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The Role of Sex Hormones in Skin Health

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ABSTRACT

This document consolidates evidence on the structure, function, and variation of the skin under both normal and pathological conditions. It aims to link these aspects to the influence of sex hormones on the skin, thereby creating a comprehensive understanding of skin health. Additionally, it outlines various treatments and their rationale for improving skin diseases, and it suggests novel therapies for certain conditions, such as acne.

Estrogens, androgens, and progesterone play crucial roles in the development, maintenance, and overall health of the skin. These hormones influence several skin functions, including the regulation of sebaceous gland activity, collagen production, skin immune defense, and skin healing. Understanding how sex hormones affect skin health is vital for developing targeted treatments for different skin conditions. Hormonal changes throughout life—such as during puberty, pregnancy, and menopause—can significantly impact skin health, highlighting the importance of maintaining hormonal balance for optimal skin condition.

This review draws on scientific data from archives such as PubMed and Scopus, as well as classic scientific publications, to enhance understanding of the role of sex steroids in the skin. We searched for keywords related to the functions of sex hormones—specifically, androgens, estrogens, and progestins—in skin health. Additionally, we examined skin structure, physical and chemical properties, the presence of sex hormone synthesis precursors in the skin, and their roles in the development and maintenance of healthy skin, as well as in various skin conditions. This review highlights several new molecules that show promising results in pharmacological and *in vitro* studies and require further investigation in clinical settings.

In conclusion, sex hormones are essential for skin health, influencing skin texture and hydration, supporting maintenance, and affecting various skin conditions. Ongoing research investigates potential treatments for skin conditions associated with hormonal changes, emphasizing the need to develop new steroidal agents that effectively reduce skin lipid production, as demonstrated in this paper.

Keywords: Skin permeability barrier, Skin health, Androgens, estrogens, progestins, Hormonal precursors in the skin, Structure, physical, and chemical properties of the skin.

Introduction

This document aims to integrate current evidence on the structure, function, and variation of the skin under both normal and pathological conditions, with a focus on sex hormone precursors and the synthesis of sex hormones within this tissue. The goal is to provide a comprehensive understanding of skin health. Furthermore, it discusses various treatments and their rationales for improving skin diseases. It also suggests potential therapies for specific conditions, such as acne, which may be of interest to clinicians.

The skin functions as a permeability barrier that separates the body from its environment. This barrier is vital for preventing excessive water and heat loss and for protecting the body from environmental hazards, such as ultraviolet radiation (UVR), pathogens, and toxins[1]. Any disruption to this permeability barrier initiates a coordinated epidermal response involving lipid production and release, ultimately helping to restore barrier balance[2, 3].

The stratum corneum is the outermost layer of the skin. It is composed of keratinocytes, which are flattened, cornified cells that produce glucosylceramides, ceramides, cholesterol, and fatty acids, all of which help regulate skin permeability[4, 5]. Glucosylceramides are formed by attaching a glucose molecule to a ceramide via β-glucosidic linkages[6]. Ceramides are a class of sphingolipids that originate from sphingosine linked to linoleic acid[7, 8], and cholesterol, a 27-carbon steroid synthesized from acetate in the skin and sebaceous glands[9, 10].

Finally, in the skin, saturated fatty acids with 14 to 28 carbon atoms are produced in the stratum corneum, with C22:0 and C24:0 being the most common types 11. These compounds are organized into stacked lamellar bilayers that help regulate both water loss through the skin and the absorption of harmful substances 1, 2. Figure 1, taken from Leprince and Simon[12], illustrates these events.

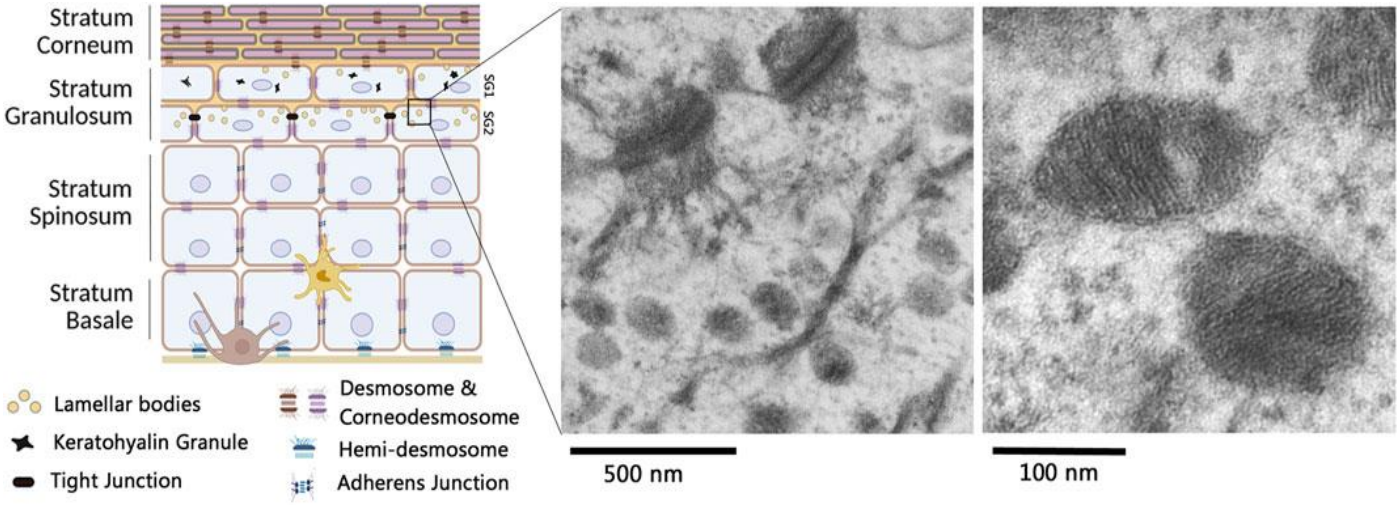


Figure 1. The diagram on the left illustrates lamellar bodies within the multilayered epidermis. The image on the right shows lamellar bodies at different scales, as observed through transmission electron microscopy[12].

The exact role of lipids in barrier permeability is not fully understood; however, some studies indicate that removing lipids from epithelial tissues increases water permeability, highlighting their essential barrier function. This finding is supported by research on porcine buccal and esophageal epithelia (see Figure 2). The figure, sourced from Diaz-Del Consuelo et al. [13], shows that after lipid extraction, the epithelial thickness appears to decrease in both buccal and esophageal samples, and the papillae become less visible.

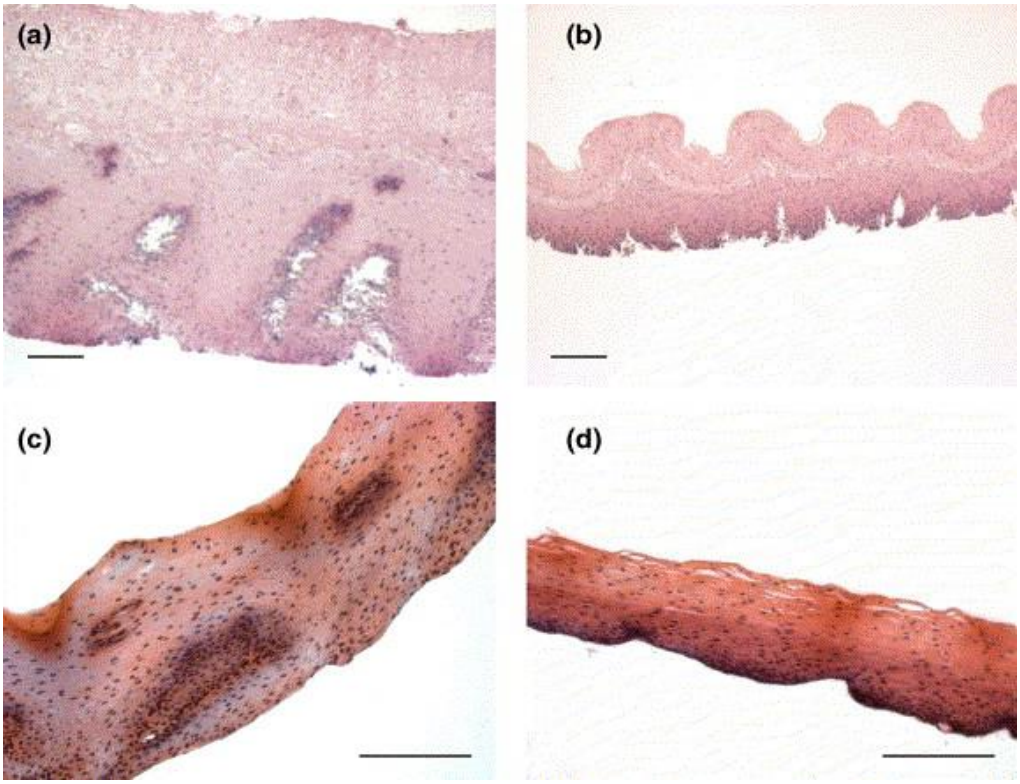


Figure 2. Porcine buccal and esophageal epithelia before and after lipid extraction. Panels a and b show the epithelia before treatment, while panels c and d display the same samples after treatment with organic solvents to remove lipids. The scale bar is 150 μm; magnification is ×100 for panels a and b and ×200 for panels c and d.

ESTRADIOL AND PROGESTERONE

Sex hormones, including androgens, estrogens, and progestins, influence epidermal permeability barrier homeostasis. Fluctuations in these hormones during menopause or the menstrual cycle can impact skin sensitivity and barrier function[14].

In adults, female skin generally retains more moisture than male skin. This difference mainly occurs because men lose significantly more water through their skin than women, prompting research into how hormones affect the skin barrier[15-17]. Previous studies have shown that androgens and progesterone can decrease the function of the epidermal permeability barrier. In contrast, estradiol (E_2) can mitigate the effects of both hormones. However, during the estrous cycle, estradiol may exacerbate the progesterone-induced breakdown of the permeability barrier. This phenomenon could be explained by estradiol's regulatory effects on the progesterone receptor, as observed in tissues influenced by both estradiol and progesterone. Consequently, this process may increase the skin's sensitivity to progesterone[14, 18].

Estrogens and androgens also influence the epidermal barrier in fetuses. Administering estrogen to pregnant mice has been shown to accelerate the development of the fetal lung-skin barrier, both in structure and function. Conversely, testosterone delays the formation of this skin barrier in fetuses[19].

ANDROGENS

Testosterone (T), produced by the testes, enters the bloodstream and binds to cells with specific hormone receptors. In tissues that rely on androgens, T is converted to its most active form, dihydrotestosterone (DHT). DHT has a higher affinity for the androgen receptor than T itself. This conversion involves reducing the double bond in the A ring of the T molecule, a process catalyzed by the enzyme 5α-reductase (SRD5A).

In human skin, androgens stimulate the growth and differentiation of sebaceous glands, promote hair growth, influence epidermal barrier function, support wound healing, and affect the skin microbiome through sebum production (Figure 3; [9, 20]). Fluctuations

in T levels can influence epidermal barrier function and permeability. Homeostasis in both mice and humans improves as epidermal barrier function strengthens. Therefore, after surgical or medical castration, androgen depletion facilitates recovery. T-treatment of castrated mice decreases epidermal thickness and reduces the density of lamellar bodies in the cytosol of cells in the stratum corneum[21].

Skin keratinocytes exhibit SRD5A activity and also express androgen receptors[22, 23]. Furthermore, the sebaceous gland can produce cholesterol, which is essential as a substrate for the synthesis of steroidal hormones, the construction of cell membranes, the formation of the epidermal barrier, and the production of sebum.

Androgens may also influence cell permeability by modulating T-cell immune activity (Th1/Th2/Th17). These cells coordinate the immune response, particularly against intracellular pathogens such as viruses and certain bacteria, while also enhancing the activity of regulatory T cells (Treg)[24].

The adrenal glands produce dehydroepiandrosterone (DHEA), which is present at significant levels in the bloodstream and boosts Th1 immune cell activity, mainly by stimulating interferon gamma production. This increase in Th1 activity heightens macrophage responses and promotes the production of pro-inflammatory factors, potentially affecting the skin microbiome.[25]

DHEA also inhibits the activity of immune helper T cells (Th2), which are involved in tissue repair, autoimmune responses, and responses to parasites. In conditions such as atopic dermatitis, the skin barrier is weakened by dysregulated Th2 cells. As a result, DHEA treatment may help improve this condition[26]. However, DHEA also plays an essential role in lowering ceramide levels by negatively affecting mitochondrial DNA. This DNA is crucial for producing enzymes such as long-chain fatty acid elongase and ceramide synthase, which are necessary for elongating fatty acid chains and synthesizing ceramides. Ceramides are essential for maintaining skin hydration and preventing the absorption of harmful substances [2, 3]. In conditions such as psoriasis and atopic dermatitis, alterations in ceramide profiles are linked to abnormal skin permeability. Therefore, assessing the effectiveness of DHEA treatment for these conditions is essential[26].

DHEA treatment improves the skin of individuals aged 60 and older by increasing hydration, epidermal thickness, sebum production, and pigmentation[9, 27, 28]. DHEA can also increase mRNA levels of procollagen and heat shock protein 47, a chaperone of type 1 collagen, in human fibroblasts, and decrease the expression of genes related to keratinocyte differentiation and cornification[28, 29]. These findings suggest that DHEA may function as an anti-aging hormone for the skin by increasing collagen production, strengthening the dermis, and regulating keratinocyte activity, as shown in Figure 3 from Labrie et al.[9]. The authors of this study demonstrated in ovariectomized rats that 12 months of DHEA treatment significantly promoted the growth, size, and secretory activity of sebaceous glands in the ventral skin (as indicated by the arrows in C, Figure 3). However, these effects were completely blocked when the antiandrogen flutamide was given alongside DHEA, as shown in D. In contrast, adding the antiestrogen EM-800 to DHEA did not cause any significant histological changes beyond those caused by DHEA alone in these sebaceous glands (as indicated by the arrow in E).

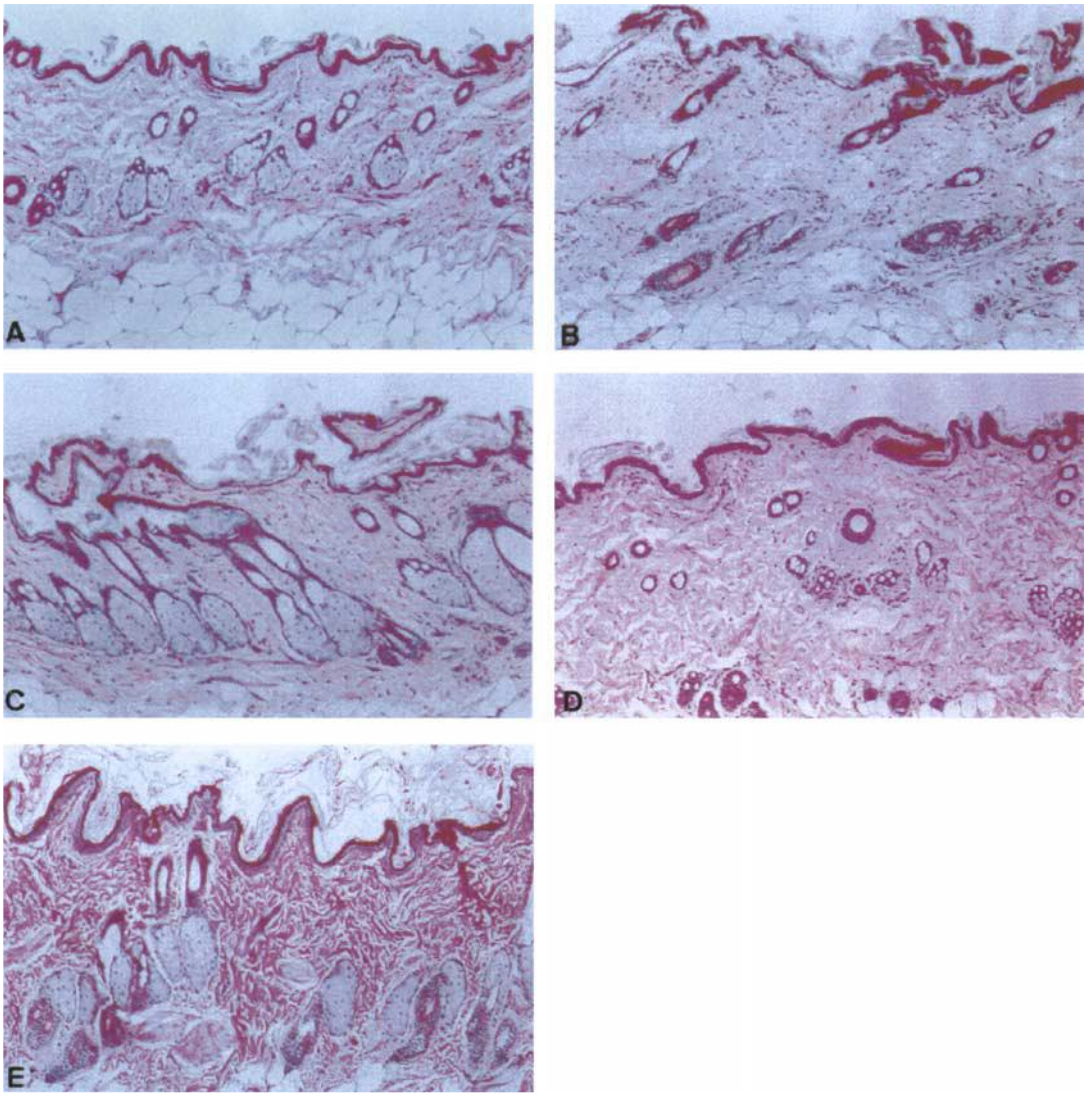


Figure 3. Effect of DHEA on the Histomorphology of Ventral Skin in Rats.
A) Intact rats, B) ovariectomized rats, C) ovariectomized rats treated with DHEA alone, D) ovariectomized rats treated with DHEA plus flutamide, E) ovariectomized rats treated with DHEA plus the antiestrogen EM-800 for 12 months.

Dehydroepiandrosterone sulfate (DHEAS) is also crucial for the function of specific cell types. For example, in Sertoli cells, DHEAS enhances junctional integrity by increasing the expression of tight junction proteins claudin-3 and claudin-5, while dehydroepiandrosterone (DHEA) does not. Therefore, DHEAS promotes cell adhesion proteins to maintain tissue cohesion by activating receptor signaling via Gα11[30, 31].

Sulfatase converts DHEAS to DHEA. Its activity is higher in women than in men, suggesting it may help regulate the skin barrier[32]. DHEAS, DHEA, androstenedione, testosterone, and DHT are the primary androgens circulating in healthy women. These androgens can promote sebocyte growth and sebum production in the sebaceous glands[33,34]. Furthermore, the sebum produced might serve as a nutrient source for *P. acnes*, a bacterium that colonizes the skin. This bacterium can hydrolyze sebum[35], converting it into fatty acids that can then trigger pro-inflammatory lesions by rupturing the skin follicular wall[36, 37] (Figure 4). Additionally, plasma levels are not the only factor influencing sebocyte development and sebum secretion; local production of these hormones can also impact these processes[9].

DHEAS plays a significant role in the development of acne in women with polycystic ovary syndrome (PCOS). In these cases, higher DHEAS levels, along with increased blood glucose levels, have been linked to more severe acne [38].

It is also important to note that changes in sebum production by sebaceous glands could trigger inflammation through interferon gamma production and activate immune responses that lead to acne lesions, as shown in Figure 4[39]). Overall, the data suggest that DHEAS plays a role in both immune responses and skin barrier regulation, as well as in the development of skin diseases[26, 32, 40].

COMMON TREATMENTS FOR ACNE

Acne vulgaris (Figure 4) is among the most common skin conditions, particularly affecting adolescents and young adults. In Mexico, the prevalence of this condition ranges from 20% to 25%. In females, the typical age of onset is 12-13 years, while in males it is 13-14 years. The condition typically presents in the second decade of life and tends to decrease in the third decade, often resolving before age 25. Its peak severity generally occurs between ages 17 and 21 and 41. Although acne is not life-threatening, it can cause significant physical and psychological issues, including permanent scarring, low self-esteem, depression, and anxiety[42]. Acne is linked to a higher risk of stigmatization, bullying, depression, anxiety, low self-esteem, and suicidal thoughts[43, 44].

This condition is classified as a chronic inflammatory skin disorder. It involves open or closed comedones (blackheads and whiteheads) and inflammatory lesions, such as papules, pustules, or nodules (often referred to as cysts), as shown in Figure 4. Acne is a multifactorial inflammatory disease that affects the pilosebaceous units of the skin. Significant factors contributing to this acquired condition include follicular hyperkeratinization, microbial colonization by *Propionibacterium acnes* or *Cutibacterium acnes*, excessive sebum production, and complex inflammatory responses involving both innate and adaptive immunity[42, 45].

Additionally, some studies indicate that neuroendocrine regulatory mechanisms, diet, and both genetic and non-genetic factors may contribute to the multifactorial causes of acne.[42, 45]. The most common topical treatments for acne include benzoyl peroxide (BP), salicylic acid, antibiotics, combinations of antibiotics with BP, retinoids, combinations of retinoids with BP, combinations of retinoids with antibiotics, azelaic acid, and sulfones.

Benzoyl peroxide (BP) is an antibacterial agent that effectively eliminates *P. acnes* by generating oxygen-free radicals. Including BP in antibiotic treatment plans can improve therapeutic outcomes and help prevent antibiotic resistance, as no cases of bacterial resistance to BP have been reported [46] Additionally, BP has a mild comedolytic effect, making it more advantageous for acne treatment.

The hair follicle absorbs topical antibiotics used to treat acne, which may have both anti-inflammatory and antibacterial effects. Commonly prescribed antibiotics for managing acne are often combined with fixed concentrations of benzoyl peroxide (BP). Notable examples include erythromycin 3%/BP 5%, clindamycin 1%/BP 5%, and clindamycin 1%/BP 3.75%. Among these, clindamycin 1% in either solution or gel form is considered the preferred topical antibiotic for acne because of its effectiveness[42]. Patients generally tolerate these agents well, and clindamycin alone is classified as a pregnancy category B medication. This suggests that such combinations may improve patient adherence to treatment plans.

Double-blind, placebo-controlled randomized clinical trials have shown that topical retinoids are effective in treating acne by preventing comedones, resolving precursor lesions such as microcomedones, and reducing inflammation. These vitamin A derivatives are available in pharmacies in three formulations with different active ingredients: tretinoin (0.025–0.1% in cream, gel, or microspheres), adapalene (0.1% or 0.3% in cream or 0.1% in lotion), and tazarotene (0.05% or 0.1% in cream, gel, or foam). Each retinoid interacts with different sets of retinoic acid receptors: tretinoin binds to alpha, beta, and gamma receptors, while tazarotene and adapalene selectively bind to beta and gamma receptors, respectively. These differences lead to slight variations in their activity, tolerability, and effectiveness[42, 45.]

Adding levonorgestrel to topical applications improved acne lesions, as demonstrated by Cabeza, Vargas, and Garcia[47]. The levonorgestrel molecule is used as a steroidal contraceptive in various formulations administered through different methods. It is also known as the morning-after pill and is a synthetic progestogen with structural similarities to progesterone. It belongs to the second generation of progestins[48]. Levonorgestrel binds to human steroid receptors *in vitro* with varying affinities: it shows increased selectivity for progesterone receptors and lower selectivity for androgen, glucocorticoid, and mineralocorticoid receptors[48]. These properties lead to a significant reduction in adverse reactions, thereby improving patient adherence to treatment.

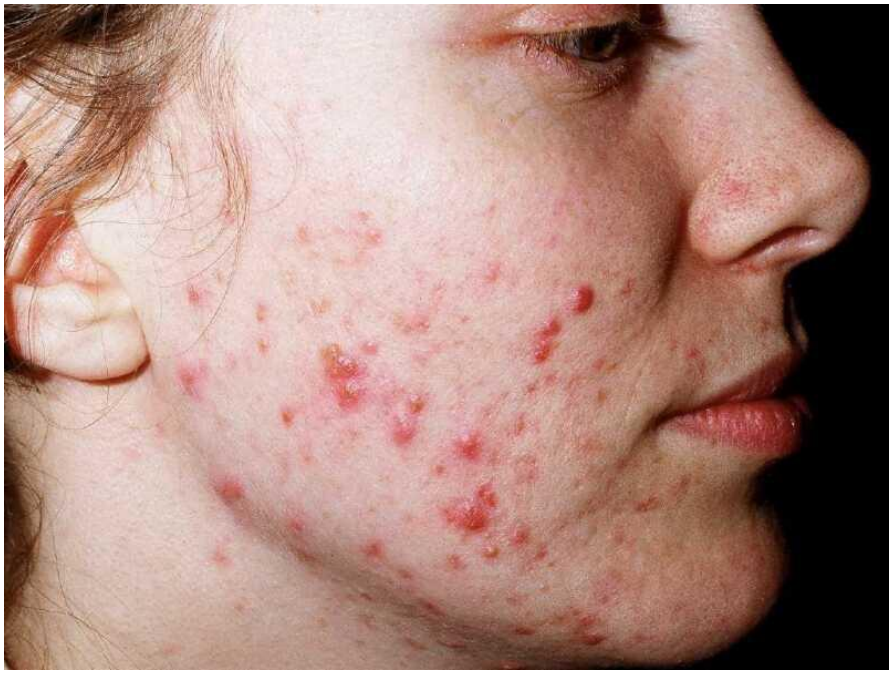


Figure 4. Acne Vulgaris DermNet New Zealand.

Sutaria AH, Masood S, Saleh HM, et al. Acne Vulgaris. [Updated 2023 Aug 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459173/

Influence of Steroidal Molecules on the Regulation of Adrenergic Function

Adrenal steroids and catecholamines are crucial in responding to stress and maintaining normal physiological functions. The interaction between these two hormonal systems holds significant physiological importance. While catecholamines target specific tissues, steroid hormones influence a wide range of physiological processes across various tissues[49].

Steroidal hormones play a crucial role in regulating β-adrenergic receptor density in various cells and tissues. For instance, administering cortisone acetate increases β-adrenergic receptor density in neutrophils by 39%. However, in circulating human polymorphonuclear and mononuclear leukocytes, corticosteroids actually decrease the density of these receptors.[50] In contrast, prednisone treatment increases receptor density in lymphocytes and granulocytes[51]. Additionally, glucocorticoids also enhance the density of β-adrenergic receptors in human lung cells[52].

Sex hormones also play a key role in regulating β-adrenergic receptors. In studies with prepubertal rats, the β-adrenergic blocker dihydroalprenolol (Figure 5) showed only weak binding affinity to β-adrenergic receptors in the uterus. This affinity increased after puberty and following acute estradiol treatment after the prepubertal stage. These findings suggest that sex hormones are crucial for

promoting β-adrenergic receptor expression in rat uterine tissue[53].

Treating pregnant rats with 17β-estradiol has been shown to decrease α1A adrenoceptor expression in the myometrium, while leaving α1D adrenoceptor expression unchanged. In contrast, progesterone does not appear to affect the mRNA or myometrial protein levels of α1-adrenoceptors; however, it does modify the G protein coupling of these receptors, thus enhancing Gi protein-dependent signaling.

Androgens have been shown to affect the β-adrenergic signaling pathway. Notably, activation of androgen receptors by dihydrotestosterone suppresses the typical increase in body temperature caused by β-adrenergic agonists in brown adipose tissue[55].

Additionally, androgens play a crucial role in lipid synthesis, which is regulated by β-adrenergic receptors, especially in the hamster flank organ model. In this model, the non-selective β1- and β2-adrenergic blocker propranolol (see Figure 5) inhibited the *in vitro* synthesis of lipids from radiolabeled acetate, even in the presence of testosterone. This highlights the role of β-adrenergic receptors in promoting lipid synthesis in this pilosebaceous unit[56]. Furthermore, stimulation of β-adrenergic receptors with isoproterenol, in the absence of testosterone, did not increase lipid synthesis, suggesting that androgens may enhance β-adrenergic receptor synthesis within the pilosebaceous units of hamsters[57].

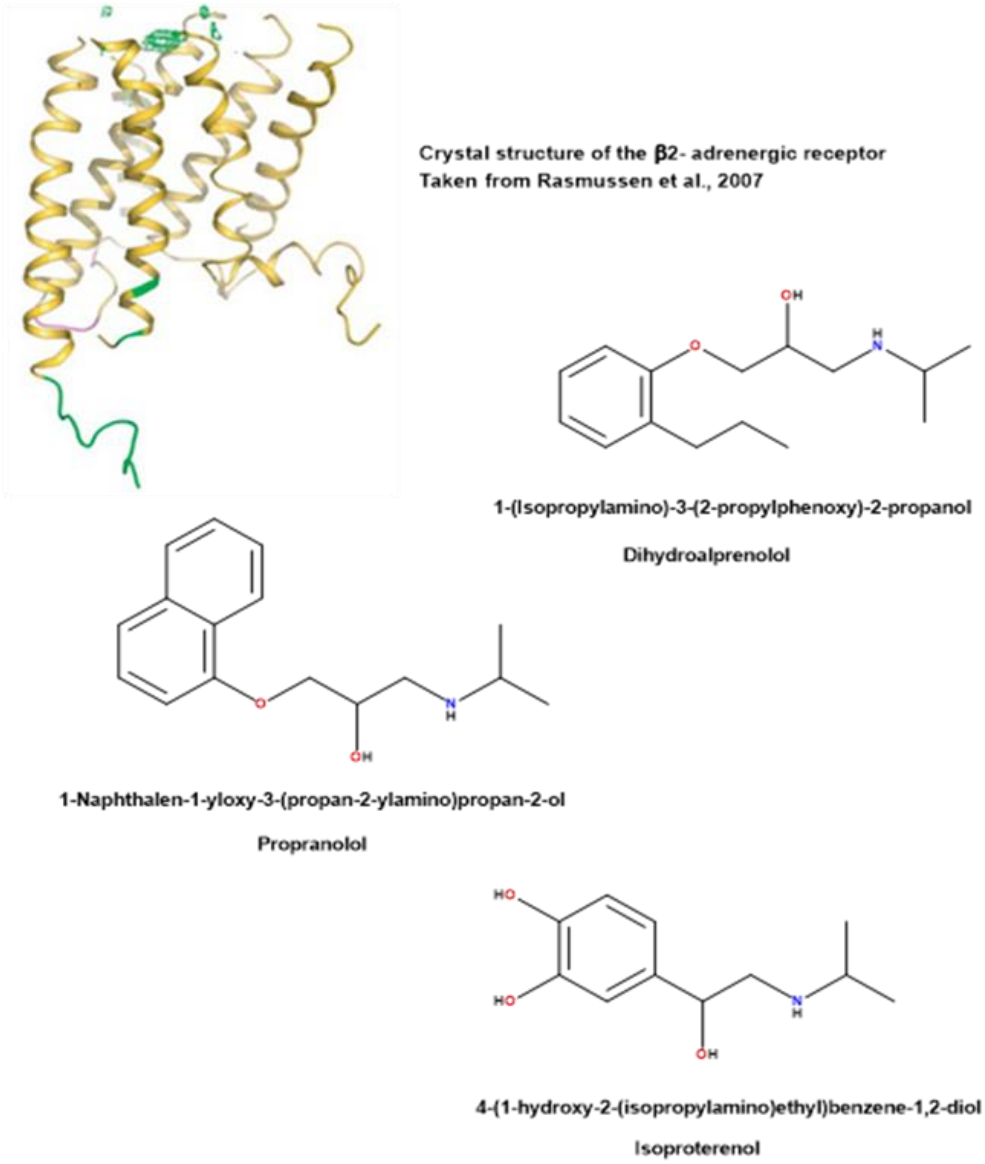


Figure 5. Structures of β2-adrenergic receptor and the compounds Dihydroalprenolol, Propranolol, and Isoproterenol.

The Influence of Sexual Steroids on Sebum Lipid Composition

Gonadal hormone production varies between men and women, causing significant effects on the skin[58]. Men typically have thicker skin because androgens promote dermal growth[58], Azzi et al., 2005, along with differences in hair growth patterns, mainly due to changes in circulating androgen levels. This dimorphism becomes more noticeable with beard growth in men and the presence of androgenetic alopecia in some. This is mainly explained by the presence of hormone receptors in various skin cell types.[60.]

In addition to gonadal hormones, the skin also functions as an intracrine organ capable of producing steroid hormones, as it contains enzymes involved in steroidogenesis[61]. Skin cells can convert DHEA into androstenedione via the enzyme 3β-hydroxysteroid dehydrogenase type 1 (3β-HSD). Androstenedione is then converted to testosterone by the enzyme 17β-hydroxysteroid dehydrogenase type 5 (AKR1C3). The AKR1C3 enzyme is present in all epidermal and sebaceous gland cells and is highly expressed in hair follicles. Finally, testosterone is converted to dihydrotestosterone by type 1 5α-reductase, an SRD5A isoform. Dihydrotestosterone binds to the androgen receptor, which then translocates to the cell nucleus and binds to the androgen response element. This triggers a well-known series of reactions that ultimately regulate protein synthesis in these cells[62, 63]. In postmenopausal women, all sex steroids produced in the skin originate from adrenal steroid precursors like DHEA, whose levels gradually decline after age 30. As previously discussed, DHEA treatment in rats increased sebaceous gland activity, and the antiandrogen flutamide blocked this effect (see Figure 3), highlighting the role of DHEA in sebaceous glands.[61] It has been previously reported that DHEA treatment has an estrogenic effect in the vagina of postmenopausal women, indicating that the tissue can convert DHEA to testosterone and testosterone to estrogens via the aromatase enzyme. However, at typical doses, this weak steroid (DHEA) does not affect the endometrial epithelium. This suggests that there are no DHEA-converting enzymes in this tissue, thereby eliminating the need for progestogens when DHEA is used for hormone replacement therapy[61]. As skin ages, it produces less sebum. This change lowers surface lipids (SSL), thereby decreasing the levels of various components in the hydrolipidic film. Additionally, in older skin, 2,3-oxidosqualene increases, while triglycerides and their hydrolytic byproducts decrease, indicating shifts in enzymatic activity[64].

In individuals aged 20 to 40, sebaceous lipids (SSLs) represent a complex mixture of non-polar lipids originating from both epidermal and sebaceous sources[65]. The composition of the mixture is characterized by the following proportions: triglycerides (TG) constitute 20-60% of the total, followed by wax esters, which account for 23-29%. Additionally, squalene comprises 10-14% of the mixture; notably, it is present exclusively in human skin among mammals[66], and free fatty acids (FFA) can vary between 5-40%. Additionally, small quantities of cholesterol and cholesterol esters account for 1-5%, as well as diglycerides (DG), which constitute 1-2% of the total lipid content[67-69].

Research indicates that testosterone, progesterone, and the synthetic progestin levonorgestrel can alter the lipid composition of sebum secreted by the flank glands of castrated hamsters[70, 71]. This evidence suggests that different steroid molecules can influence the sebum composition in these glands.

Additionally, the effects of testosterone and progesterone on the mRNA levels of lipid enzymes, including glycerol-3-phosphate acyltransferase (GPAT), β-hydroxy-β-methylglutaryl-CoA synthase (HMG-CoA-S), β-hydroxy-β-methylglutaryl-CoA reductase (HMG-CoA-R), phosphatidylinositol synthase (PI-S), and squalene synthase (SQ-S), have been documented previously [72, 73] using the same hamster model, as shown in Figure 6. These data indicate that, except for squalene synthase, topical application of a vehicle (5 µL of ethanol) decreased

the mRNA expression of all other enzymes measured in intact animals. Gonadectomy, however, reduced the expression of all remaining enzymes studied, except for glycerol-3-phosphate acyltransferase (Figure 6. The data in this figure are from Lezama et al.[73]). Conversely, topical application of progesterone and testosterone to the hamster flank organs increases the mRNA synthesis of all these enzymes involved in lipid synthesis in the hamster pilosebaceous unit. Overall, these data confirm the role of sex hormones in lipid synthesis[73].

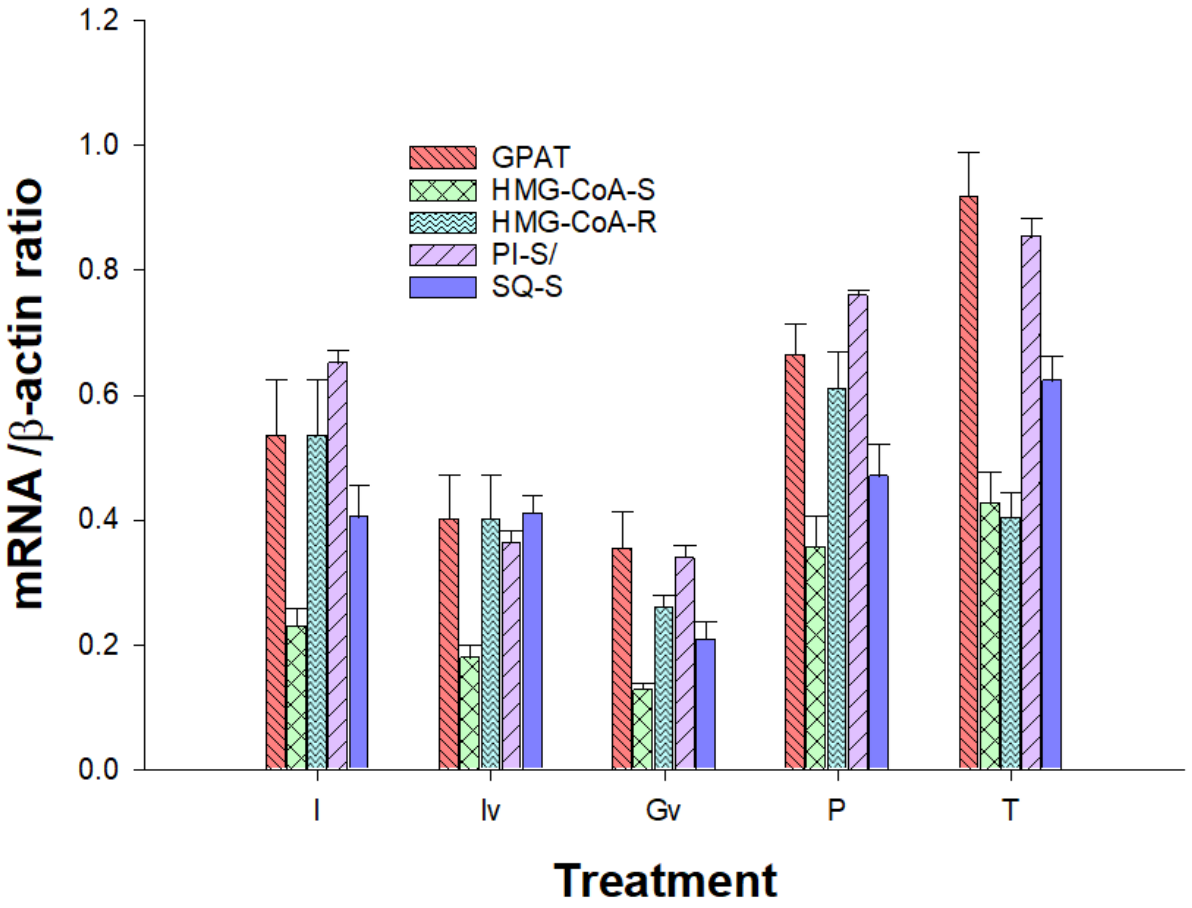


Figure 6. Effects of testosterone (**T**) and progesterone (**P**) on the mRNA levels of lipid enzymes, specifically glycerol-3-phosphate acyltransferase (**GPAT**), β-hydroxy-β-methylglutaryl-CoA synthase (**HMG-CoA-S**), β-hydroxy-β-methylglutaryl-CoA reductase (**HMG-CoA-R**), phosphatidylinositol synthase (**PI-S**), and squalene synthase (**SQ-S**) in the flank organs of hamsters treated pharmacologically with T or P [73].

Impact of Novel Steroidal Derivatives on Inhibition of Sebaceous Gland Lipid Synthesis.

Understanding how lipids contribute to skin health and how sex hormones influence this organ has led to the development of various biologically active steroids to regulate sebum secretion in cases of abnormal production.

The study by Cabeza et al. used hamster flank organs as a model for sebaceous tissue, demonstrating that inhibitors of 5α-reductase type 1 (SRD5A1) can effectively block *in vitro* lipid synthesis from acetate induced by testosterone[74-76]. Because the SRD5A1 enzyme is essential for converting testosterone into dihydrotestosterone in the flank organs by reducing the double bond in testosterone, as shown in Figure 7[76], this signaling pathway is necessary for lipid production in this pilosebaceous unit.

The process of testosterone reduction involves transferring a hydride from reduced nicotinamide adenine dinucleotide phosphate (NADPH) to the

5α-position of testosterone, as shown in Figure 7[77]. During this reaction, an enolate forms at carbons 3 and 4. An electrophilic residue (E^+) within the enzyme active site probably stabilizes this enolate. This stabilization increases the molecule's polarity, enabling it to accept a hydride from NADPH at carbon 5. As a result, when the enzyme catalyzes this reaction, dihydrotestosterone is produced, and $NADP^+$ is released (Figure 7).

The overall data suggest that inhibiting SRD5A activity could decrease lipid production in the skin. In this context, Cabeza et al. synthesized various pregnenolone derivatives and assessed their ability to inhibit this enzyme's activity[73, 75, 78]. Additional experiments showed that these steroidal derivatives also reduced the incorporation of labeled acetate into lipids (Figure 8), indicating that SRD5A inhibitors can block lipid synthesis from acetate as a precursor[10, 75, 78]. Pharmacological treatment with these steroids [7, 8, 13], combined with testosterone, in the flank organs of castrated hamsters, reduced *in vitro* lipid synthesis compared to treatment with testosterone.

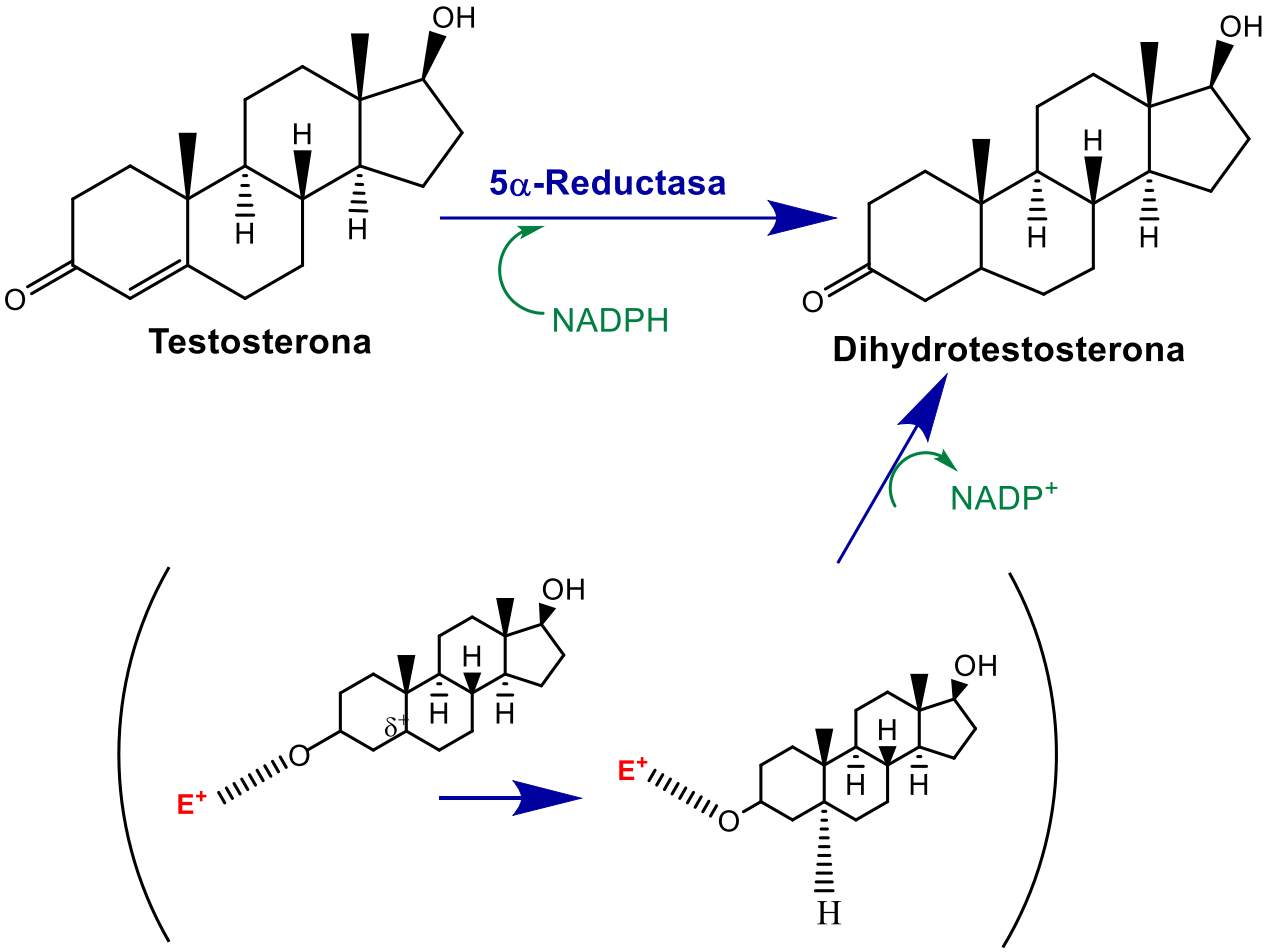


Figure 7. Testosterone (T) is converted into dihydrotestosterone (DHT) in androgen-dependent tissues by the enzyme 5α-reductase (SRD5A 1/2) and the cofactor $NADPH^+$.

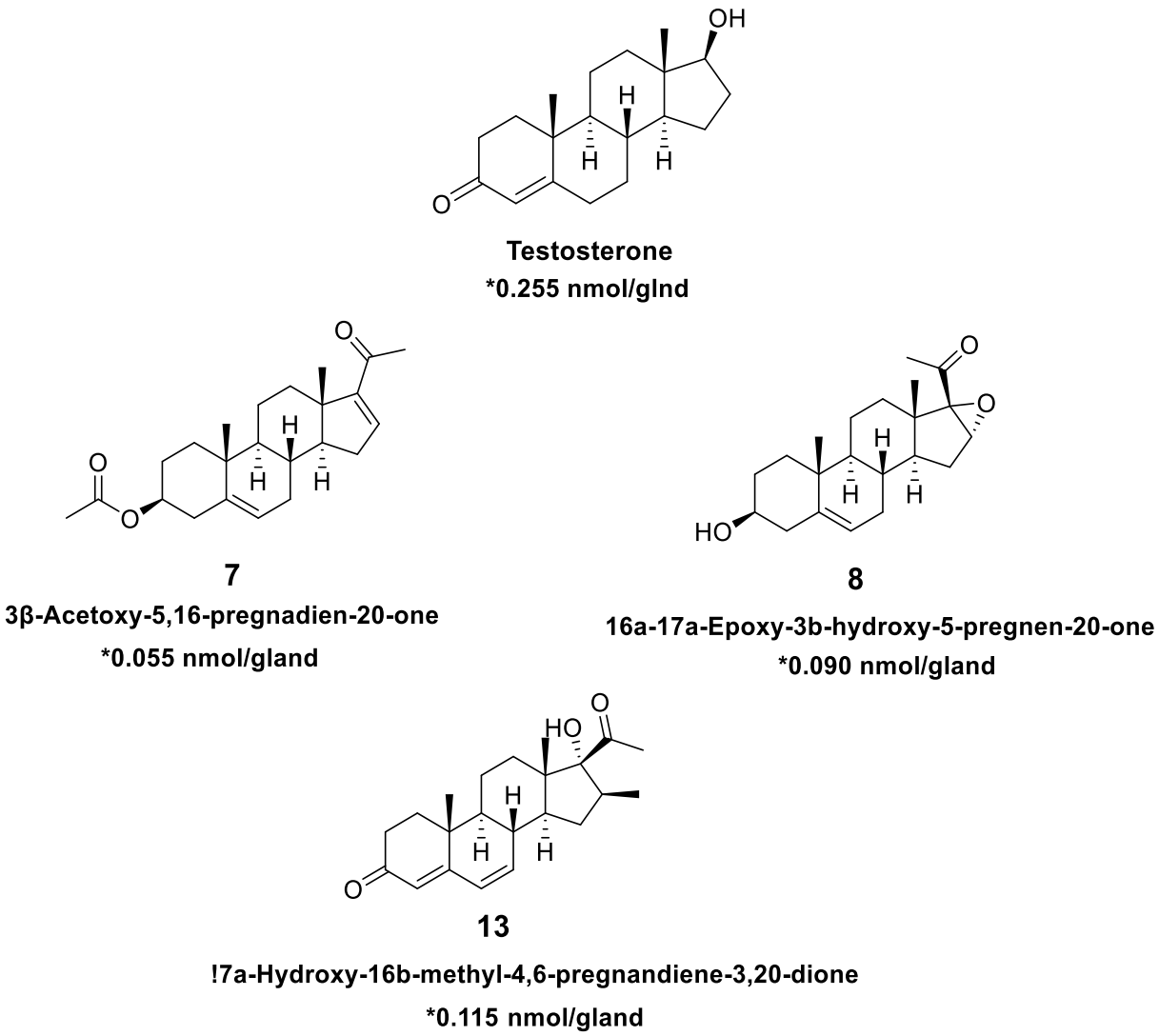


Figure 8. Derivatives of 3β-acetoxi-5,16-pregnandien-20 7, identified as inhibitors of SRD5A activity[73]. *Indicates the concentration of labeled lipids per gland, formed after 24 hours of incubation in the medium.

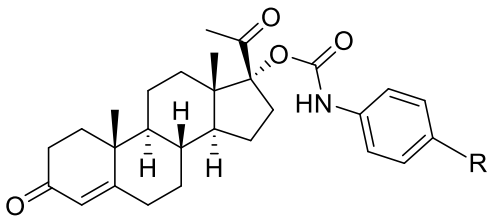
Previously, a novel series of pregnane derivatives with a carbamate moiety at C-17 78 was synthesized. These steroids were identified as inhibitors of SRD5A1 enzyme activity. The amount of the pregnane derivative previously reported to inhibit the activity of this enzyme by 50% (IC_{50}) is listed in Table 1. Steroids **8**, **8a-8b**, and **9,** shown in Table 1, also reduced the size of pigmented spots in female hamsters treated with testosterone (T). Additionally, treatment with T plus **8**, **8a-8b**, and **9** in these glands decreased mRNA expression of glycerol-3-phosphate acyltransferase (GPAT) and β-hydroxy-β-methylglutaryl-CoA reductase (HMG-CoA-R) to levels seen in glands from gonadectomized hamsters. These enzymes are well known for their role in lipid synthesis.

Lopez-Lezama et al. reported the mRNA levels of glycerol-3-phosphate acyltransferase (GPAT), β-hydroxy-β-methylglutaryl-CoA reductase (HMG-CoA-R), and phosphatidylinositol synthase (PI-S) in female hamsters' flank organs after treatment with either topical progesterone (P) combined with derivatives **8, 8a, 8b,** and **9**, using reverse transcription PCR (RT-PCR) [73]. The combination of P with compounds **8, 8a, 8b,** and **9** resulted in a significant decrease in the enzyme's mRNA levels compared to P alone[73].

The overall results highlight the role of sex hormones in lipid synthesis and release in hamster flank organs, as well as their influence on sebum composition. Furthermore, the effects of synthetic

steroid molecules on lipid makeup indicate a potential new therapeutic application for this class of molecules.

Table 1. Structure-Activity Relationships of Steroidal Pregnane Carbamate Derivatives on 5α-Reductase Enzyme Inhibition[73].

Structure	R	5α-reductase IC_{50} [nM]
 **17α-Phenylcarbamoyloxypregn-4-ene-3,20-dione**	H (**8a**)	10±2
	F (**8**)	200±45
	Cl (**9**)	190±39
	Br (**8b**)	50±8

Conclusion

The literature reviewed in this study underscores the importance of sex hormones in maintaining skin health. These hormones influence various aspects of the skin, including its texture, hydration, and overall condition. Current research continues to investigate viable treatment options for skin conditions associated with hormonal changes, underscoring the need for innovative steroid agents that effectively reduce skin lipid production, as indicated by the data analyzed in this article.

Conflict of interest:

We declare there is no financial conflict of interest.

Research funding and acknowledgment:

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Data availability:

The data for this experiment are available in the supplementary material file and the repositories of the Hormone Laboratory of Universidad Autónoma Metropolitana-Xochimilco.

Author's contribution:

All authors contributed equally to the development of this work and consented to

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