Review Article

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Hormonal Pathogenesis of Acne - Simplified

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Abstract

Acne vulgaris is a common chronic inflammatory disease of the pilosebaceous unit. General pathogenesis is well known to all. With increasing incidence of polycystic ovarian disease and other hormonal disorders due to stress and lifestyle changes, the incidence of acne resistant to regular antibiotics and retinoids is increasing, with increasing need for hormonal therapy in acne as well. There are numerous hormones responsible for the eruption of acnes, with androgens playing mainly an influence role in sebum production in acne formation. Proper understanding of the hormonal pathogenesis of acne helps us in better management. This article reviews the essentials of hormonal influence in acne pathogenesis, discusses the hormonal therapies most utilized in the treatment of acne.

Keywords: Acne vulgaris, Hormones, Pathogenesis

INTRODUCTION

Acne vulgaris is a common disorder of the pilosebaceous unit. It means prevalence in adolescence is estimated to be 70-87%.[1] Its cutaneous manifestation is well known to clinicians and have been amply described. The endocrine causes and associated disease states are less commonly described. Hence, the hormonal pathogenesis of acne is well emphasized in this article.

Sebaceous glands and sebum production play a central role in the development of acne. Sebaceous gland is hormonally regulated which in turn affects the pilosebaceous unit. Let us discuss the role of hormones one by one.

Androgens

Perhaps the most preformed and well known effect of hormones on the pilosebaceous unit is the one caused by androgens, more specifically:

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1. Sebaceous gland enlargement
2. Sebocyte proliferation
3. Lipid metabolism[2,3]

Majority of the circulating androgens are produced by gonads and the adrenal gland, but they are also locally produced, in sebocyte from dehydroepiandrosterone (DHEA) sulfate, an adrenal precursor hormone.

Androgen receptors are expressed in the basal layer of the sebaceous gland and in the outer root sheath keratinocytes of the hair follicle.[4,5] When free testosterone enters the cell. It is quickly reduced to 5-dihydrotestosterone (5-DHT) by the 5α-reductase enzyme. The activity of 5α-reductase is increased in the sebaceous gland in proportion to the size of the gland.[6] DHT is ~5-10 times more potent than testosterone in its interaction with the androgen receptor. On binding to its receptor protein, DHT is translocated to the nucleus and initiates the transcription of androgen-responsive genes. DHT increases the mRNA of proteins involved in fatty acid, triglyceride squalene, and cholesterol synthesis. This effect is mediated by sterol response element binding proteins (SREBP's). By inhibiting SREBP's effect with 25-hydroxy cholesterol, there was a 50% decrease in lipid synthesis increase by DHT alone.[7] Androgens exert their effect on sebaceous glands by increasing the proliferation of sebocytes and increasing lipid production through SREBP's.

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It is now clear that pilosebaceous units possess all the steroid metabolizing enzymes needed to convert DHEA sulfate (DHEAS) to the mid potent androgen, DHT including 3β-hydroxysteroid dehydrogenase[8] and 5α-reductase.[9] Type-1 isoenzyme of 5α-reductase and Type-2 isoenzyme of 17β-hydroxysteroid dehydrogenase are predominant in sebaceous gland,[10,11] infundibular keratinocytes, and epidermis.

Furthermore, sebocytes have the biosynthetic capacity to produce their own androgen from cholesterol through the Cytp450 side-chain cleavage system (P450 Scc).[12] Along with its cofactors adenodoxin, adrenodoxin reductase, and the transcription factor, steroidogenic Factor 1, P450 scc converts cholesterol to pregnenolone, which is also the precursor for estrogen synthesis. Conclusion from this theory is that the skin has its own capacity to metabolize androgens suggesting that skin exercises local control over the ultimate effects of circulating androgen on the target tissue.

Estrogens

The most potent estrogen is estradiol, which is produced from testosterone by the action of the enzyme aromatase. Aromatase is active in the ovary, adipose tissue and other peripheral tissues. Estradiol can be converted to the less potent estrogen, estrone by the action of the 17β-hydroxysteroid dehydrogenase enzyme. Both aromatase and 17β-hydroxysteroid dehydrogenase are present in the skin.[13] Various mechanism of the role of estrogens on sebum production are: (A) Inhibition of gonadal testosterone production through negative feedback suspension of gonadotrophin,[14,15] (B) increased production of (sex hormone-binding globulin [SHBG]) by the liver, thereby decreasing free serum testosterone,[14,16,17] (C) direct opposition of androgen within the sebaceous gland,[14,16] (D) gene regulation of sebaceous gland growth and lipid production.[14,16]

Growth Hormone (GH)

GH is secreted by the pituitary gland and stimulates the production of insulin-like growth factors (IGF's) in the liver and peripheral tissues. GH receptor is found in hair follicles and the acini of sebaceous glands.[17] clinical observations suggest that GH may influence acne formation.[14,17] In a pattern similar to androgen, the natural course of acne from its onset to puberty to its peak in mid-adolescence and subsequent decline corresponds to GH levels. Furthermore, conditions of GH excess, such as acromegaly, are associated with acne development and sebum overproduction.

IGF-1

GH stimulates IGF-1 production women with acne have significantly higher levels of IGF-1 compared with women without acne. IGF plays a role in acne through its effects on androgens, sebaceous gland growth, and lipogenesis. These roles are supported by the following scientific evidence:

1. IGF-1 has the ability to stimulate adrenal averages synthesis and inhibit the production of hepatic SHBG which leads to subsequent increase in the androgen[18]
2. IGF-1 induces sebocyte proliferation by stimulating DNA synthesis.[19] IGF-1 receptors are expressed in hair follicles and peripheral cells of the sebaceous gland. Because these receptors are located where basal highly mitotic cells of the gland beside, there is a possibility that IGF-1 may directly stimulate the sebaceous epithelium by acting as atrophic factor
3. IGF-1 stimulates sebaceous gland lipogenesis by increasing expression of the transcription factor SREBPs which regulates key genes involved in lipid biosynthesis.[18]

Insulin

Insulin is structurally related to IGF-1 and can bind To IGF-1 receptor.[19] although it most likely acts as a mixed IGF-1 agonist/antagonist, its direct effects on sebocytes are distinct from IGF-1. In very high doses, insulin up-regulates GH-receptors expression on sebocytes, thereby potentiating GH-induced differentiation. In addition, insulin may act as a key regulator of lipid biosynthetic enzymes by stimulating ovarian and adrenal androgen production and inhibiting hepatic SBHG production. Insulin decreases IGF binding protein, which maximizes free IGF-1 concentrations to act on target tissues[20] and increases testosterone bioavailability and DHEAS concentrations. High foods with high glycemic load elevate plasma insulin concentrations, which regulate levels of androgens, IGF-1 and IGF binding protein, promotes unregulated tissue growth and enhances androgen synthesis.

Corticotrophin Releasing Hormone (CRH)

CRH is secreted by the hypothalamus and binds to receptors of the anterior pituitary, which in turn synthesizes proopiomelanocortin (POMC). POMC is degraded into adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone (MSH) and ultimately regulates cortisol production.[21]

In the skin, a complete GRH, GRHBP and CRH receptor system has be found *in-vivo* studies[22] CRH is released by dermal nerves and sebocytes in response to pro-inflammatory cytokines and stimulates its receptors in paracrine and autocrine fashions. The main cutaneous target of CRH is the sebaceous gland. It inhibits sebaceous proliferation, promotes sebaceous differentiation and induces sebaceous gland lipogenesis by enhancing androgen bioavailability.[23] It also interacts with testosterone and GH through complex regulatory systems and stimulates the conversion of DHEA to testosterone.

Melanocortins

POMC is produced by the anterior pituitary in response to CRH from the hypothalamus. POMC is broken down into the melanocortins ACTH and MSH. Human sebocytes express the melanocortin receptors MC-1R and MC-5R, through which ACTH and MSH regulate various effects on sebaceous gland.[24-26] MC-1R is involved in immunoregulation of interleukin-8 (IL-8) and MC-5R is involved in sebocyte differentiation and lipogenesis.[27]

Glucocorticoids

Cortisol, a stress hormone under the direct regulation of ACTH promotes sebocytes proliferation and differentiation mediated through steroid - induced activation of toll-like receptor-2, a pro-inflammatory mediator.[28]

CONCLUSION

Pathogenesis of acne involves a complex interplay of most of the hormones in the Body, which are affected by various endogenous and exogenous stress factors. Hence, a thorough evaluation of the hormonal profile must be done in resistant acne and acne associated with systemic diseases keeping in view the hormonal pathogenesis of acne.

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