THE ROLE OF HORMONES IN THE PATHOGENESIS OF PSORIASIS VULGARIS

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Abstract

Psoriasis vulgaris is a chronic, common skin disease, which affects the patient's quality of life to the highest degree. Several exogenous factors and endogenous hormonal changes may act as triggers for psoriasis.

The skin possesses a true endocrine system, which is very important in multiple systemic diseases. A number of conditions are associated with psoriasis, and its severity can also be influenced by hormones. Even though the sex hormones and prolactin have a major role in psoriasis pathogenicity, there are a lot of other hormones which can influence the psoriasis clinical manifestations: glucocorticoids, epinephrine, thyroid hormones, and insulin.

Keywords: psoriasis vulgaris, sex hormones, prolactin, glucocorticoids

Introduction

Psoriasis vulgaris, an immunologically mediated skin disease, is a common disorder, having as main pathogenetic mechanisms the chronic inflammation and keratinocytes hyperproliferation [1]. The keratinocytes differentiation is altered and the expression of genes in the psoriasis plaque may also be affected [2]. The antimicrobial peptides and proteins production during the innate and adaptive immune response reflect the genetic susceptibility to psoriasis [3].

Psoriasis vulgaris is not a life threatening disease, but it affects severly the quality of life; there is still no causative treatment [4].

Due to the psoriasis chronicity and the absence of a curative treatment [5], the disease prevalence remains a question [6]: it was estimated to more than 3% in the United States and Canada [7] and between 0.6 to 6.5% in Europe [8].

The onset of psoriasis vulgaris may be at any age, but two peaks were observed, around 20-30 and over 50 years of age [9]; pediatric psoriasis can reach about 30% of all cases [10]. The early onset of chronic plaque psoriasis in white population was associated with 36 genetic loci [11], a finding which supports the assumption that the age of onset is, at least partially, genetically determined [12].

Triggering factors of psoriasis

Psoriasis can be precipitated by multiple factors, exogenous or endogenous.

Among the exogenous triggers there are physical factors (friction, injury, injection site, surgical scar, pressure points, scalding, burning, ultraviolet or X radiation), seasonal variations [13], chemical factors (cauterization, chronic alkaline damage, toxic agents) [13,14]. Other exogenous precipitating factors can be alcohol consumption [15,16], smoking [5], drugs (gold salts [17], lithium, antihypertensives – beta-blockers, antimalarials, antifungals, which have all a strong causal relationship and can trigger or worsen the psoriatic clinical phenomena [18,19,20]; even diet can precipitate symptoms [5].

Infections with one of the following agents can trigger or exacerbate psoriasis: Streptococcus Beta Haemolyticus [21], Streptococcus pyogenes [22], Hepatitis C virus [23,24], Varicella zoster virus [25], herpes simplex virus [26], Human immunodeficiency virus [27], Candida albicans [28], upper respiratory pathogens [29].

Other risk factors for psoriasis onset are skin injuries, in the context of Köbner phenomenon [30,31].

The endogenous factors are also triggers for psoriasis. Here can be mentioned the allergies [32,33] and hormonal changes [5], but the most common trigger for several inflammatory skin diseases, including psoriasis, is the emotional stress [34,35].

Skin: hormones target and synthesis organ

The skin, the central nervous system and the endocrine system have a common embryological origin and they all express the same, numerous mediators [36]. For example, human skin produces, activates or inactivates neuropeptides like serotonin [37]; some opioid peptides and their receptors are also expressed in the skin [38].

The normal skin development and function is influenced by hormones: for example, the growth hormone stimulates keratinocyte proliferation [39], and thyroid hormones act directly on hair follicles [40]. The skin is a neuroendocrine organ, capable of hormone synthesis and release [41]: corticosteroids and sex hormones are synthesized and transformed [42] (with sebocytes playing a central role in cutaneous androgen metabolism [43]); catecholamines are synthesized by keratinocytes and melanocytes [36].

Dermal fibroblasts present strong circadian rhythm [44] and melatonin is implicated in the regulation of hair growth cycle [45] and is metabolized [46]. Prolactin is also implicated in hair growth regulation, and scalp skin and hair follicles are sources of prolactin [47].

The cutaneous endocrine system is highly important in multiple systemic diseases [48].

Conditions associated with psoriasis

A large spectrum of diseases with hormonal involvement are associated with psoriasis: depression [49], arterial hypertension [50] and other cardiovascular disorders: atherothrombotic disease or transient ischemic attack [51], nonalcoholic steatohepatitis [52], chronic inflammatory bowel disease [53] and Crohn's disease [54], dyslipidemia, obesity, metabolic syndrome [55], insulin resistance [56] and diabetes mellitus, respiratory diseases, including asthma [57], chronic kidney disease [58], uveitis [54], malignant lymphoma [55]. The treatment of those associated diseases might aggravate psoriasis [57].

The role of hormones in psoriasis

The hormones also have an important influence on the severity of psoriasis clinical manifestations. This fact is indicated by the disease frequency peaks during puberty [59] and menopause [60], besides the peaks around the age of 30 and 50 years [61]. Therefore, the hormonal variances,

major changes and the hormonal diseases could represent risk, triggering or modulating factors in the evolution of psoriasis.

1. Sex hormones and psoriasis

Psoriasis is a chronic inflammatory disease, characterized mainly by the involvement of Th1 type of T lymphocytes [62], and also by neutrophils, dendritic cells, and mast cells, all major inflammatory cytokines producers: interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), and *interleukins (*IL-2, IL-12, IL-17 and IL-23) [63,64].

Estrogens influence the immune responses, modulating the development and activation of immune cells, through the influence and control exerted upon the expression of different cytokines [65].

In vitro and *in vivo* studies demonstrated the anti-inflammatory effects of estrogens: they decrease the neutrophil's blood level and keratinocytes production of some macrophage-attracting cytokines [66], and they increase the production of IL-10 by B lymphocytes and dendritic cells [67]. Those estrogens effects may also decrease the psoriatic inflammation. Other effect of estrogens is the decreasing of matrix metalloproteinase activity in fibroblasts [66], which lowers the destruction of extracellular matrix and the release of growth factors, another pathogenic psoriatic link.

The effects of estrogen are differently mediated by estrogens receptor-α (ER-α) and β (ER-β) [68,69,70] (Figure 1). Among negative effects of estrogens in psoriasis, some should be mentioned: the suppression of apoptosis and the stimulation of proliferation at keratinocyte level, the stimulation of growth factors production in macrophages, keratinocytes and fibroblasts [66], which can stimulate the development of neovascularization, a pathogenic way in psoriasis [71].

At the same time, Progesterone, which is a commonly indicated drug, can precipitate some forms of psoriasis (pustular) [20].

1.1. Pregnancy

Extremely high levels of hormonal and immunological changes occur during pregnancy, as maternal adaptations to the developing fetus.

The evolution of psoriasis is variable during pregnancy [72]. At mid pregnancy (around 30th week of gestation), the patients' psoriatic symptoms can diminish (in >50%) or worsening (in >20%) [73]. A possible explanation could be that at this moment, there is an immunity shift from Th2 to Th1, mainly due to the increased levels of estrogen, progesterone and cortisol [74].

Other chronic immune diseases Th1-driven were shown to improve during pregnancy, such as multiple sclerosis [75] and rheumatoid arthritis [76]. Therefore, it was supposed that the increased hormone levels improve the psoriatic symptoms [77].
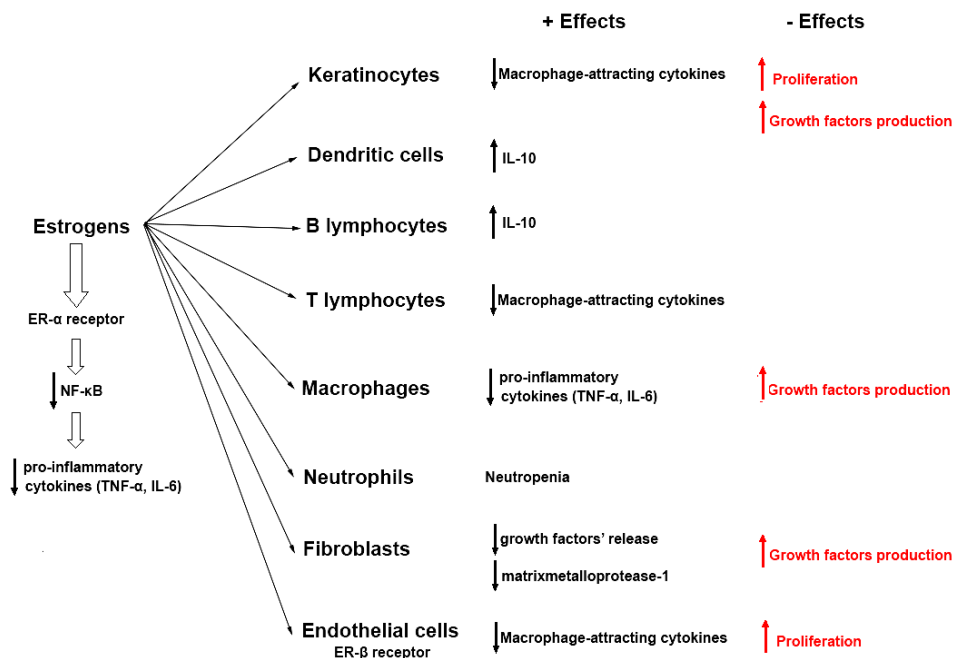
Figure 1. Positive and negative effects of estrogens, differently mediated by ER-α and ER-β [62-71].

Due to the decrease in hormonal levels after parturition and during menopause, the psoriasis severity seems to accentuate [63]. In these conditions, it was assumed that the flares occurring in the postpartum period represent rather a return to the initial level than a true worsening [73].

A moderate or severe form of psoriasis can increase the risk for a poor outcome in pregnancy [78], abortions, eclampsia, premature rupture of membranes, or macrosomia [79], but this can be due to the multiple comorbidities associated with psoriasis, which can represent risk factors in pregnancy.

Definitely, psoriasis does not represent a contraindication for a pregnancy [77]. If a systemic treatment is necessary, mothers are told not to nurse because the drugs may be excreted in milk [80].

1.2. Menopause

During menopause, the estrogen level decline and a low-grade inflammation may appear [81], meaning that menopause may aggravate the psoriasis evolution [82]. This fact is in concordance with the observation that after menopause the incidence of chronic inflammatory diseases in women became closer or higher than the incidence in males [83].

1.3. Androgens

The epidermis, dermis and hair follicle and the associated sebaceous glands express androgen receptors, and the skin is an important androgen target [84]. Androgen hormones influence the homeostasis of the epidermal barrier, the growth and differentiation of the hair and the sebaceous gland [85]. They also antagonize the macrophage's production of *vascular endothelial growth factor* (VEGF), which can prolong the inflammation and the wound healing [69]. The adrenal androgens decrease in chronic inflammatory diseases [86] and the therapies based on androgen can aggravate/exacerbate psoriasis [87].

2. Stress hormones and exercise

Endocrine and immune reactions are both highly influenced by stress. At the same time, the evolution is marked by the important stressful moments in life [63]. The hypothalamic-pituitary-suprarenal axis controls the stress hormones, cortisol and epinephrine, which are antagonists and have important effects on immune system.

Immune cells (macrophages, lymphocytes T and B) express beta-adrenergic receptor [88] and epinephrine induces multiple but dual immune responses: promotes macrophages responses through increasing secretion of cytokines TNF-α, IL-1, IL-10 [89], and regulates the level of T and B lymphocyte function. Also, it has bee observed that an acute activation of the sympathetic nervous system attenuates the innate immune response [90].

The immunomodulation in stress takes place through intersections in signaling cascade at different levels: for example, stress signals in immune response are regulated through the key Nuclear Factor-kappaB (NF-κB) and the epinephrine stimulation of β2-adrenergic receptors, expressed on immune cells, intersect with the NF-κB signaling cascade [91] (Figure 2).

Glucocorticoids prevent the inflammatory changes by inhibiting the migration of leukocytes and suppressing T cells [92]. The stimulation of epinephrine and adrenergic receptors may also exert some corticosteroid effects [93].
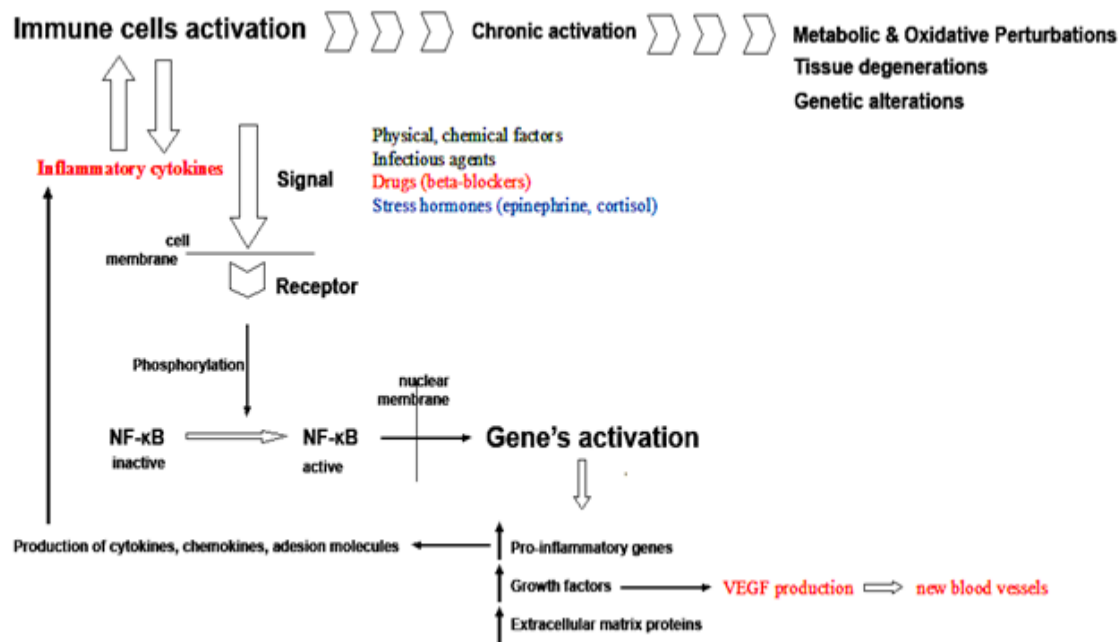
Figure 2. Loop of keratinocytes activation: stressing factors activate the immune cells, which produce cytokines that cause inflammation, which in turn activates more cytokine-producing cells, altering the keratinocytes proliferations and genetic expression. VEGF production is a major pathogenic factor in psoriasis.

The cortisol response to stress is diminished in psoriasis [94]. The psoriatic patients present higher levels of epinephrine and adrenocorticotropic hormone and lower levels of cortisol and corticotrophin releasing factor [95]. Epinephrine can modulate the remission phase and cortisol the eruption phase [22].

The stress link in psoriasis is sustained also by the fact that a regular physical activity may have favorable effect on psoriasis evolution. Through metabolic and psycho-neuro-immune effects, a regular exercise influences positively the metabolic comorbidities, lowers the risk and the onset of psoriasis [53].

3. Prolactin

Prolactin (PRL) is the pituitary hormone of lactation and reproduction. The epidermal keratinocytes express receptors for prolactin [96] and the hormone has proliferative effects on keratinocytes [97], epithelial cells, and lymphocytes [98].

There is a true "PRL–skin connection" [99]. PRL exerts a variety of immunostimulative effects which may promote the development of psoriasis [100]: it enhances keratinocytes chemokine production (IL-17) and favors infiltration with Th lymphocytes [96,101], stimulates IFN-γ production and promotes angiogenesis [102], regulates the maturation of T cells [103]. According to those multiple immune roles, hyperprolactinemia was observed in several autoimmune diseases (lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, Hashimoto's thyroiditis, multiple sclerosis) [104].

PRL is involved in the psoriasis etiopathogenesis [105] and this role of prolactin is sustained by the observations that psoriasis can be aggravated during the development of prolactinoma [106]. A significant decrease in prolactin level in patients with psoriasis was noticed after systemic treatment [98]. Several studies have shown a positive relation between serum prolactin levels and psoriasis severity [107,108,109]. Bromocriptine, used in prolactinoma, may be useful in the psoriasis treatment [108].

4. Thyroid hormones

The thyroid hormones present receptors expressed in the skin and they are important factors that can stimulate skin proliferation [110], by increasing the level of epidermal growth factor [111].

Arguments for the aggravating effect of thyroid hormones in psoriasis are the following: the psoriasis can be intensified by an excessive production of thyroid hormones [112], the free thyroxine is increased significantly in the psoriatic patients [113], in severe psoriasis, there are increased levels of *thyroid-stimulating hormone* [111], and the patients with thyroiditis had longer disease periods [113].

Also, it has been shown that the antithyroid drugs have an anti-proliferative effect on psoriasis [112]. For example, propylthiouracil, exhibits antiproliferative and immunomodulatory effects and is beneficial in psoriasis [114]. There were reported cases of psoriasis resolution after thyroidectomy [115,116].

5. Leptin, ghrelin, insulin & obesity

The metabolic syndrome, including obesity and

diabetes mellitus, are strongly associated with psoriasis [57].

Leptin is an adipose cell hormone with long-term action that decreases the appetite and suppresses food intake. Ghrelin is released primarily in the stomach and is a fast-acting hormone, increasing the appetite and playing a role in meal initiation [117].

Ghrelin can antagonize the insulin system [118] and there is a negative correlation between severity of psoriasis and ghrelin level [119].

Also, there is a relationship between leptin, obesity and psoriasis. But there are contradictive reports regarding the leptin levels in psoriasis, significantly decreased [120] or higher [121]. But, an argument for the leptin molecular link between psoriasis and metabolic comorbidities is represented by the higher serum levels of leptin in overweight or obese psoriatic patients [122].

Strongly associated with insulin resistance are both psoriasis [123] and obesity [124]. In both, there are also common pro-inflammatory pathways involved (TNF-α, IL-6). Reducing the obesity chronic low-level inflammation may improve insulin sensitivity and leptin levels [125].

Conclusions

Even though the sex hormones and prolactin are the most implicated in psoriasis pathogenesis and clinical manifestations, there are a lot of other hormonal mechanisms with significant influence on the evolution of psoriasis, therefore new therapeutic ways need to be explored.

At the same time, a hormonal assessment should be performed in patients with psoriasis, in order to correctly diagnose and treat pathologies that may be related with psoriasis exacerbations.

Due to the pathogenic complexity, there a curative treatment for psoriasis is still missing and hormonal therapeutic interventions may relieve the clinical phenomena in psoriasis.

Ackowledgement

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