinemia was associated with the most severe complications of SLE. High serum prolactin was a marker for central nervous system involvement in juvenile SLE (83), and prolactin levels were elevated in serum and urine from patients with severe lupus nephritis (84).

SOURCE OF CIRCULATING PROLACTIN IN SLE

The source of excessive circulating prolactin in SLE patients has not been determined. Some of these patients have prolactinomas (85), and others have hyperprolactinemia secondary to recognized causes such as drugs, hypothyroidism, or renal insufficiency (78). Human lymphocytes are capable of producing prolactin, and it is believed that this prolactin acts locally to stimulate lymphocyte proliferation in an autocrine or paracrine manner (2). Lymphocytes from SLE patients actively secrete prolactin (86). It is not known, however, if measurable prolactin of lymphocyte origin is circulating in these individuals. Circulating antibodies to prolactin (87) may contribute to aberrant regulation of prolactin secretion and predispose to hyperprolactinemia in SLE patients.

One study has shown that quiescent SLE is associated with very low levels of homovanilic acid, a finding suggesting that impaired dopamine turnover and altered dopaminergic tone could result in hyperprolactinemia (88). When lupus disease is inactive, however, the hypothalamic-pituitary response may be normal (89).

PROLACTIN-LOWERING THERAPY IN SLE

Several treatment studies have shown that suppression of circulating prolactin with bromocriptine is an effective means of treating SLE (90, 91, 92+). Seven lupus patients with mild to moderately active disease were treated in an open-label study with the prolactin-suppressing drug, bromocriptine. After 6 months, disease was suppressed significantly. Five patients became hyperprolactinemic after bromocriptine was stopped. All of the subjects had increased activity of lupus in the 5-months period that followed the treatment period (90). The double-blind study of Alvarez-Nemegyei and associates (91) showed that treatment with a fixed low dose of bromocriptine (2.5 mg/day) for one year reduced the expected number of lupus flares. In a more recent study, patients with active SLE were randomized to receive either bromocriptin, in a dose designed to suppress serum prolactin to a concentration <1 ng/ml, or hydrochloroquine, 6 mg/kg. Patients were selected so that at entry, they did not have either life-threatening disease or progressive disease that involved a major organ. Treatment was given for one year. Preliminary data from 24 patients were reported recently (92). In 11 bromocriptine-treated patients, the SLE Activity Measure (SLAM) (93) decreased from (mean \pm SEM) 14.0 ± 1.1 at entry to 7.5 ± 0.8 ($p<0.05$) after one year of treatment. In 13 SLE patients who were randomized to receive hydrochloroquine, the mean SLAM score decreased from a baseline value of 13.4 ± 1.3 (entry) to 9.0 ± 1.4 ($p<0.001$). Prednisone doses, the numbers of patients who started and stopped prednisone, and numbers of patients who left the study were similar in both treatment groups.

The reports of efficacy of bromocriptine treatment are encouraging. Additional treatment studies may confirm the early findings that are reported above, leading to further use of hormonal modification in treating lupus and other autoimmune diseases. For the present, it is important to understand that treatment with dopamine agonists such as bromocriptine is best confirmed to therapeutic trials. In the experience of the author, bromocriptine should not be relied upon to treat severe, life-threatening autoimmune disease. Prolactin-lowering therapies may, however, find a place in the future as adjuncts to control less severe forms of autoimmune diseases such as SLE.*

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