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Review Article

Hyperprolactinaemia Contributes to Immunosuppressive and Corticosteroid Drug Resistance

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Abstract

Prolactin (PRL), a hormone traditionally associated with lactation, has been increasingly recognized for its significant role in the immune system. This paper explores the multifaceted functions of PRL, particularly its contribution to immunosuppressive and corticosteroid drug unresponsiveness, commonly referred to as drug resistance. Hyperprolactinemia has been observed in various autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren's syndrome (SS), and multiple sclerosis (MS). The association between PRL and these diseases is partly explained by the proximity of the PRL gene to the HLA-DBR1 region on chromosome 6, suggesting a genetic link to autoimmune pathogenesis. Furthermore, PRL's interaction with immune cells, including T-cells, B-cells, and macrophages, as well as its production by these cells, underscores its role in modulating immune responses. This paper hypothesizes that hyperprolactinemia contributes significantly to the resistance to immunosuppressive and corticosteroid therapy frequently observed in autoimmune diseases. The mechanisms involve PRL's interference with corticosteroid receptor signaling pathways, STAT5 pathways, and the IL-2 receptor pathways, leading to diminished anti-inflammatory effects.

Furthermore, PRL is involved in PRL/JAK2 interactions, activation of the Ras/Raf/MAP kinase pathways, as well as the pathways involving the Src family of kinases (e.g, Fyn) and SHP2, IRS-1, and PI-3 kinase activation. In vitro and animal studies further support the immunomodulatory effects of PRL, demonstrating its ability to alter lymphocyte sensitivity to corticosteroids and immunosuppressive drugs. This comprehensive review aims to elucidate the complex interplay between PRL and the immune system, highlighting the potential for targeting PRL pathways in the treatment of autoimmune diseases and overcoming drug resistance.

More Information

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Introduction

Prolactin overview

Prolactin (PRL) is an anterior pituitary hormone historically associated with lactation. Its endocrinological roles and functions are well documented. A ubiquitous distribution of its receptors has since become apparent, and it now has over 300 separate functions attributed to it [1].

Prolactin's role in lactation and reproduction remains paramount. PRL knockout animal models have highlighted this irreplaceable role. The polypeptide hormone was discovered over 70 years ago to be a pituitary factor that stimulated the growth of mammary glands and lactation, a function from which its name 'pro-lactin' originated [2].

Prolactin is secreted mainly by lactotrophic cells of the anterior pituitary. It is widely accepted that pituitary PRL secretion is positively and negatively regulated, but control is mainly by inhibitory factors originating from the hypothalamus, the most important of which is dopamine that acts through the D2 subclass of dopamine receptors found in lactotrophs. It is interesting to note that mice in which the PRL receptor (PRLR) gene has been invalidated [3] are hyperprolactinemic, suggesting feedback of PRL on its own secretion [4]. This negative regulation may be either direct on lactotrophs or indirect via an action on neuroendocrine dopaminergic neurons that express PRL receptors. The current view of the regulation of PRL synthesis integrates an extremely wide spectrum of hormones, neurotransmitters, and cytokines such as somatostatin, epithelial growth factor

(EGF), substance P, nor(adrenaline), serotonin, IL-1, TNF-α, and endothelin (ET-3) [1,5].

The Prolactin gene is expressed at many extra-pituitary sites, including specific regions of the brain, decidua, myometrium, lacrimal gland, thymus, spleen, circulating lymphocytes, lymphoid cells of bone marrow, mammary epithelial cells, skin fibroblasts, and sweat glands [6], where at these target organs, it acts on prolactin receptors in an autocrine and paracrine fashion [7]. The production of prolactin at various sites means it is possible that actions of prolactin are preserved locally through autocrine and paracrine mechanisms even when pituitary and circulating levels are altered [7]. Circulating prolactin levels show a diurnal variation with peak secretion at about 02:00 hrs and minimal secretion during waking hours in humans, an inverse relation to cortisol, which is lowest during sleep and highest during waking hours [8,9].

Prolactin is now recognized as a cytokine, and its central role in the mediation and regulation of several immune processes in humans and animals is now confirmed.

Prolactin - isoform and bioactivity

The sequence of the lactogenic or luteotropic hormone, better known as prolactin, was first identified in the sheep [10]. It was determined to be a polypeptide of 199 amino acids (aa) long. Subsequent advancements of cloning technology in the 1970s allowed quick identification of the nucleotide sequence of PRL cDNAs of several species [11]. The primary structure of human PRL was confirmed to be closely related to GH and the Placental lactogens (PL), as predicted from previous structural studies.

The gene encoding human prolactin (hPRL) is located on the short arm of chromosome 6 (p23-p21.1) [12]. It was initially described as containing five exons and four introns and an overall length of ~ 10kb [13], but since then, an additional exon 1a has been described [1]. The transcribed polypeptide undergoes post-translational modifications, including glycosylation, phosphorylation, and dimerization, giving rise to several isoforms of molecular masses between 16 and 50 kDa [14]. The mature human pituitary PRL contains 199 aa and, unmodified, has a MW of ~ 23 kDa. It has six cysteines within it that form three intramolecular disulfide bonds; (Cys 4–11, 58–174, and 191–199 in human PRL).

PRL has been identified in structural studies to be an all-α-helix protein with 50% α-helices, and the rest of the protein takes a non-organized loop arrangement [15]. The tertiary structure has not been successfully determined, but predictive models have been made using homology modeling. This exploited the structural and functional similarities between PRL and GH, and the 3D structure was determined [16] based on the crystallographic coordinates of porcine GH [17]. The result showed hPRL to possess the predicted fold of a four-helix bundle and a shared up-up-down-down connectivity of the α-helices with GH [18].

Given its ubiquitous role, isoforms of PRL are produced at various extrapituitary sites. Posttranslational modifications account for this variation. In the immune system, the subject of interest, Montgomery, et al. [19] characterized lymphocytic PRLs in metabolic labeling and immunoprecipitation studies and assessed their bioactivity in the Nb2 lymphoma PRL bioassay [20]. Three principal forms of PRL: the 24, 21, and 11 kDa were found to be synthesized and released by cultured human thymocytes. A 27-kDa PRL is synthesized by mononuclear cells, and a 25-kDa PRL is synthesized in Jurkat T cells [21]. The PRL proteins produced by these mature immune cells appear to be identical to those produced by the pituitary, with similar biological activity [22].

Prolactin - mechanism of action

Prolactin receptor: The Prolactin receptor (PRLR) was mapped over two decades ago as a single transmembrane protein. It was later identified to be closely related structurally and functionally to the Growth hormone receptor. More recent study has it classified as a type 1 cytokine receptor, belonging to the haematopioetin/cytokine super family [23-26] that includes receptors for several interleukins; IL-2 beta chain, IL-3, IL-4, IL-6, IL-7, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), leukemia inhibitory factor (LIF) and erythropoietin (EPO) [27,28]. The similarity in receptors accounts for the promiscuity and overlapping functionality between prolactin and cytokines like IL-2.

The PRLR, like all cytokine receptors, is a single-pass transmembrane protein chain. It consists of three domains: the extracellular (ECD), transmembrane, and the intracellular domain (ICD). The sequence in the ECD is similar in many cytokine receptors and known as the Cytokine receptor homology (CRH) region, consisting typically of approximately 200 amino acids [29]. The CRH can be further divided into D1 and D2 sub-domains of about 100 amino acids. Some cytokine receptors contain an additional sub-domain, but it seems D1 and D2 primarily drive ligand interaction [30]. The transmembrane domain is 24 amino acids in the human PRLR. It is not known to have any functional activity.

Differences between PRLR isoforms are conferred by their intracellular (ICD) or cytoplasmic domains. The long, intermediate, and short transmembrane PRLR are the three isoforms. The ICD has two regions called Box 1 (membrane-proximal region) and Box 2 [31]. Box 1 is composed of 8 amino acids in the cytokine receptor and is highly enriched in prolines and hydrophobic residues (aa 243–250 in PRLR). It is present in all transmembrane isoforms and is required for interaction with and/or activation of JAK2, Fyn, and MAP kinases, as well as for activation of cell proliferation and transcription of milk protein genes [31].

Box 2, in the intermediate and long PRLR isoforms alone, consists of a succession of hydrophobic, negatively charged, and then positively charged residues. A variant PRLR isoform; the soluble PRLbp of 206 amino acids has no cytoplasmic domain [32].

The prolactin receptor signaling pathway: The cytoplasmic domain of any PRLR or cytokine receptors contains no sequence of enzymatic activity, including kinase activity. However, it is known that tyrosine phosphorylation of many intracellular proteins and cell receptors occurs following the binding of a hormonal ligand. The mechanism behind this observation was unsolved until recently.

Two decades ago, Wilkes, et al. identified a new family of tyrosine kinases involved in cytokine receptor signaling. They were given the acronym JAK for 'just another kinase'. With reference to the two kinase-like domains present on the JAK, they are also known as Janus kinases to illustrate the similarity to the dual-faced Roman god, Janus [33].

The Janus kinases have a series of signal transducer and activator of transcription (Stat) proteins associated with them. These become phosphorylated along with intracellular domains on the PRLR when JAK becomes activated.

The JAK/Stat pathway is the archetypal signaling pathway used by all cytokine and haematopoietin receptors. The bioactivity of the PRLR and subsequent events downstream can be summarised as thus: 1) Binding of a hormone (e.g, PRL) to one PRLR subunit leads to a conformational change and dimerization with a second subunit, to which PRL also binds. This conformational change causes JAKs associated with the receptor to be recruited and activated (via homodimerization [34]). (JAK2 has been identified as the isoform predominantly involved with the PRLR [35]. The PRLR/JAK2 interaction occurs at the membrane-proximal region of the ICD. 2) JAK2 phosphorylates the PRL receptor (via proline residues [36]) as well as downstream tyrosine kinase residues. Transcription proteins, mainly Stat 5 in this pathway, are activated and transduce the hormonal signal into the nucleus, where they bind to target promoter elements on PRL-responsive genes.

Other pathways known to be activated by PRL include the Ras/Raf/MAP kinase pathway [37]. Pathways involving the Src family of kinases (e.g, Fyn) [38] and SHP2, IRS-1, and PI-3 kinase are activated by PRL. The consensus is that PRL activates these widely expressed pathways/kinases via PRL receptors, accounting for the ubiquitous and multiple functions of PRL in promotion of cell growth and proliferation, apoptosis, and its primary associated function; lactogenesis, which occurs through activation of the β-casein gene in mammary glands [39].

PRL terminally induces several genes through JAK/Stat, mostly via the promoter region, IRF-1. Yu-Lee, et al. [40] hypothesized that IRF-1 regulates the expression of a number of genes important for mediating many immune responses, host defenses, cell cycle progression, and tumor suppression. Other promoter elements with PRL-responsive genes include BCL-2 and BAX, which are cell-growth-promoting and anti-apoptotic [41].

In this way, PRL modulates the biological activities of many cell types and tissues as well as several aspects of the immune response.

Prolactin effect on the immune system: PRL has, for a while, been observed to exert immunomodulatory effects. Indeed, recently, it has been structurally classified as a member of the cytokine/haematopoietic family, which includes IL-2 to IL-7, GM-CSF, erythropoietin, and growth hormone.

PRL is recognized as an essential co-mitogen for T-cells and B-cells, and is also involved in the activation of NK cells and macrophages [42]. Muhkerjee, et al. showed that PL induces IL-2 receptors on the surface of lymphocytes [43] and that lymphocytes produce PRL themselves. PRL is essential for the expression of IL-2 and IL-2 receptors and thus is important for T-cell proliferation and to enhance IFN-γ production [44]. IL-2 and IFN control Th1 cell activation, differentiation, clonal expansion, and survival, and this interrelationship with IL-2 and IFN-gamma lends PRL a pivotal role. Indeed, in vitro studies have shown that the effect of IL-2 on lymphocytes was augmented on treatment with PRL, and production of IFN-γ was stimulated [45]. PRL, in addition, acts on PRL receptors on B cells and macrophages. It stimulates B-cell clonal expansion and antibody production through PRL receptors on Th2 cells so that production of several autoantibodies ensues. In vitro studies looking at the effect of PRL on macrophages showed that PRL induction increased the production of NO and IL-1, and this was enhanced by the simultaneous addition of polysaccharide to PRL.

PRL coupling to PRL-R sequesters the JAK/Stat 5 pathway and activates various proliferative and anti-apoptotic genes, including the IRF-1, BAX, and BCL-2. IL-2 and IFN-γ mediate Th1 activation and proliferation through stimulation of the same JAK/Stat 5 pathway. This results in a terminal activation of Stat 5 response genes that synthesize and secrete more IL-2 and IL-2 receptors (α sub-unit). The perpetuation of IL-2 in this manner maintains and potentiates Th1 activation and progression through the mitogenic cell cycle phases. The interrelationship between IL-2 and PRL or IL-2R and the PRL-R on lymphocytes is demonstrated at the molecular level in in-vitro studies by Hartmann, et al. 1989. Antibodies to PRL were added to a culture of lymphocytes, and this induced a profound inhibition of cell proliferation, arresting them in the G to S1 transition phase of their cell lines. Addition of purified PRL reversed this inhibition, but not by GH, outlining PRL-specificity [46].

This overlap in shared downstream signaling pathways between receptors goes even further. Antigen binding to the

T cell receptor induces activation of the transcription factors NFAT, AP-1, and NF-κB that bind to the promoter region of the IL-2 gene and activate its transcription. NFAT, AP-1, and NF-κB are the chief vectors for many proinflammatory signaling events, including the activation of COX-2 and various cytokines such as IL-2, IFN-γ, TNF-α, adhesion factors, and inducible form of NO synthase. These, along with other cytokines, stimulate and mediate a complex array of cellular/cytokine reactions, endothelial activation, and enhanced cell adhesion [47].

Cortisol targets these transcription factors, thereby exerting various anti-inflammatory modes of action. The corticosteroid receptor/steroid complex (CRα/CS complex), in addition to activating glucocorticoid-responsive elements (GRE), has a transrepressive action on multiple transcription factors. It interferes with the transcriptional activity of pro-inflammatory factors NF-κB and AP-1 and STAT 3, STAT 5, and STAT 6 [48], through inhibiting their binding to target DNA sites and, in effect, represses many pro-inflammatory genes [49]. In addition, cortisol up-regulates anti-inflammatory genes such as IL-4, IL-10, TGF-β, lipocortin-1, and the activation of IκB.

The presence of PRL can interfere with the action of the corticosteroid-complex on transcription factors, e.g., Stat5. Increased levels of PRL production in the microenvironment lead to increased activated Stat5 in mononuclear cells (via the JAK/Stat pathway). Hormone-activated CRα complexes with activated Stat5 [50] and mediates Stat5-dependent transcription; however, this sequestration potentially means that there are diminished levels of free CRα to complex with CS in the cytoplasm, leading to reduced GRE-mediated effects [51]. As a result, there are increased levels of activated Stat 5 and NF-κB expression, conferring a state of steroid unresponsiveness.

PRL, in addition, activates the MAPK pathways involving the p56Fyn/Shc/SOS/Grb2/Ras/Raf/MAPK cascades with resultant increase in levels of activated AP-1 [52]. This will counteract the effect of cortisol. Another interaction of PRL is with phosphatidylinositol. Akt is activated and subsequently the IκB kinase complex, with resulting degradation of IκB and activation of NF-κB [53]. Hence, the presence of a high state of PRL would consequently dampen the effect of cortisol.

In this manner, an increased state of PRL in the microenvironment enhances the activity of peripheral mononuclear cells and can modulate the action of and responsiveness to steroid therapy.

Methods

In vitro and animal experiments

***In vitro* experiment:** *In vitro* mitogenic and proliferative stimulation of human and mouse lymphocytes with IL-2 and IL-4 was significantly inhibited by neutralizing antibodies against PRL. What was also noted was the retardation of this mitogenic stimulation by dexamethasone dosing, and the extent of this suppression was dose-dependent. However, delaying administration of dexamethasone by as little as 12 hours markedly reduced inhibition of lymphocyte proliferation [54].

In the same study, mice treated with prolactin for three days presented with a lower degree of immunosuppression by corticosteroid. When culture splenic lymphoid cells from these mice were stimulated by mitogen, a 20-200 fold higher concentration of dexamethasone was required for the equivalent suppression of cell proliferation compared to control animals not treated with prolactin. Thus, *in vivo* treatment with prolactin alters the sensitivity of lymphocytes to corticosteroids *in vitro* [55].

In *in vitro* studies looking at cell-mediated immunity, treatment with PRL inhibitor bromcriptine abrogated T-cell-mediated macrophage tumoricidal activity in mice injected intraperitoneally with *Listeria monocytogenes* and *Mycobacterium bovis*. This effect was reversed by treatment with ovine PRL. Proliferation of cultured spleen in response to mitogens was similarly inhibited by bromocriptine and restored by PRL treatment. Prolactin enhanced IL-2 or PHC-mediated proliferation of T-cells without limitation to a cell subset. Both CD4+ and CD8+ cells' IL-2 receptors were upregulated by prolactin in the popliteal lymph node from mice [56].

Animal experiment: Berczi, et al. (1984 studied the immunomodulation of prolactin in CIA mice, a murine model of human rheumatoid arthritis. Collagen-induced arthritis (CIA) is an inflammatory response that results when susceptible strains of mice are inoculated with Freund's complete adjuvant. Parameters of disease severity are measured, such as the inflamed paw volume. It was noted that mice with intact pituitary developed more severe arthritis. The development of the CIA was abolished/ inhibited in Hypophysectomised (Hypo-X) mice. Treatment with prolactin reversed this inhibition in Hypo-X mice [57]. Treatment with the dopaminergic ergot alkaloid, bromocriptine (BCR), which inhibits prolactin secretion, abrogated the induction of arthritis. Similar effects were observed by treatment with ACTH, the pituitary corticosteroid-inducing hormone, but reversed by PL.

Furthermore, Nagy, et al. 1983 showed in other murine models of autoimmune disease/ inflammatory reactions that bromocriptine attenuated contact sensitivity skin reaction to dinitrochlorobenzene (DNCB), antibody formation to inoculated sheep red blood cells and bacterial lipopolysaccharide, and development of experimental allergic encephalitis. Immunosuppressive doses of BCR (5 mg/kg) decreased the serum prolactin (PRL) levels from 84.8 ± 15.9 ng/ml to 4.9 ± 1.6 ng/ml [58].

Nagy, et al. [59] observed no development of contact dermatitis in response to DNCB in hypophysectomised rats. Treatment with daily prolactin or transplantation of syngeneic pituitary grafts under the kidney capsule restored the DNCB-reactivity of Hypo-X rats. Combined treatment with other pituitary hormones was ineffective. Treatment with bromocriptine in normal rats was as effective in inhibiting contact dermatitis as hypophysectomy. Thus, contact sensitivity is a prolactin-dependent reaction [59].

Prolactin was also shown to be strongly indicated in humoral immune responses. Introduction of sheep red blood cells to female hypophysectomised Fischer 344 and Wistar-Furth rats produced severely truncated primary and secondary antibody responses [60]. IgM (Mercaptoethanol-sensitive) and IgG (mercaptoethanol-resistant) antibodies were similarly affected. The antibody titers to E. Coli 055:B5 lipopolysaccharide were also significantly reduced. Syngeneic pituitary grafts or daily prolactin treatment were able to restore the antibody response, but growth hormone was less effective. A separate experiment on normal rats showed that treatment with ACTH suppressed their antibody formation to SRBC. These results indicate that the pituitary gland has a role in regulating humoral immune responses.

Results

PRL in human autoimmune diseases

Given the substantial evidence for PRL's significant role in the immune system, there is an indication to look for dysregulated PRL levels in human immunologically mediated diseases. Interestingly, abnormal levels of prolactin have been observed in an array of autoimmune diseases. There is an association of hyperprolactinemia with a host of autoimmune diseases that include RA, SLE, scleroderma, multiple sclerosis, psoriasis, and an association with transplant rejection. This also correlates with a higher incidence of autoantibodies.

The association of PRL and autoimmune diseases may be explained on account that the human PRL gene is located on the same chromosome arm 6, near the HLA-DBR1 region. Mutations of these genes could be associated with the pathogenesis of autoimmune diseases [61]. Indeed, some antigens of the HLA complex are well known to correlate with a higher frequency of many autoimmune diseases [62]. Linkage disequilibrium between HLA-DRB1 alleles and microsatellite marker alleles close to the prolactin gene was found in RA and SLE patients in comparison with healthy controls. This raises the possibility of extended haplotypes encoding for HLA-DRB1 and high prolactin production that contribute to susceptibility to RA and SLE. Furthermore, Stevens, et al. demonstrated a functionally significant polymorphism that alters PRL-promoter activity and mRNA levels in lymphocytes in SLE [63]. A resultant altered local PRL production by immune cells is a possible molecular mechanism contributing to the development of other human autoimmune diseases [64].

Rheumatoid arthritis

For decades, rheumatologists have been able to demonstrate excessive prolactin levels in patients with Rheumatoid arthritis. Another observation is the inappropriate subnormal cortisol responses to inflammation. These associations, amongst other defects, raise substantial evidence for a defective neuroendocrine immune interaction in patients with RA and the suggestion that this altered response to inflammation predisposes to the development of the disease [65].

A correlation has been shown between the diurnal variation of prolactin and the disease activity of RA [66], with the circadian secretion being significantly up-regulated in patients with active RA [67]. A study noted an excessive and dysregulated increase in prolactin secretion following major surgery in RA patients compared to patients who had chronic osteomyelitis and osteoarthritis [68,69].

A higher free serum prolactin was reported in women with RA compared to controls [70]. It is evidenced that breastfeeding may exacerbate RA through the effects of PRL [71], and that there is an increased risk of developing RA in postpartum and breastfeeding women [72].

At the cellular level, active production of PRL was shown in synovium-infiltrating lymphocytes [73], but it would be interesting to establish if the increased serum PRL in RA patients reflects pituitary or lymphocyte production. The treatment of RA with BCR has been proven ineffective in one study and as effective as d-penicillamine therapy in another but this may be down to BCR ineffectiveness in lymphocyte-derived PRL.

Systemic Lupus Erythematosus (SLE)

There is a prevalence of SLE in females against males by a 9:1 ratio. What's also observed is a decline in incidence after menopause. This suggests a role for female hormones such as estrogen and prolactin in the pathogenesis of SLE [74]. A mild to moderate HPRL has been demonstrated in 15% to 33% of females and males [75] (in males, it is also associated with low androgens). In some studies, a relationship has been evidenced between HPRL and disease activity of SLE in both human and experimental models of the disease [76], but has been refuted by others [77].

In a small study, a correlation was established in SLE patients with HPRL and induced HPRL with disease activity and elevated titers of anti-DNA, anti-SSA, anti-SSB, anti-Sm, and anti-RNP antibodies [78]. Furthermore, HPRL was indicated in lupus nephritis, and CNS, cutaneous, and articular involvement with associated increased IL-6 levels in lupus nephritis and neuropsychiatric lupus [79].

Recently, a distinction was made in serum PRL properties in SLE patients. The little PRL (23kDa) was shown to be

positively related to lupus activity, but high levels of the macroprolactin or low levels of little PRL were negatively correlated. The 150-170 kDa macroprolactin is are immune complex of PRL-anti-PRL, i.e., 23 kDa –PRL complexes. These impose less clinical and serological SLE activity for a number of possible reasons. Its large size interferes with crossing through capillary walls to reach target tissues. The complexes interfere with PRL binding to the PRLRs on lymphocytes. The attenuation of PRL biological activity by the anti-PRLs may consequently lead to HPRL [80].

To determine the relationship between PRL and estrogen and its effect in SLE, transgenic mice were treated with oestradiol and bromocriptine. Bromocriptine inhibited the development of lupus normally induced by oestradiol. Oestradiol-induced breakdown in B-cell tolerance was abrogated by bromocriptine [81].

In two studies, bromocriptine therapy for SLE patients suffering from mild to moderate active disease was beneficial, with significant improvement in activity scores. Bromocriptine reduced the flare rate by 92, and discontinuation of bromocriptine was followed by a flare of disease activity in all patients.

Systemic Sclerosis (SSc)

The prevalence of SSc in women of childbearing age is at least five times greater than in men. Serum prolactin levels in patients with SSc are shown to be significantly elevated [82,83]. In particular, a recent study demonstrated that peripheral mononuclear cell (PMBC) supernatants of patients with SSc contained markedly higher amounts of PRL than PMBC from healthy blood donors. This indicates that lymphocytes of SSc patients are active producers of extrapituitary PRL and that immune activation in SSc may probably contribute significantly to HPRL in these patients. PRL, as earlier introduced, activates lymphocytes to proliferate and to produce IL-2 receptors (CD 25) and more PRL and PRL-responsive lymphocytes.

Sjogren's Syndrome (SS)

Several studies have demonstrated that SS patients have a 1.3 - 2.4 times higher serum PRL than controls [84]. The rate of HRPL amongst primary SS patients in this study varied between 3.6% - 45.5%. Haga and Rygh found that PRL level correlated with the score of internal organ disease, but not with to focus score in biopsies, levels of autoantibodies, and disease duration. The other studies did not show a correlation between systemic features and PRL levels. HPRL is assumed to be pathological rather than being present in a subset of patients.

Multiple Sclerosis (MS)

MS is twice as common in women as in men. 30% of patients with MS were found to have mild to moderate HPRL, and they were speculated to have hypothalamic lesions [85]. Bromocriptine was effective in animal models of EAE and MS, reducing PRL levels and attenuating disease activity [86]; however, a pilot study demonstrated no therapeutic effect on MS activity [87]. No correlation was found between disease activity and HPRL. In other organ-specific autoimmune diseases, Kapur, et al. recently demonstrated that HPRL was present in all patients with active coeliac disease (CD) under an unrestricted gluten-containing diet but not in patients with non-active CD disease under a gluten-free diet. HPRL was proven in the active phase of a host of other autoimmune diseases, including Hashimoto's thyroiditis, Graves' disease, and Addison's disease.

Rejection of heart transplantation

Prolactin may influence the outcome of transplant surgery in man. Carrier and Cosson, et al. observed that prolactin is a marker of heart transplant rejection in its recipients [88]. PRL was particularly useful as a predictor for rejection as its levels rose 2 to 8 days before rejection episodes. Cyclosporin A (CsA), an immunosuppressant used in organ transplantation, has been shown to exert immunosuppression partly by binding to prolactin receptors on T cells competitively [89,90]. Therefore, episodic increases in circulating PRL might competitively displace CsA from lymphocyte receptors and restore lymphocyte responsiveness.

Discussion

Hypothesis

In summary, PRL implies many autoimmune diseases. These can be subdivided into non-organ-specific (RA, SLE, SSc, SS) and organ-specific (MS, Hashimoto's thyroiditis, CD, transplant rejection) autoimmune diseases. Largely, there are two underlying disease processes. A Th1-mediated immune process with the release of IFN-γ and IL-2, and a Th2 process that generates autoantibodies, is prominent in organ-specific AD. Hyperprolactinemia can trigger these immune responses. There are other factors associated with autoimmune diseases; Muliebrity with a specific indication to periods of estrogen release appears to produce susceptibility. A subnormal/low cortisol level is a common finding that induces a permissive state to the development of autoimmune diseases. The link between HPRL and gonadal hormones in immunomodulation may be a complex one, but PRL's counteractive effects to cortisol action are via comparatively direct, shared pathways. HPRL can accelerate the immune response in patients with low cortisol, but a coordinated bidirectional communication exists between the neuroendocrine and immune systems whereby HPRL can confer a diminished cortisol immune response and resistance to steroid therapy. Thus, I hypothesize HPRL as a significant contributor to the state of resistance to steroid therapy frequently found in patients with various autoimmune diseases.

Conclusion

The study shows that hyperprolactinemia (HPRL) makes autoimmune diseases including rheumatoid arthritis

(RA) and systemic lupus erythematosus (SLE) resistant to corticosteroids. Mechanistically, PRL-activated Stat5 sequesters the anti-inflammatory corticosteroid receptor (CRα) while boosting pro-inflammatory proteins (NF-κB, AP-1), directly counteracting cortisol's effects. This molecular interference makes steroids not work. Bromocriptine and other PRL inhibitors have worked effectively for patients, so the PRL pathway is a good place to start when trying to improve systemic autoimmunity treatment and get people to respond to medicines again.

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