

# Androgen action on human skin – from basic research to clinical significance

Zouboulis ChC, Degitz K. Androgen action on human skin – from basic research to clinical significance.  
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**Abstract:** Androgens affect several functions of the human skin, such as sebaceous gland growth and differentiation, hair growth, epidermal barrier homeostasis and wound healing. Their effects are mediated by binding to nuclear androgen receptors. Androgen activation and deactivation are mainly intracellular events. They differ from cell type to cell type and between cells at different locations. The major circulating androgens, dehydroepiandrosterone sulfate and androstenedione, are predominantly produced in the adrenal glands, and testosterone and 5 $\alpha$ -dihydrotestosterone are mainly synthesized in the gonads. Testosterone in women and 5 $\alpha$ -dihydrotestosterone in both genders are also synthesized in the skin. Skin cells express all androgen metabolizing enzymes required for the independent cutaneous synthesis of androgens and the development of hyperandrogenism-associated conditions and diseases, such as seborrhea, acne, hirsutism and androgenetic alopecia. The major thrust of drug design for the treatment of androgen-associated disorders has been directed against several levels of androgen function and metabolism. Partial effectiveness has only been achieved either by androgen depletion, inhibition of androgen metabolism or blockade of the androgen receptor.

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## Introduction

The first recognition of the role of androgens in the pathogenesis of cutaneous disorders probably came from Aristotle as early as the 4th century BC, as he noticed the relation between the occurrence of androgenetic alopecia and the gender or sexual maturity (1). In 1942, Hamilton's pioneering work on castrates subjected to testosterone injections provided the scientific evidence for androgen activity on human skin, and hence provoked further investigation of the cutaneous effects of androgens (2).

Several functions of the human skin, especially of the appendages, appear to be strongly dependent on biologically active androgens. Their effect is mediated by binding to nuclear receptors. Lack of functional androgen receptors (ARs), e.g. in the total androgen insensitivity syndrome, prevents the action of androgens on

skin appendages (3). Androgen activation and deactivation are mainly intracellular events. They can differ from cell type to cell type and between cells in different locations (4).

## Androgens relevant to the skin

The circulating androgens dehydroepiandrosterone sulfate (DHEA-S) and androstenedione are predominantly produced in the adrenal glands, and testosterone and 5 $\alpha$ -dihydrotestosterone (DHT) are mainly synthesized in the gonads. These androgens reach the skin via the bloodstream, whilst testosterone in women and DHT in both genders are also synthesized in peripheral organs, including the skin. Androgens affect several cutaneous structures. DHEA-S is the androgen with by far the highest serum concentration in both sexes and is considered to be the most important regulator of sebum secretion

(5,6) (Table 1). DHEA-S is only a weak androgen but sebocytes, and probably also dermal papilla cells, have the enzymatic capacity to convert DHEA-S, and also androstenedione, into more potent androgens such as testosterone and dihydrotestosterone (7). Androstenedione and testosterone have also been shown to stimulate sebum secretion in humans (8,9). DHT seems to be necessary for male beard growth and scalp hair recession, whereas testosterone alone is sufficient for the stimulation of axillary and pubic hair growth (10). Thus, the skin is regarded as a peripheral organ that locally synthesizes significant amounts of androgens with intracrine or paracrine actions.

### Androgen receptor

Androgens act through a single nuclear receptor, the AR. AR is a ligand-activated, intracellular transcription factor that belongs to the steroid/nuclear receptor superfamily (7,11,12). Like all nuclear receptors, AR is a soluble molecule with a proclivity for employing transcriptional regulation as a means of promoting its biological effects. In common with other steroid receptors, AR is compartmentalized in the cytoplasm, existing in polymeric complexes that include the heat shock proteins hsp 90, hsp 70 and hsp 56. The association of androgens with AR results in dissociation of the heat shock proteins. This in turn exposes a nuclear translocation signal previously buried in the receptor structure and initiates transport of the ligand-receptor complex to the nucleus. There, AR occupies androgen response elements in the promoter regions of androgen-regulated genes to initiate the signaling cascade.

AR is present in epidermal and follicular keratinocytes, sebocytes, sweat gland cells, dermal papilla cells, dermal fibroblasts, endothelial cells and genital melanocytes (4,13–15). It is stabilized by ligand binding and is up-regulated in fibroblasts and sebocytes (16,17).

Table 1. Plasma concentrations (nmol/l) and relative androgenic strength of androgens in adults (38)

	Men	Women	Relative androgenic strength
Dehydroepiandrosterone sulfate	1300–6800	1300–6800	1
Androstenedione	3.0–5.0	3.5–7.0	2
Testosterone	10–35	< 3.5	20
5 $\alpha$ -Dihydrotestosterone	0.87–2.6	0.17–1.0	60

### Androgen metabolism in the skin

Having recognized the key effects of biologically active androgens on the skin, their local synthesis and degradation have received special interest. Five major enzymes are involved in the activation and deactivation of androgens (Fig. 1) (1,4). In a first step, steroid sulfatase metabolizes DHEA-S to dehydroepiandrosterone (DHEA). Subsequently, 3 $\beta$ -hydroxysteroid dehydrogenase/ $\Delta^{5-4}$ -isomerase ( $\Delta^5$ -3 $\beta$ -HSD) converts DHEA to androstenedione. Two isoforms of this enzyme have been described. Human skin seems to express exclusively the type 1 isoform. Several studies have led to the conclusion that cutaneous  $\Delta^5$ -3 $\beta$ -HSD is located in the sebaceous glands (4). Enzyme activity has also been detected in the dermal papillae of human terminal hair follicles (18).

In a further step, androstenedione is activated by conversion to testosterone through 17 $\beta$ -hydroxysteroid dehydrogenase (17 $\beta$ -HSD). The cutaneous expression of 17 $\beta$ -HSD is mainly concentrated in the pilosebaceous unit and epidermal keratinocytes. So far, eight isoforms of this enzyme have been identified (1). 17 $\beta$ -HSD types 1, 3 and 5 support the formation of more active androgens, whereas the oxidative reaction induced by 17 $\beta$ -HSD types 2 and 4 inactivates the potent sex steroids. The human sebaceous gland possesses the cellular machinery needed to transcribe the genes for 17 $\beta$ -HSD types 1–5; of these, strong 17 $\beta$ -HSD type 2 mRNA and protein expression has been detected (4,19). The predominance of the strongly pro-oxidative 17 $\beta$ -HSD type 2 suggests its protective role against the effects of locally excessive amounts of potent androgens (19). A greater reductive activity of 17 $\beta$ -HSD (types 3 and 5) has been noted in sebaceous glands from facial areas compared with acne non-prone areas, suggesting an increased net production of potent androgens in facial areas. In addition, human sebocytes, but not keratinocytes, express 17 $\beta$ -HSD type 3, underlining the major regulatory role of the sebaceous gland in cutaneous androgen activation (4). In hair follicles, 17 $\beta$ -HSD is localized in outer root sheath cells. Anagen hair mainly express high levels of type 2 and moderate levels of type 1 17 $\beta$ -HSD (20). This is compatible with early studies which showed androstenedione to be the major metabolite of cultured human hair follicle keratinocytes incubated with radiolabeled testosterone (1). 17 $\beta$ -HSD enzyme activity has also been shown in cultured epidermal kera-

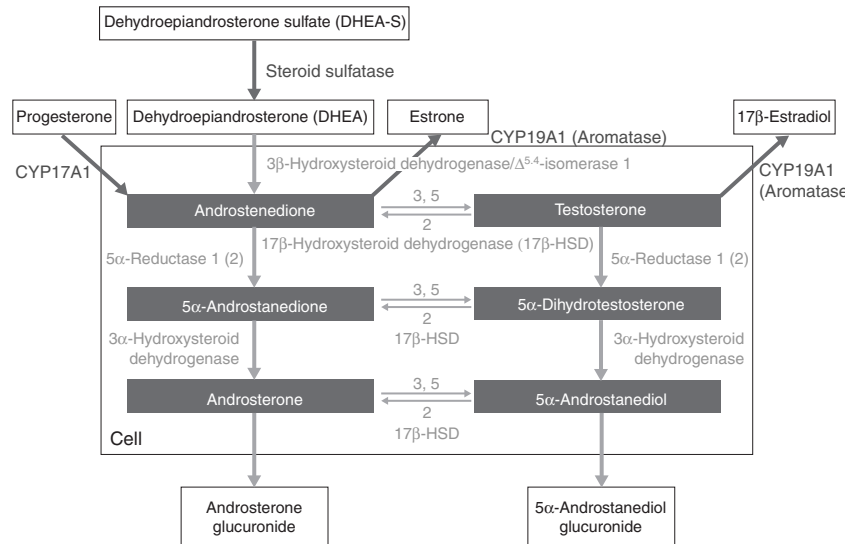


Figure 1. Metabolism of androgens in human skin.

tinocytes and in the microdissected apocrine sweat gland (1).

5 $\alpha$ -Reductase irreversibly converts testosterone to DHT, the most potent naturally occurring androgen in tissue (21). Two isoforms have been described, and type 1 dominates in the skin (22,23). Predominant expression of the enzyme in sebaceous glands, but also in sweat glands, epidermal cells and hair follicles, has been detected. Finally, 3 $\alpha$ -HSD, an enzyme existing in three isoforms, catabolizes active androgens to compounds that do not bind the androgen receptor (4). By glucuronidation, water-soluble compounds are eliminated through the kidney. Alternatively, aromatase can convert testosterone and androstenedione to estrogens in certain cell types (1).

In addition to its capacity to activate and inactivate adrenal and gonadal androgens, the skin, especially the sebaceous gland, is capable of synthesizing cholesterol, which is utilized in cell membranes, in the formation of the epidermal barrier, in sebum and, interestingly, also as a substrate for steroid hormone synthesis (24). The autonomous formation of sex steroids provides human skin with the ability to adjust the levels of sex steroids according to local needs (4,24,25). The local level of each sex steroid thus depends on the expression of each of the androgen- and estrogen-synthesizing enzymes in each cell type, with sebaceous glands and sweat glands being the major contributors (4,26).

### Androgens and the sebaceous gland

Malfunctions of AR, e.g. induced by polymorphisms with a reduced number of CAG

trinucleotide repeats, are associated with androgen-dependent skin diseases or conditions including acne (27). Moreover, the association between cutaneous hyperandrogenism and skin disorders such as acne and androgenetic alopecia in males has been suggested by several studies. Skin in acne patients produces higher rates of testosterone and DHT than in healthy individuals. In addition, elevated plasma levels of DHT and 3 $\alpha$ -androstenediol glucuronide have been found in female patients with acne, whereas DHEA-S, androstenedione and testosterone are normal (28). Androgens stimulate sebocyte proliferation, an effect dependent on the area of skin from which the sebaceous glands are obtained; facial sebocytes are mostly affected (29). In contrast, androgens as single compounds seem to be unable to modify sebocyte differentiation (30), which is stimulated by co-incubation with peroxisome proliferator-activated receptor (PPAR) ligands (31).

### Androgens and the hair follicle

Androgens have strong effects on hair growth and act through AR on dermal papilla cells (26). Malfunctions of AR are associated with hirsutism in women and androgenetic alopecia (27). Dermal papilla cells mediate the growth-stimulating signals of androgens by releasing growth factors that act in a paracrine fashion on the other cells of the follicle (32). Androgens cause enlargement of the hair follicles in androgen-dependent areas (beard in male adolescents, axillary and pubic hair) but, paradoxically, in scalp follicles of susceptible men, androgens foster miniaturization and shortage of hair in the

anagen stage, leading to common baldness. These controversial effects may be explained by genetically determined differences in the response of papilla cells to androgens in different body areas during a lifetime (26). As in acne, higher rates of testosterone and DHT are locally produced in androgenetic alopecia (33). In addition, excessive amounts of tissue active androgens have been shown to induce apoptosis of dermal papilla cells through the bcl-2 pathway (34). The conversion of testosterone to the more potent DHT by the enzyme 5 $\alpha$ -reductase type 2 enhances androgenic effects on hair follicles, as deduced from observations in men with a deficiency of the enzyme. These individuals produce little or no beard growth and do not develop androgenetic alopecia (35). Consistently, the inhibition of type 2 5 $\alpha$ -reductase by finasteride has been proven to slow or even reverse the progression of androgenetic alopecia (36).

#### **Further effects of androgens on human skin**

Testosterone has been shown to perturb the epidermal barrier homeostasis in adult human skin (37,38). In addition, Ashcroft and Mills reported an AR-mediated inhibition of cutaneous wound healing in adult individuals (39). Endogenous testosterone inhibited cutaneous wound healing in males and was associated with an enhanced inflammatory response. Blockade of androgen action via AR antagonism accelerated wound healing significantly.

#### **Androgen excess**

Androgen excess can provoke hirsutism and seborrhea. In addition, androgen excess may trigger or aggravate acne. Important causes are gonadal or adrenal neoplasms, XYY genotype, Cushing's syndrome, polycystic ovary syndrome and congenital adrenal hyperplasia (CAH). Exogenous (iatrogenic) triggers of androgen excess include testosterone, glucocorticoids and oral contraceptives containing progestins with residual androgen activity.

In CAH, defects of enzymes involved in adrenal cortisol synthesis result in subnormal cortisol levels (40). This is compensated by an increased pituitary secretion of adrenocorticotropin (ACTH). Thus, normal cortisol blood levels are achieved at the cost of an excess production of adrenal androgens, which are responsible for clinical signs. The enzyme most

often defective in adrenal hyperplasia (95%) is 21-hydroxylase. In a few instances, other intermediary enzymes are responsible (11 $\beta$ -hydroxylase, 17 $\beta$ -hydroxylase or 3 $\beta$ -HSD) (41). 21-Hydroxylase deficiency represents a heterogeneous group of allelic variants of the 21-hydroxylase gene. One or both alleles may carry various mutations, leading to more or less severe impairment of 21-hydroxylase activity (40). Severe defects produce classic forms, which manifest themselves in infancy (virilization and/or salt wasting, if mineral corticoids are also affected) or in childhood (pseudopubertas praecox, growth disturbances). In non-classic forms, less severe signs occur before or after puberty (late-onset forms), including acne, hirsutism or irregular menses. CAH may even remain asymptomatic (cryptic form). Whereas in women or prepubertal children suffering from acne, disorders of androgen metabolism are frequently suspected (42), there may be a tendency to underestimate the role of androgen excess in men with acne. Indeed, a few published studies have indicated the relevance of this phenomenon. Men with persistent acne have significantly higher serum levels of androgens than do aged-matched controls (43), and excess androgens of adrenal origin are frequently detected in men with severe (cystic) acne (44).

#### **Treatment**

The major thrust of drug design for the treatment of androgen-associated disorders has so far been directed against several levels of androgen function and metabolism (1). However, only partial effectiveness has been achieved by androgen depletion, inhibition of androgen metabolism or blockade of the AR. In addition, major adverse events can occur, as effectiveness is only associated with the systemic application of such compounds.

Acne and androgenetic alopecia of female pattern as manifestations of systemic or local androgen excess are best treated by eliminating the cause (tumors, drugs) or by antagonizing androgen action. Oral contraceptives are used in women with polycystic ovary syndrome, CAH or hyperandrogenism. Both estrogens and anti-androgenic progestins contribute to the anti-androgenic effect (45,46). Cyproterone acetate exhibits the strongest anti-androgenic activity of the progestins due to a dual activity: AR blocking and  $\Delta$ 5-3 $\beta$ -HSD inhibition (4,46). In male acne patients with CAH, low-dose gluco-

corticoids (e.g. methyl prednisolone 4 mg every other day) are administered to suppress ACTH-mediated adrenal androgen production (47). These hormonal treatments are best combined with other anti-acne regimens for quicker relief (48). Finasteride is the first selective androgen metabolizing enzyme inhibitor to be introduced, targeting androgenetic alopecia (1). In addition to the anti-androgenic therapeutic regimens, hirsutism is treated by various epilation techniques, including laser and flash light devices.

### Conclusion and outlook

Similar to the classical steroidogenic organs, such as the gonads and adrenal glands, the skin and its appendages, hair follicles, sebaceous glands and eccrine/apocrine glands are armed with all the necessary enzymes and receptors required for independent androgen synthesis, metabolism and function. Steroid sulfatase, type 1  $3\beta$ -HSD, type 3 and 5  $17\beta$ -HSD and type 1  $5\alpha$ -reductase are the major steroidogenic enzymes responsible for the formation of potent androgens, whilst type 2  $17\beta$ -HSD,  $3\alpha$ -HSD and aromatase inactivate excess androgens in order to achieve androgen homeostasis (1,4). Changes in isoenzyme and/or AR levels may have important implications in the development of hyperandrogenism and the associated skin diseases. Rapid pharmacological advancement in this field and the design of other specific potent antagonists may provide better control or even prevention of acne, hirsutism and androgenetic alopecia in the near future (1,17,45,48). Moreover, PPAR ligands and inhibitors could potentiate, in combination with anti-androgens, their effect in acne (49). Skin aging and wound healing may represent additional interesting therapeutic targets of anti-androgenic therapy.

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