The prolactin role in systemic lupus erythematosus: where we are

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ABSTRACT

Prolactin (PRL) is a fundamental hormone to galactopoiesis. Nevertheless, it has many other actions, including a cytokine that modulates immune system. Most of immune cells secretes PRL, which stimulates proliferation, differentiation and maturation of T and B lymphocytes, amplifies IL-2 action and inhibits lymphocytes apoptosis. There are many evidences of the role of PRL in physiopathology of autoimmune diseases, especially systemic lupus erythematosus (SLE), as shown by data from epidemiologic and animal models studies, in vitro and in vivo. Monomeric PRL, the biologic active isoform, correlates positively to lupus activity, while macroprolactinemia, characterized by an autoantibody anti-PRL, correlates negatively. There are still some issues that deserve more studies: which is the PRL origin in hyperprolactinemic patients (pituitary versus extrapituitary)?; is PRL bioactivity increased?; is there any mutations or polymorphisms in PRL gene and PRL receptor gene?, can hyperprolactinemia treatment or PRL antagonist change SLE natural history?

Keywords: *prolactin, hyperprolactinemia, systemic lupus erythematosus, cytokine, autoimmunity.*

INTRODUCTION

Prolactin (PRL) is a protein that performs a double action: as a hormone, due to pituitary production, and as a cytokine, secondary to extrapituitary production.[1] In human beings, the most known function of PRL is the hormonal action that stimulates the final mammary development and guarantees galactpoiesis.

PRL, when playing a cytokine role, presents autocrine and paracrine actions in several organs and tissues, participating in functions related to reproduction, metabolism, water and electrolyte control, growing and development, immunological system modulation.[1]

PRL is considered a cytokine for many reasons: it is secreted by immune cells; its receptor belongs to the family of cytokine receptors type 1 (interleukins, erythropoietin, thrombopoietin, leptin, granulocyte macrophage-colony stimulating factor, granulocyte-colony stimulating factor); it shares the intracellular signalization route with other cytokines; and the gene which codifies it is located in chromosome six, next to the HLA complex.[2]

Although there are many evidences about the participation of PRL in the immune system, its exact role in physiology and pathophysiology of autoimmune diseases is yet to be totally clarified. Among the studies about PRL and autoimmune diseases, systemic lupus erythematosus (SLE) is the paradigm.

EXTRAPITUITARY PROLACTIN

The expression of the PRL gene, as well as its receptor, has been registered in many other sites besides the pituitary gland, such as the brain, myometrium, lachrymal gland, thymus, spleen, mammary epithelial cells, fibroblasts, circulating lymphocytes and lymphoid cells of the bone marrow, among others. PRL can also be found in diverse fluid compartments other than blood, such as liquor, breast milk, sweat and amniotic fluid[1] (Figure 1).

Pituitary PRL is always taken as a model when the discussion involves action mechanisms, genic regulation, molecular heterogeneity and receptors structure. Pituitary PRL acts as an ordinary hormone, secreted by the gland, transported via circulation, acting in target cells through membrane receptors, and unleashing a series of own events, like lactation.

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Besides this classic hormonal action, extrapituitary PRL presents an action under adjacent cells (paracrine action) and under the very cells that produce it (autocrine action). Extrapituitary PRL secretion, however, does not seem to interfere with the serum concentration of PRL. As a result, the serum dosage of PRL does not correlate linearly with its autocrine and paracrine actions.[3]

The composition of the final extrapituitary PRL protein is identical to the pituitary one and they both share one same gene; however, the messengers RNA's and the promoting regions are distinct, as well as its transcription control.[4]

Pituitary PRL is transcribed from the activation of a proximal promoter, whose main activator is estrogen and main inhibitor is dopamine. Extrapituitary PRL transcription is controlled by a superdistal promoter. Extrapituitary PRL expression is cell-specific and independent of Pit-1,[2] an important transcription factor of PRL genes, growth hormone and thyroid-stimulating hormone.

PROLACTIN AND THE IMMUNE SYSTEM

Many studies suggest the role of PRL[5,6] as an important factor in immunomodulation, but the real implication of this "cytokine-hormone" in the complex immune system is still unknown.

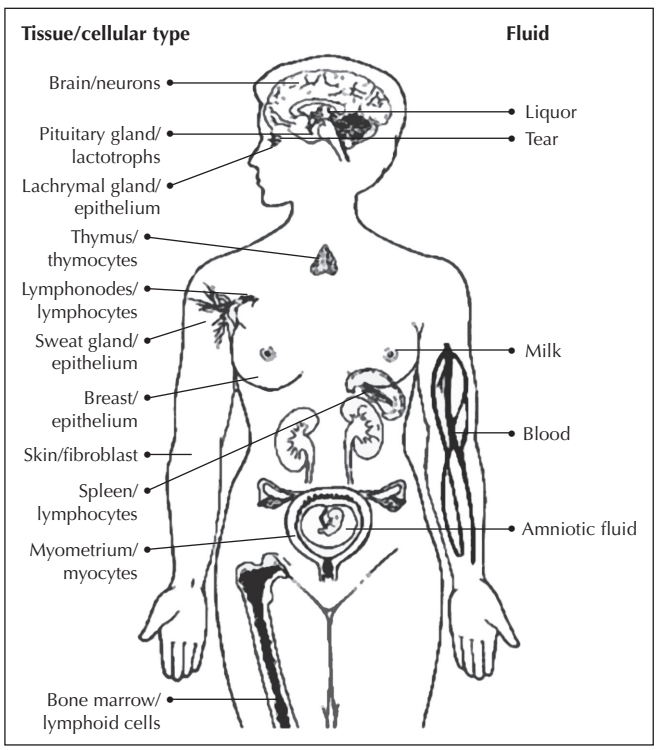

Figure 1. Sites of extrapituitary prolactin production.

In 1991, Nagy and Berczi[7] reported that hypophysectomized female rats remained with 10% to 20% of the lactogenic activity. Within two months, this activity gradually raised to 50%. In animals submitted to immunoneutralization of PRL, there was an important reduction in the lactogenic activity, causing multiple immunological deficiencies and death. These findings didn't occur in the group of hypophysectomized female rats without immunoneutralization. Because of these results, the authors suggest that PRL is involved in vital functions, probably kept by its extrapituitary production.

As a counterpart, the fundamental role of PRL in the immune system was not confirmed in the studies with knockout mice for the PRL receptor,[8] in which there wasn't any immunodeficiency.

Nevertheless, PRL production, distribution, physiological and pathophysiological functions and regulation can differ between species, since there are differences between rats and mice; the extrapolation in humans should be done with careful evaluation.[9]

The observation that most human autoimmune diseases affect females and that such diseases activity can get worse during pregnancy and in the postpartum period suggests that estrogen and PRL can modulate the immunological activity.[10] There are several evidences of the interrelation between hormones, especially PRL, and the immune system:

Cytokines such as interleukins (IL) 1 and 2 influence the secretion of pituitary hormones, such as PRL.[11,12]

The cells of the immune system express PRL receptors, among other hormones.[13]

PRL activates the kinase C protein, essential for the proliferation of T cells, induces the expression of IL-2 receptor and stimulates the gamma interferon (INF) production through INF1 (*interferon regulatory factor 1,* IRF-1) regulation factor, which regulates the maturation and differentiation of the B and T cells.[14]

Such data points towards an immunomodulating role of PRL, justifying that in knockout animals the absence of PRL does not completely compromise the immunity.

PRL has also a regulatory role in the lymphopoiesis process. In the short term, it stimulates the proliferation of T lymphocytes, the expression of IL-2 and its receptors, and it has a comitogenic effect with IL-2.[15] Chronically, it stimulates the activation of mononuclears, the differentiation and maturation of B and T cells; increases the antigens presentation, and of autoantigens;[16] and increases immunoglobulin production.[17]

PRL, of either pituitary or extrapituitary origin, activates the intracellular signalization pathway JAK2/STAT, incrementing the IRF1expression, which stimulates INF-gamma transcription. IRF1 is a transcription factor involved in Th1

response, antiviral and antibacterial, in which macrophagic, dendritic cells and NK (natural killers) cells also participate.

Summing up, the complete spectrum of the immune functions of PRL is still very controversial. Nevertheless, there are evidences that physiologic levels of circulating PRL are necessary to keep the immune competence, and both the hypoprolactinemia and the hyperprolactinemia are implicated in immunological damages, with the possibility of immunosuppression or autoimmunity development respectively.[18]

HYPERPROLACTINEMIA AND SYSTEMIC LUPUS ERYTHEMATOSUS

The prevalence of hyperprolactinemia in the general population is lower than 5% , and the main causes are shown in Table 1. Nevertheless, the average of hyperprolactinemia prevalence in lupus patients is 20% to 30%, varying from 8% to 69,7%,[19-24] usually with only slightly elevated levels (Table 2).

In vitro studies demonstrate alterations in the immune system of lupus patients, concerning PRL:

Mononuclear cells are more sensitive to PRL action for immunoglobulin production, even in physiologic concentrations.[25]

In vitro PRL is able to induce immunoglobulin and anti-DNA synthesis.[26]

As a counterpart, one publication suggests that there is no alteration in pituitary PRL secretion in patients with SLE.[27] The authors evaluated the anterior pituitary gland function, through basal hormonal dosages and stimulatory tests, in 11 patients with SLE and nine control individuals. There was no difference in the PRL dosages in both groups. These data reinforce the hypothesis that the increase of PRL in some patients was due to the local production by immune cells.

Once demonstrated that there is a correlation between SLE and hyperprolactinemia, it is legitimate to question the correlation between PRL and SLE activity.[27-29] The data in literature are conflicting[23] (Table 3), however, most studies point to a positive correlation,[21,23,25,30-33] including some organ-specific lesions, like cutaneous, articular, renal and central nervous system onset.[17]

The disagreeing results about the correlation between PRL and SLE activity[23] can be explained by the heterogeneity of the groups of patients studied, by the use of different index to measure SLE activity, by the inclusion of patients with variable disease duration, and by the diverse methodologies used for PRL testing. The presence of hyperprolactinemia is associated with diverse autoantibodies, like antinuclear, anti-dsDNA, anticardiolipin and antimicrosomal.[17]

The high prevalence of hyperprolactinemia in SLE patients and in many other autoimmune diseases (Table 4) reinforces the

Table 1
Causes of hyperprolactinemia

Physiological
Gestation
Lactation
Physical activity
Stress
Mammary stimulus
Pharmacological
Antipsychotics
Phenothiazine
Haloperidol
Risperidone
Antiemetics
Metoclopramide
Domperidone
Antidepressives
Sulpiride
MAO inhibitors
Tricyclics
Serotonin recapturers inhibitors
Others
Opioids
Estrogens
Verapamil
Proteases inhibitors

Pathological
Pituitary Adenomas
Prolactinoma
Acromegaly
Other pituitary lesions
Not working adenoma
Cushing's disease
Metastasis
Empty saddle
Sellar cysts
Infiltrative diseases (hypophysitis, sarcoidosis, tuberculosis, histiocitosis)
Vascular (aneurism)
Hypothalamic diseases
Tumors (meningioma, craniopharyngioma, glioma, hamartoma, others)
Cysts
Infiltrative diseases (hypophysitis, sarcoidosis, tuberculosis, histiocitosis)
Section of the pituitary shaft
Actinic lesion
Others
Primary hypothyroidism
Chronic renal insufficiency
Cirrhosis
Thoracic wall lesions
Macroprolactin
Autoimmune diseases
Idiopathic

Table 2
Prevalence studies of hyperprolactinemia in SLE

Study	N (patients)	Hyperprolactinemia (%)
Vera-Lastra, 2003[19]	43	69,7
Moszkorzova, 2002[20]	80	40
Pasoto, 2002[21]	36	8
Jara, 2001[16]	43	69
Pacilio, 2001[23]	78	26.9
Jacobi, 2001[24]	60	28.3
Jara, 1991[22]	45	22
Orbach, 2007[34]	100	21

*PRL > 20 ng/mL. PD = pattern deviation

involvement of PRL.[34,35] In 1029 sera of patients with diverse autoimmune diseases, Orbach *et al.* confirmed the presence of hyperprolactinemia in lupus, and observed this finding for the first time in 24% of the patients with polymyositis.[34]

PROLACTIN BIOACTIVITY IN SLE

Since not all individuals with SLE present hyperprolactinemia, and, in great part of the cases, the hyperprolactinemia found is discrete, it is legitimate to question the PRL biological activity of these patients.

A model largely used in the literature for evaluating PRL bioactivity is the bioassay with Nb2 cells, from the lymphoma of a castrated rat from the Noble lineage. This methodology is very sensitive, although not very specific, once these cells express a murine and mutated PRL receptor. These differences in relation to immune human cells can justify the different results found.[36] Some authors found greater bioactivity in patients,[23,38] while others didn't find differences.[38,39]

Table 3
Studies of correlation between hyperprolactinemia and SLE activity[23]

Authors	Patients with SLE (serum PRL > 20 ng/mL, %)	Patients M/F	Correlation with disease activity
Jara *et al.*	22.2	0/45	Yes
Pauzner *et al.*	19.5	12/70	No
Buskila *et al.*	15.9	4/59	No
Ostendorf *et al.*	2.2	14/168	No
Mok *et al.*	35	3/69	No
Pacilio *et al.*	30.6	3/46	Yes
Rovensky *et al.*	31	4/31	No
Ferreira *et al.*	37.5	1/23	No
Miranda *et al.*	42	1/25	Yes
Scali *et al.*	18	168	Yes
Zoli *et al.*	20	0/20	Yes
Orbach *et al.*	21	4/17	No

Table 4
Autoimmune diseases related to hyperprolactinemia[35]

Rheumatologic autoimmune diseases	Other autoimmune diseases
Rheumatoid arthritis	Celiac disease
Systemic lupus erythematosus	Diabetes mellitus type 1
Systemic sclerosis	Grave's disease
Sjögren's syndrome	Hashimoto's thyroiditis
Polimiosite	Addison's disease
	Multiple sclerosis

PROLACTIN ISOFORMS

In 1992, Hattori *et al*.[40] described the presence of a specific immunoglobulin anti-PRL, which caused reduction of renal depuration, of degradation and of negative retro feeding grips of the hypothalamus, which would explain the hyperprolactinemia in the presence of this antibody. The aggregate form of PRL and autoantibody presents molecular weight of more than 100 kDa and it is called macroprolactin. In most normo and hyperprolactinemic individuals, the main isoform circulating is monomeric PRL, with 23 kDa; however, an average of 25% of individuals with hyperprolactinemia can present macroprolactin as the main circulating isoform, situation denominated macroprolactinemia.

The presence of anti-PRL antibody is found with higher frequency in patients with SLE. Its presence was associated to a greater prevalence of macroprolactinemia. In turn, macroprolactinemia seems to confer protection to lupus activity, probably because macroprolactin is a poorly biologically active isoform and it is found more frequently in patients with SLE in disease remission, while biologically active monomeric PRL correlates with the disease activity. This data can partially explain the conflicting results and reinforce the fact that monomeric PRL is involved in the pathophysiology of autoimmunity.[39,41-43]

PROLACTIN AND R-PROLACTIN POLYMORPHISM

In patients with active SLE, the presence of mutation or polymorphisms of PRL or its receptor could justify the greater action of PRL under the immune system, without hyperproclactinemia. Nevertheless, Mellai *et al.*[44] didn't find polymorphism in PRL and its receptor in 217 patients with SLE and 707 controls. Stevens *et al.*[45] associated SNP (single nucleotide polymorphism) in the distal promoting region of lymphocytes to the presence of SLE (PRL1149-G). The matter still deserves new studies.

HYPERPROLACTINEMIA TREATMENT IN SLE

The literature describes studies in animals and some clinical protocols with use of bromocriptine in individuals with SLE.

The NZB/NZW mice represent an excellent model for SLE study, in which estrogen is an important accelerating factor,

and bromocriptine, a dopaminergic agonist, one of the main inhibiting factors of the disease evolution. Bromocriptine is able to suppress the renal disease and increase the survival of the treated animals.[46]

There are series of reported cases in which an improvement of the lupus activity occurred in patients who have taken bromocriptine, including those with and without prolactinome.[47] A recent pilot open study with lupus pregnant women, divided in two groups, one in use of bromocriptine (2,5 mg/day) and prednisone (10 mg/day), and the other with only prednisone (10 mg/day), showed that the first group had less mother-fetal complications (abortion, premature placental detachment, preeclampsia, among others) than the one without bromocriptine.[48] Nevertheless, considering that extrapituitary PRL transcription doesn't depend on dopaminergic action, the therapeutical mechanism remains unknown. Publications demonstrated that lupus patients treated with bromocriptine presented a lower disease activity.[46,49] Some authors suggest that bromocriptine activates suppressive T cells CD8+ in experimental models[50] in a nonspecific way.

There is evidence of the presence of dopaminergic receptors in murine lymphocytes. However, this effect in vitro occurred with dosages about 50 times larger than the one used in vivo in NZB/NZW mice.[46]

It is worthy to highlight that the conventional treatment for SLE also promoted a reduction of the PRL values in patients with slight hyperprolactinemia (20 to 40 ng/mL).[47]

Bromocriptine is still unauthorized for routine use in patients with SLE, which means that new data have to be published to support the use of this medication in such patients.

CONCLUSIONS

PRL is a cytokine that presents some defined functions in immunomodulation, especially in relation to Th1 response.

There are diverse evidences correlating PRL and SLE activity. The literature suggests the hypothesis that PRL production by lymphocytes is the one mostly affected. Therefore, due to SLE morbidity, as well as to relevant side effects of the drugs currently available for its treatment, new studies become important for the real evaluation of PRL role in its etiopathogeny, aiming the potential use of dopaminergic agonist drugs. Additionally, the detailing of the most prevalent isoforms and the verification of this PRL (pituitary vs. lymphocytarian) can bring new data for the therapeutical use of these drugs and still open new opportunities for the development of other specific treatment medications, such as a PRL receptor antagonist.

Although evidences clearly show the role of PRL in immunomodulation, whether the presence of hyperprolactinemia is the cause, effect or just an epiphenomenon in the lupus activity is still not determined. Therefore, until the present moment, PRL testing in lupus patients shouldn't be performed as a routine practice, only in certain research centers. The indication of PRL serum testing in lupus patients is the presence of hypogonadism (infertility, menstrual irregularity), with or without galactorrhea, as proceeded in any clinical situation. The use of bromocriptine for lupus activity is still experimental.

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