Interplay Between Prolactin and Pathogenesis of Psoriasis Vulgaris

Delia BOTEZATU\textsuperscript{a}, Mihaela TOVARU\textsuperscript{a,b} Simona-Roxana GEORGESCU\textsuperscript{a,b}, Oana-Diana LEAHU\textsuperscript{c}, Antoanela CURICI\textsuperscript{d}, Calin GIURCANEANU\textsuperscript{b,c}

\textsuperscript{a} Department of Dermato-Venereology, “Dr. Victor Babes” Clinical Hospital of Infectious and Tropical Diseases, Bucharest
\textsuperscript{b} Division of Dermato-Venereology, “Carol Davila” University of Medicine and Pharmacy, Bucharest
\textsuperscript{c} Department of Dermato-Venereology, University Emergency Hospital ELIAS, Bucharest, Bucharest
\textsuperscript{d} Synevo, Central Laboratory of Bucharest
\textsuperscript{e} “Dr. Victor Gomoiu” Children’s Clinical Hospital, Bucharest

Abstract

Introduction: The polypeptide hormone prolactin (PRL) represents the pituitary modulator of lactation and reproduction. Currently, we discuss the wide range of PRL actions “beyond the mammary horizon”. Multiple studies had showed the role of PRL as a cytokine, with comparable structural motifs, similar receptor structures and signal transduction pathways. Almost two decades ago it was first hypothesized that PRL acts as a neuroendocrine modulator of both skin epithelial growth and the skin immune system. Moreover, it was described the PRL circuit between the skin and the central nervous system. Psoriasis vulgaris, an immunologically mediated skin disease, is a common disorder, having as main pathogenetic mechanisms the chronic inflammation and keratinocytes hyperproliferation. Psoriasis vulgaris is not a life threatening disease, but affects seriously the quality of life; there is still no causative treatment.

Methods: After we describe the essentials of general PRL biology, the almost ubiquitous distribution of its receptors and the vast list of extrapituitary PRL-expressing tissues, our aim is to summarize clinical observations that provide insights into how PRL may impact on the psoriatic skin and define research for better characterize the complex role of PRL in human skin biology and pathology.

Results: Focusing on psoriasis, as a stress-related disease, we then discuss the possible role of PRL/PRLR in its pathology and may identify one potential biological marker and therapeutic targets for the management of this autoimmune skin disorder.

Conclusion: This theory/concept can now be integrated into current views on the multilevel neuroendocrine-immune communication along the brain-skin axis in health and disease. Due to the pathogenic complexity, there is no curative treatment for psoriasis and pharmacological modulation of PRL may represent a future target to restrict the lesions in psoriatic patients.

Keywords: Prolactin, signaling pathway, cytokine, psoriasis vulgaris
INTRODUCTION

The skin is not only an important physical barrier to the environment and a key interface between the nervous and immune system, but also a major endocrine organ. The skin, central nervous system and endocrine system have a common embryological origin and express the same, various mediators (1). Among its complex neuroendocrine activities, include production of the pleiotropic 23 kDa hormone prolactin (PRL)(2). Human skin is a source of prolactin. Most scientists associate PRL with control of lactation and the common association of prolactinoma with hyperprolactinemia. Nevertheless, it is also a passkey in control of reproduction (3). Moreover, it has a pivotal part/role in upregulated on psychoemotional and physical stress (2). Its receptors are expressed on many cell types including immune cells, keratinocytes and several PRL immuno-modulatory functions have been described (4).

Psoriasis vulgaris is an inflammatory, immune-mediated skin disease, often triggered or exacerbated by psychoemotional stress (5, 6) and influenced by genetics and epigenetic modifications triggered by environmental factors. This dermatosis is a common disease which affects approximately 2% of the world’s population, rarely life-threatening, but can damage significantly the patient’s quality of life. Due to the lack of a biological marker of disease, psoriasis is still a clinical diagnosis which is distinguished by typical or atypical manifestations and morphologic patterns. Psoriasis vulgaris may present with mutable clinical manifestations and from time to time, its clinical diagnosis can be difficult (7, 8).

Essentials about prolactin, its regulation and receptors

Prolactin is primarily produced under inhibitory dopaminergic control in the anterior pituitary gland; its gene is located on chromosome 6 in humans. In addition to its systemic effects as a hormone, prolactin acts locally as a cytokine (9, 10). It belongs to PRL/growth hormone (GH)/placental lactogen family of protein hormones (3). Among its variants, it also exist smaller variants of human prolactin (14, 17, 22 kDa) which are biologically active and may antagonize some of the functions of 23 kDa human prolactin (11). For example, the classic form of 23 kDa has proangiogenic properties in contrast to antiangiogenic functions exerted by the 16 kDa type (12). Prolactin, which serum levels vary between pregnant women (150-200ng/mL), non-pregnant women (10-25ng/mL) and men (5-10ng/mL) is secreted in a circadian rhythm (2).

The regulation and secretion of classic pituitary prolactin is complex and include a wide variety of hormones, growth factors, drugs, amino acids and peptides (3, 13). Its circadian rhythm is sustained by a complex inhibition-disinhibition system (13). The inhibition part is maintained by the pulsatile dopaminergic signal from hypothalamic neurons which down-regulates pituitary PRL secretion (13, 14). These effects are neutralized by secretion-stimulatory elements like oxytocin, thyrotropin - releasing hormone (TRH) and estradiol (3, 13, 15, 16).

Studies mentioned in literature showed that were identified prolactin expressions in extra-pituitary sites such as uterus (endometrium), placenta, mammary gland, ovaries, testis, prostate, brain, lymphocytes and adipose tissue (13, 17). This fact represented a significant progress in PRL research. PRL-expressing extrapituitary tissues express an alternative promoter, upstream of the pituitary-specific start site in the human PRL gene (18).

New research revealed that prolactin receptors (PRLR) belong to the cytokine receptor superfamily and are related to the GH receptor (19). PRLR signals among activation of the signal transducer and activation of transcription 5 (Stat5) via associated Kinase Jak2 (2, 20). Gadd et al (21) have described 6 PRLR isoforms which might evoke their distinct biological properties depending on their ability to activate specific signaling cascades (19, 22). Apart from pituitary and mammary gland, prolactin receptors are also expressed in other sites including lung, heart, liver, thymus and skin (3, 23).

Role of prolactin in skin physiology and its expression in human skin

It was first hypothesized that prolactin acts as a neuroendocrine modulator of both skin epithelial growth and skin immune system almost two decades ago. Furthermore, it was named a “PRL circuit” between the skin and the central nervous system (24). Current views point out the multilevel neuroendocrine-im-
mune communication through the “brain-skin axis” in health and disease (25-27). Foitzik et al (2) mentioned the presence of PRL and PRLR in several cutaneous cell population including keratinocytes, fibroblasts, sweat and sebaceous glands (2). All of these works suggest that PRL contributes to a variety of both physiological and pathological cutaneous process.

Regulation of pituitary secretion includes dopamine, the key inhibitor and hypothalamic thyrotropin-releasing hormone (TRH) and estrogen like potent stimulators (3, 12, 23). It was thought that the control of pituitary PRL secretion and transcription was different from that on extrapituitary sites. This concept was found on the existence of the pituitary specific transcription factor (PIT)-1 and an alternative extrapituitary PRL promoter (12). To make the difference between anterior pituitary cells and the expression of some of their hormone products, PIT-1 is needed. Studies on human decidua, which was the best-extrapituitary PRL producing tissues studied, showed PRL transcription was PIT-1, but its production was neither inhibited by dopamine or bromocriptine, nor stimulated by TRH and estrogen (28). Bromocriptine is a dopamine agonist, synthetic ergoline derivate which effect is to inhibit PRL secretion (12). Gil-Puig et al. demonstrated PIT-1 mRNA and protein expression in human breast tissue where it was found to increase cell proliferation (29). Whether human skin expresses PIT-1 and regulates intracutaneous PRL expression remains to be investigated. Suggests that at least some key endocrine controls of pituitary PRL secretion also function in human skin were made (29). The limited available data in the literature propose that TRH and estrogen administration might be performed in the management of skin and hair disorders associated with aberrant PRLR-mediated signaling (2, 12, 29). Nonetheless, caution must be performed before conclude these preliminary results.

Human skin is abounded innervated, produces neuropeptides and neurotransmitters and is a reservoir and target of a diversity of hormones, hence creating multiple levels of neural-endocrine-immune interplay within the same organ (26, 27). Physical and psychological stress can modulate intracutaneous neural-endocrine-immune interactions, summed up under the term “brain-skin” axis (12, 24). Skin exhibits complex neuroendocrine regulatory circuits (24). Organ cultured microdissected human scalp, hair follicle expressed TRH and its receptor and demonstrate a functional peripheral equivalent to the hypothalamic-pituitary-adrenal (HPA) axis, complete with corticotrophin-releasing hormone (CRH) and cortisol synthesis, as much as feedback inhibition of follicular CRH expression by cortisol (12, 24).

Connections between prolactin, its receptors and key skin cell population

Prolactin, being an important mediator of the “brain-skin” axis, its effects on skin cell populations must be pointed out (24).

Keratinocytes are notable epidermal cells and have an important role by maintaining the epidermal barrier, participating in skin immune system, regulating cutaneous antimicrobial defenses and supporting to the skin’s integrity (14). PRL and its receptors have been demonstrated in human and murine hair follicle keratinocytes, both in situ and in vitro (2, 30, 31). Hair follicle (HF) keratinocytes are alike to epidermal keratinocytes, but perform different functions, corneocyte and trichocyte generation, respectively (30). PRL has been reported to have proliferation-stimulating effects on cultured epidermal keratinocytes (32). PRLR expression is upregulated in keratinocytes after the onset of terminal differentiation (33). The precise pathways through which prolactin stimulates proliferation of keratinocytes are as yet unknown, although LeBaron et al. in 2007 demonstrated the activation of Stat5 in murine basal epidermal cells after PRL stimulation. PRL also modulates cytokine/chemokine production in keratinocytes (34). Kanda et al. (2007) showed that prolactin can enhance interferon-γ-induced chemokine (C-X-C motif) ligand
(CXC) 9, 10, 11 production in human neonatal foreskin keratinocytes via activation of signal transducer and activator of transcription (STAT)1, nuclear factor κB (NF-κB) and Interferon regulatory factor (IRF)-1, through Janus Kinase (JAK)2 and mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) pathways (12, 35). This statement led to speculation that prolactin might facilitate T cell infiltration into psoriatic plaques (35). Hence, theoretically, targeting local prolactin production could be a potential treatment strategy in management of selected inflammatory skin diseases.

Dermal fibroblasts are well-known for sustaining and remodeling the extracellular matrix of the skin, demonstrating support and for normal wound healing. Richards et al. showed that human dermal fibroblasts produce both prolactin and prolactin receptor (36). The detected 23 kDa prolactin protein, in vitro, is identical to pituitary and decidual prolactin (12, 36). Furthermore, the prolactin mRNA detected by northern blotting is 150 bp larger than the pituitary mRNA transcript, consistent with the expression of the 5’ non-coding exon express in extrapituitary sites (2, 36). At present, there are no laboratory techniques to identify proteolytic forms of prolactin that might be expressed in human skin. Langan et al. mentioned that the documented effects of prolactin in human hair growth in vitro are antagonized by a specific prolactin receptor antagonist, suggesting that the 23 kDa isoform is predominantly expressed (12).

Endothelial cells are involved in many aspects of vascular biology, including their significant role in inflammation and angiogenesis (2, 12). Angiogenesis is a feature of psoriasis and of the anagen phase of hair follicle cycling (37, 38). Indeed, serum levels of vascular endothelial growth factor (VEGF) correlate with the presence and severity level of psoriasis, chronic, hyperproliferative T-cell mediated inflammatory skin disease, whose pathogenesis remains incompletely understood (12, 38). Low levels of prolactin mRNA and the expression of prolactin protein in endothelial cells have been reported (39). Proangiogenic effect was reported in vivo from the 23 kDa prolactin (40), rather than the 16 kDa prolactin which has antiangiogenic reaction (41) and diminishes nitric oxide production by inhibiting its synthase production in endothelial cells (42). Moreover, Lee et al. and Tabruyn et al. demonstrated that the 16 kDa prolactin inhibits VEGF and stimulates endothelial cell apoptosis (41, 43). It sums up that in human, these facts could emphasize the process of aberrant vascular proliferation in psoriasis vulgaris (12).

PRL and PRLR are also present in human sebaceous glands (12). In fact, prolactin stimulates sebum production in humans. Thus, women with hyperprolactinemia exhibit hirsutism and seborrhea and patients treated with hyperprolactinemia-inducing neuroleptic drugs, also develop seborrhea (12, 24). Serafini et al. mentioned that PRL and PRLR might be implicated in psychosomatic stress on acne vulgaris and might also be related to effects on peripheral androgen metabolism (44). However, there is no consensus as to whether pituitary or skin derived prolactin is mainly responsible for these effects (2, 12).

Sweat glands are small tubular structures, a skin appendage which can be categorized in two main types relying on their secretory product and mechanism of secretion (2). Roles as osmo- and thermoregulation are relevant. Besides the sweat glands roles on non-mammals which were demonstrated in studies (45), actually, prolactin modulates chloride concentration in human sweat; therefore, human sweat glands exhibit prolactin immunoreactivity and speculations about the role of prolactin in cystic fibrosis pathogenesis were made (46).

Paus et al. observed that in human male occipital scalp, prolactin exerts inhibitory effects on hair growth, in vitro, which could sustain the concept of telogen effluvium seen in patients with hyperprolactinemia (24, 26). The modulatory effects on prolactin, in vitro, could be site or gender-specific because in organ-cultured female mice stimulates hair follicle in frontotemporal region (12). Besides the demonstrated direct adaptor role of prolactin on hair follicle cycling on the mice, in human scalp, hair follicle expresses both prolactin and prolactin receptor at the mRNA and protein level, as in human skin (2). Treatment of organ-cultured human scalp HF in anagen VI with high dose of prolactin (400 ng/mL), at levels present in patients with hyperprolactinemia due to macroprolactinoma, resulted in premature catagen development, important inhibition of hair shaft elongation, reduced proliferation and increased apoptosis of hair bulb keratinocytes (2, 12, 47). This reveals that intrafollicular PRLRs are functional and, as a consequence, human skin, including human scalp HFs, represent direct targets, not only extrapituitary sources of PRL (2, 30, 47).
Clinical relevance of prolactin, focus on psoriasis vulgaris

In dermatology practice, reduced, but intriguing evidence indicates to PRLR-mediated signaling role in psoriasis vulgaris (2). Despite that role of PRL in psoriasis vulgaris pathogenesis is still unclear, participation of prolactin in gender-specific development of autoimmune diseases has become accepted (48-51). Multiple studies reported autoimmune diseases like systemic lupus, systemic sclerosis, Reiter’s syndrome, rheumatoid arthritis, diabetes mellitus, Addison’s disease and autoimmune thyroid diseases have all been associated with elevated serum prolactin levels (52-56).

Psoriasis vulgaris is known as a chronic, recurrent, immune-mediated inflammatory disease with a conceded genetic predisposition (8). Psoriasis may begin on any age; two peaks were observed: around 20-30 and over 50 years of age, pediatric psoriasis can arrive about 30% of all cases; it is usually uncommon under the age of 10 years (8). An earlier age of onset and a positive family history are associated with possession of HLA Class I antigens, particularly HLA-Cw6, considering that, Henseler and Christophers proposed two different types of psoriasis: type I with onset age before 40 years, HLA-associated and type II with age of onset after 40 years and lack of HLA involvement. In spite of that, no evidence demonstrated of different respond on treatment between them (1, 8). Although, the early onset of chronic plaques psoriasis in white population was connected with 36 genetic loci which led to the fact that the age of onset is, partially, genetic influenced (1).

Interplay between environmental and genetic factors is convincing for the development of the disease (1). Exogenous factors like chemical ones (cauterization, chronic alkaline damage, toxic agents); physical triggers like injury – in the context of Köbner phenomenon, friction, surgical scar, injection site, scalding, burning, pressure points, X radiation; seasonal variations; alcohol consumption; smoking; drugs (antimalarials, gold salts, lithium, beta-adrenergic blocking agents, non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, antifungals) have been linked with psoriasis vulgaris and have a causal relationship by acting as a trigger in the initiation of the disease process or exacerbation of pre-existing disease (1, 8). Infections with agents like Streptococcus Beta Haemolyticus, Streptococcus pyogenes, Herpes simplex virus, Herpes Zoster virus, Hepatitis C virus, Human Immunodeficiency Virus, Candida albicans are well-recognized as precipitating factors in this dermatosis (8). (However, convincing evidence is lacking.) Endogenous factors such as allergies or hormonal-related changes have been identified to elicit the psoriatic lesions (1). Most common endogenous trigger for this inflammatory skin disease is represented by emotional stress. Considerable clinical proof exists for the role of stress in the onset and exacerbation of psoriasis vulgaris. Gupta et al reported several psycho-cutaneous features, including increased exacerbations and worse disease correlated with stress activity (57).

The psoriasis area and severity index (PASI) is the ideal clinical marker to appreciate psoriasis severity, besides being the most widely used tool to determine the disease severity in clinical trials and practice. It has the advantage to be sensitive to changes in the affection, hence to reflect improvement or worsening of this der-
matosis (58). However, PASI has its limitations; for example, in the mild form it is not so sensitive in changes in small areas of involvement (59, 60). Indeed, there are other approaches to assess psoriasis severity like the percentage of involved body surface area, the Physician’s Global Assessment. Focusing on aspects of the quality of life that are affected by skin disease, we have the Dermatology Life Quality Index (DLQI) (61). Unfortunately, all of these tools are clinical markers. Biological ones for diagnosis and prognosis of psoriasis help to establish its severity and monitor the therapeutic response. The identification in patient’s serum of predictive biological markers of psoriasis vulgaris course would be valuable in clinical practice.

**Immunological changes in psoriasis, cytokines induction of prolactin and its receptors**

The pathophysiology of *psoriasis vulgaris* is multifactorial and is still not completely elucidated. *Psoriasis vulgaris*, a prototypical T helper 1 (Th-1), T helper 17 (Th-17) and T helper 22 (Th-22) mediated inflammatory disease is currently characterized as an immune mediated inflammatory disease correlated with systemic inflammation resulting in increased risk for associated comorbidities (58, 62).

Among the mechanisms involved in psoriasis, Th1/Th2 proportion, Th17/Treg balance, and IL-23/Th17 axis appear to be particularity seminvasive (58). Recently, IL-9 producing Th9 cells and IL-17 producing γδT cells have been found to play significant roles in the pathogenesis (7). New discoveries in the pathogenesis of psoriasis have led to novel modalities of therapy (62).

More than three decades ago, it was first asserted that bromocriptine, an ergoline derivate, the dopamine agonist induced respite of psoriatic lesions, even psoriatic arthritis (63). This theory enlightened concepts/ideas to demonstrate a role of prolactin in the pathogenesis of this chronic, inflammatory disease (24). The pathological hallmarks of psoriasis as mentioned are keratinocyte hyperproliferation, dysregulated angiogenesis and expression of proinflammatory T helper (Th) 1 cytokines (64). *Psoriasis vulgaris* is often triggered or exacerbated by psychoemotional stress (5, 6). Given that PRL represents a classic neuroendocrine mediator of stress responses, it has been hypothesized that effects of stress on psoriasis are controlled by modifications in serum PRL levels (24). Dunna and Finlay observed during pregnancy that female patients with psoriasis tend to be stable and on the early months postpartum, psoriatic lesions may worsen. This led to presume the link between the physiological hyperprolactinemia associated with lactation with the exacerbated course of psoriatic lesions (65).

Girolomoni et al. showed that prolactin stimulates human epidermal keratinocytes proliferation (32), as well as VEGF production in vitro demonstrated by Garcia de la Torre et al. (66) and PRL exerts varied proinflammatory activities (67). Furthermore, prolactin may contribute in development of psoriatic plaques by stimulating interferon γ (IFN-γ) (52), but simultaneously the inhibition of T-suppressor cell functions by PRL may also serve to facilitate the advancement of psoriatic lesions (2, 64). As mentioned, PRL incites production of certain chemokines in human keratinocytes, potentially facilitating Th1 cell infiltration into epidermis and supporting the development of psoriatic plaques (12, 24, 35). Moreover, Kanda and Watanabe observed that by activating STAT1, NF-κB and IRF-1, PRL enhances IFN-γ-induced transcription and secretion of key chemokines (CXCL9, CXCL10, CXCL11), hence promoting the infiltration of type 1-T helper cells into psoriatic lesions (35). Due to that, cyclosporine A (CsA) is an efficient treatment for psoriasis (68). Hiestand et al. showed that PRL competes with CsA for a common binding site on T lymphocytes and prolactin secretion also inverses the immunosuppression induced by CsA (69). Neidhart et al. demonstrated that CsA inhibits PRL-mediated induction of ornithine decarboxylase and also that CsA and bromocriptine have synergistic effects on autoimmune diseases (70). Therefore, this idea might allow lower-dose CsA therapy in psoriasis (2).

Sánchez Regaña and Umbert Millet, in 2000 reported three cases of psoriasis in association with prolactinoma and that treatment with bromocriptine led to a better therapeutic response of the cutaneous lesions (71). Dilme-Carreras et al. found a positive correlation between serum PRL levels and the corresponding index PASI (psoriasis area and severity index) (72). Husakova et al. in 2015 demonstrated correlation between increased PRL serum levels and psoriatic arthritis, therefore elevated
PRL serum levels might represent a marker of inflammatory joint disease in patients suffering from psoriasis vulgaris (73).

Recently, it has been shown that PRL enhances inflammation and Th1 and Th17 cytokine production in a mouse model with imiquimod-induced psoriasisform skin changes (74). PRL is overexpressed in psoriatic skin lesions (75).

Due to the modest number of reported case with correlation between hyperprolactinemia and psoriasis vulgaris (71, 72, 76), this association remains to be proven. Even though, increased prolactin serum levels have been reported in patients with psoriasis, frank evidence that the incidence of psoriasis is increased in patients with hyperprolactinemia is lacking.

Nevertheless, in view of the recognized increase of human serum PRL levels upon psychoemotional stress (77) and the exacerbating effect of psychological stress in patients with psoriasis vulgaris (6, 12), it would be interesting to examine the effects of psychological stress on pituitary PRL production correlated with clinical and molecular markers on patients with psoriasis vulgaris versus healthy volunteers.

CONCLUSION

As a prototypical interface organ, where the nervous, immune and endocrine systems interconnect with environmental stimuli (2), the skin presents an instructive, easily accessible and clinically relevant model to determine the functions and regulation of extrapituitary PRL production. Larger studies are clearly needed to validate the available preliminary evidence that cutaneous PRL effects and/or PRL production might be gender- and/or site-dependent, not unlike those of androgens.

Finally, on the basis of reviewed evidences presented above, we can conclude with the notion that PRL and PRLR-mediated signaling could be targeted therapeutically in a dermatological context. As a consequence, the progress of an efficient, well-tolerated alternative to bromocriptine therapy, as anti-PRL agent remains the pivotal challenge to carrying the “prolactin-skin connection” into dermatological therapy (2).

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