CONTINUING MEDICAL EDUCATION

PHYSIOLOGICAL ANDROGENETIC CHANGES IN THE SKIN

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Androgens are substances which possess the ability to induce and maintain the secondary sexual characters of the male. Androgens induce in the skin and appendages a number of changes which are of the highest emotional significance to each one of us. Any deviation from the normal, causes great psychological distress. This deviation can be either a quantitative change in the amount of androgens produced or a qualitative variation in the cutaneous response to the sex hormones. This abnormal peripheral response is probably a genetically determined trait.

This review is written primarily for the clinical dermatologists. A brief and a rather simplified review of the complex biochemistry of the androgens is followed by the physiological actions of the androgens on the skin.

BASIC CHEMISTRY OF ANDROGENS[1]

All the steroid hormones contain a cyclopentanoperhydrophenanthrene nucleus as their basic structure. This cyclopentanoperhydrophenanthrene nucleus consists of 3 hexane rings (A-C rings) and a single pentane ring (D ring). The carbon atoms in the nucleus are numbered in a predetermined sequence beginning with ring A (Fig. 1). Androgens are C-19 steroids. They have substituent methyl group at C-18 and C-19 positions. It is this substitution which gives this group of steroids their predominantly androgenic potential.

Depending on the substitution at the 17 position, the androgenic steroids can be either (a) 17 beta- hydroxysteroids (17 HS), or (b) 17 beta ketosteroids (17 KS). The 17 HS are the more potent androgens and are formed by enzymatic conversion of 17 KS. Though there are more than 50 androgenic steroids, some are clinically more important, either because of their biopotency or because of the concentrations in which these are present. The 3 important naturally occurring 17 HS are, (a) testosterone and 5 alpha dihydrotestosterone (DHT), (b) androstenediol, and (c) androstanediol. Although all these contribute to the plasma androgenicity, testosterone is quantitatively the most important of the circulating androgens because of its biopotency and concentration. DHT is 150 times more potent than testosterone and is very important as the tissue active androgen. The 17 HS are abundantly present in the males. The 2 important 17 KS are, (a) dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) and, (b) androstenedione. The 17 KS are weaker androgens in the bioassay systems and are probably androgenic mainly by virtue of the extent to which these are converted into 17 HS.

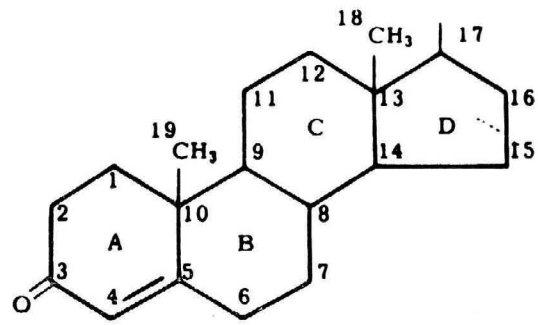

Fig. 1. Structure of androgens.

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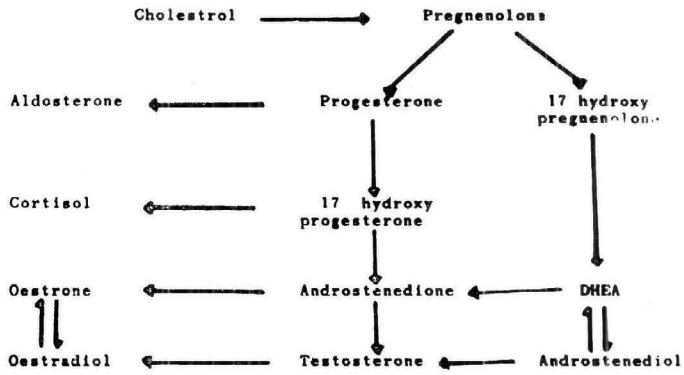

Fig. 2. Synthesis of androgens.

However, recent studies have shown that these are capable of exerting direct actions on cellular metabolism. 17 KS are the most abundant androgenic steroids secreted in the females.

SYNTHESIS OF ANDROGENS[2]

The starting point for the synthesis of hormonal steroids is cholesterol (Fig. 2). Cholesterol is converted to pregnenolone by way of dihydroxycholesterol. Pregnenolone is further converted to progesterone. In the adrenal cortex, progesterone can be converted to aldosterone, or by way of 17 alpha hydroxyprogesterone to cortisol; neither of these conversions occurs in the gonads.

Testosterone, the principle androgen is formed from one of the two precursors, androstenedione or DHEA. Both of these are formed from pregnenolone—the first via progesterone and 17 alpha hydroxyprogesterone and the second via 17 alpha hydroxypregnenolone. Oestradiol is derived from testosterone and oestrone from androstenedione.

SOURCES OF ANDROGENS

The testes, ovaries, adrenals and certain other tissues like the skin, subcutaneous tissue, liver, prostate and placenta can all synthesize androgens, either from cholesterol or other intermediary steroids.

The testes are the main source of androgens in the males. In the normal young male, the testes secrete 4-10 mg of testosterone daily (Table I). There is a significant decrease both in the total and the free plasma testosterone with advancing age. Almost half of the testosterone is excreted in the urine as 17 KS, while the other half is excreted as testosterone glucuronide.

Table I. Normal figures for androgens for women and men.

	Women	Men
Plasma testosterone (mg/10 ml)	0.02-0.2	0.4-1.0
Urinary excretion of testosterone glucuronide (mg/24 hour)	4-10	40-200
Testosterone production rate (mg/24 hour)	1-3	4-10

That the ovaries possess the potential to produce androgens has long been evident.[3] The ovaries secrete mainly 17 KS like DHEA, DHEAS and androstenedione. Twenty five percent of the daily testosterone production in female subjects is contributed by the ovaries.[4]

The adrenals are the main source of the 17 KS, mainly DHEA and DHEAS.[5] Small amounts of testosterone also are synthesized in the adrenals. In the males the relative contribution of testosterone by the adrenals is insignificant, but in females, even this small amount

forms 25% of the total daily production of testosterone.[4]

Certain tissues like skin, prostate, subcutaneous tissues and liver contain enzymes which can convert pre-hormones and 17 KS to testosterone and it is this conversion which accounts for 50% of the testosterone production in the females. The principle 17 KS converted to testosterone in the periphery, are androstenedione (40-60%)[6] and DHEA (15%).[7]

The testosterone present in the blood of adult females originates from the ovaries (25%),[4] adrenals (25%)[4] and peripheral tissues (25%).[6,7] The level of plasma testosterone fluctuates during the menstrual cycle.[8] Other androgens like DHEAS and DHEA, androstenedione are also present in the blood of adult females. In the adult males almost all the circulating testosterone is contributed by the testes. The contribution of adrenals and the peripheral tissues is relatively small.

METABOLISM OF ANDROGENS.[9]

Androgens are degraded in the liver to 17 KS like androsterone, epiandrosterone and etiocholanolone. Testosterone is, in addition, converted to testosterone glucuronide. Excretion of 17 KS as their sulphates and glucuronides is a reflection of the production of the hormones by the testes and adrenals. In the males, the testes contribute one-third of the urinary KS and the adrenals about two-thirds, while in the females almost all of the urinary KS is derived from the adrenals.

CONTROL OF ANDROGEN PRODUCTION

Plasma androgen levels are not regulated finely because the various tropic hormones (ACTH, LH and FSH) which control androgen secretion are themselves directly controlled by hormones other than androgens.[10] It has been postulated that some other hormonal factors, also alter androgen production and metabolism. Several candidates have been proposed and prolactin has attracted a lot of attention in this regard. Prolactin has effects on the adrenal and gonadal production of androgens probably via prolactin receptors.[11] It is also known to have an effect on the tissue metabolism of androgens but its exact role remains obscure. In rodents, it augments the action of LH on the Leydig cells of testes.[12] The secretion of prolactin in mammals is controlled by a tonic inhibitory influence of the hypothalamus, probably, by a prolactin inhibiting factor.[13] In addition, androgens may be playing a modifying feed-back role in prolactin secretion.[14] Prolactin is a stress hormone and its secretion is increased in various depressive and emotional disorders.[14]

Further, the peripheral androgen metabolism is not under negative feed-back control.[10] The peripheral androgen metabolism is determined to some extent by the perinatal and adult androgenic milieu which is thought to control the levels of sex hormone binding globulin (SHBG).[15]

TRANSPORT OF ANDROGENS[16]

The androgenic steroids are bound mainly to a globulin—SHBG and minimally to albumin. Changes in the A and D rings of the steroid nucleus alter the affinity of the androgens to the globulin. Generally, the 17 HS (testosterone, dihydrotestosterone and androstenediol) bind well, while the 17 KS (androstenedione, DHEA and DHEAS) bind poorly. It is generally accepted that the free hormone enters the cells and exerts its action. Protein binding of a hormone is thought to iron out acute fluctuations of steroid production and it also reduces the renal loss. the degree of plasma protein binding also affects the metabolic clearance of hormones.

The thyroid hormones and estrogens increase the SHBG levels while androgens decrease them. It is an interesting and intriguing possibility that the adult SHBG levels are programmed by subtle differences in the androgen levels during the fetal life with subsequent modulation by the

estrogen-androgen balance which develops after puberty. The androgens depress while the estrogens elevate SHBG levels.[15]

ACTION OF ANDROGENS ON THE SKIN

Of the structural and functional changes in the skin induced by androgens, those of greatest clinical significance concern the activity of sebaceous glands, the pattern of hair growth and the activity of the apocrine sweat glands. Androgens also have action on the collagen, skin pigmentation as well as on the eccrine glands.

CELLULAR METABOLISM OF ANDROGENS IN THE SKIN

The sebaceous glands and some hair follicles are unquestionably specificand rogen targets. The cellular events concerned with the response of target tissues to androgens can now be summarised (Fig. 3). The steroid hormones are transported in the plasma complexed with SHBG. About 1% of the testosterone is not complexed and it is this free androgen which enters the cells.[15]

After entry into the cell, the testosterone is extensively metabolised.[17] When human skin is incubated with labelled 14C-testosterone, 5 alpha DHT is the major metabolite.[18,19] The enzyme required for this conversion is 5 alpha reductase. Though the maximum activity of 5 alpha reductase is present in the perineal tissue (prepuce, scrotum, labia majora and clitoris), skin from other sites like face, abdomen, breast, back and limbs also shows the presence of this enzyme.[20] In adults, the 5 alpha reductase activity is higher in areas sensitive to testosterone like acne bearing skin[21] and hairy regions of women with idiopathic hirsutism;[22] it is also concentrated in the sebaceous glands and also in the apocrine glands.[19] Subjects with 5 alpha reductase deficiency do not suffer from seborrhoea or acne.[23]

The 5 alpha DHT so formed, is specifically bound, with a high affinity, to a cytoplasmic receptor protein. The presence of this receptor protein was first demonstrated by Bruchovsky and Wilson[24] in the ventral prostate of rat. Similar receptors have since been demonstrated in the hamster costo-vertebral gland, a sebaceous gland homologue.[25] The receptor has been detected in the sebaceous glands of patients with seborrhoea, though not in normal subjects.[26] Keenan et al[27] have also demonstrated a cytoplasmic receptor protein in the human skin. Adults with absence of the intracellular androgen

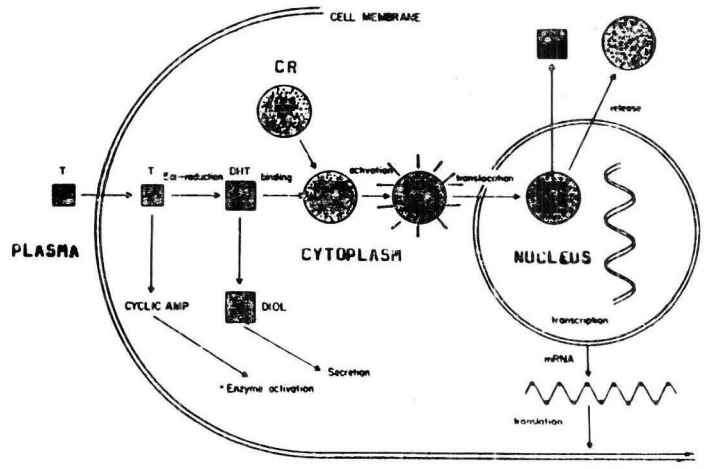

Fig. 3. Cellular metabolism of androgens in the skin.
T : testosterone; DHT : 5 alpha dihydrotestosterone; DIOL : androstanediols; CR : cytoplasmic receptors.

receptors are deficient in pubic and axillary hairs.[28] The 5 alpha DHT receptor complex is converted to an activated form, which is translocated into the nuclear chromatin and is retained for a finite period of time at precisely defined nuclear acceptor sites. The receptor-steroid complex initiates the events of androgen response, which involve transcription of messenger RNA, its passage to ribosomes and protein synthesis. The receptor-steroid complex is finally degraded.[29]

To this classical model of androgenic action must be added several other possibilities. Testosterone itself, may directly stimulate the sebaceous glands, probably through the cAMP system.[30] Testosterone may be reduced to androstanediols which stimulate sebaceous gland secretion.[31,32] Androstanediols have been found to be selectively retained in the microsomes and may affect secretory activity at the translational (cytoplasmic) level as distinct from the transcriptional (nuclear) level.[33] Conversion of 17 HS to 17 KS has also been demonstrated in the hair follicles.[34] These 17 KS, especially androstenedione can directly stimulate human sebaceous secretion[35] and hair follicles.[36] In addition, skin can convert DHEAS and DHEA, produced by the human adrenal cortex, to more potent androgens.[37-39] This conversion requires the presence in the skin of an enzyme 17 beta hydroxysteroid dehydrogenase (17 beta HSD).[40] DHEA has, by itself, been shown to stimulate sebum production both in the castrated males[41] and in intact males treated with ethinyl estradiol.[35] Finally, even all these additions do not encompass all the cellular actions of androgens and it must again be emphasized that not all functions of androgens in the skin are mediated by 5 DHT.

SEBACEOUS GLAND : Many studies in animals and human beings have established that the sebaceous gland activity is stimulated by androgens. Testosterone increases the division of sebocytes, the sebocyte size and the production of sebum.[42,43] The sebaceous glands are minute in the prepubertal period, but undergo a vast enlargement at puberty when the sebum output increases by more than five fold.[44] Administration of testosterone in prepubertal boys increases the size of the sebaceous glands and also the sebum excretion. However, in adult males, administration of testosterone has no effect because the glands are probably under maximal stimulation by the endogenous androgens.[45] Castrated adult males secrete half as much sebum as normal males but substantially more than prepubertal boys. In the castrated adult male, the sebaceous gland activity is dependent on the adrenal androgens.[46] The secretion of sebum in adult females is a little less than that in normal males and is more than that of the castrated males. Androgens other than testosterone also definitely stimulate sebaceous gland activity.[32,47,48]

The androgenic influences on the sebaceous gland are modulated quite significantly by other endocrine substances, namely the pituitary melanocyte stimulating hormone peptides[49] (particularly the beta-lipotropin moiety), thyroid hormone[50] and cortisol.[51] These hormones appear to act synergistically with androgens to permit the sebaceous gland to respond to androgenic stimulation optimally. Also significant in this regard are substances, such as prolactin, growth hormone and insulin.

The most frequent disorder of sebaceous glands is acne vulgaris. The natural evolution of acne seems to be linked to the rising levels of androgens occurring at puberty. In the relationship between androgens and the development of acne, two factors need to be considered, namely, the possible over-production of the androgens centrally and/or an enhanced metabolic conversion to potent androgens peripherally in the pilosebaceous unit, and these factors will be considered in detail in a forthcoming article.

HAIR : The first conspicuous androgen-dependent change in the hair pattern occurs in both the sexes at puberty. Coarser, longer and darker hairs progressively replace fine vellus hairs. The extent of replacement depends on the age, sex, race and genetic predisposition of the individual and on the presence or absence of deviation from the state of normal androgen metabolism. The transition from vellus to terminal hairs occurs in an orderly sequence, on the pubic hair, followed by axillary hair, and then over a period of years on the legs, thighs, forearms, buttocks, chest, back, arms and shoulders. On the face, terminal hair first appear at the sides of the upper lip, then on the chin, sides of the cheeks and the rest of the beard area.[52]

Androgens are responsible for this change. Conversion of the facial vellus hair to terminal hair is parallel with the rise in the level of androgens which occurs at puberty.[53] Prepubertal castration reduces the growth of beard, further indicating that androgens are essential for the growth of beard.[54] Testosterone administration stimulates the growth of beard in eunuchs and old men.[55] The role of androgens is further demonstrated by the response of hirsute women to antiandrogen agents like cyproterone acetate.[56] Pubic and axillary hair growth is also androgen dependent. It is deficient in testicular feminisation, a condition in which there is a lack of intracellular androgen receptors, and also in women suffering from adrenal insufficiency.[57] There is circumstantial evidence that hypophysial hormones play a permissive role for the action of androgen on sexual pattern of hair growth. Growth hormone deficient subjects show a less than normal responsiveness to androgens.[58]

The view that testosterone needs to be reduced to 5 alpha DHT by the enzyme 5 alpha reductase is supported by the absence of the normal sexual pattern of hair development in cases of 5 alpha reductase deficiency.[59] The different distribution of sexual hair in both the sexes and its gradual development in a standard pattern at puberty is probably due to the presence of varying activity of 5 alpha reductase and other enzymes at these sites as well as due to the presence of receptors with differential affinity for androgens at these sites. Less of 5 alpha DHT is formed along with other weaker androgens in the facial skin of women as compared to the axillary and the pubic skin. So the lower circulating androgens in females stimulate the growth of axillary and pubic hair but not the facial hair.[60]

The second change induced by androgens is the progressive replacement of terminal hairs in the scalp by vellus hair. This replacement is subject to a variety of variables like the sex of the individual, his age as well as the genetic predisposition. There is a shortening of the anagen phase of the follicular cycle as well as a decrease in the size of the follicle. This is followed by an increased shedding of the hair. A bitemporal recession of the frontal hair and sparsity of hair on the vertex becomes visible.[61] This change may begin even as early as the second decade. By the age of 50 years, about 60 percent of the Caucasoid men show at least some degree of vertical alopecia and bitemporal recession.[62]

If the growth of hair on the face and body and the deficiency of hair on the scalp are androgen mediated, the question arises whether hirsutism and androgenic baldness are provoked by excess androgen production or because of an increased peripheral response. This controversy will be discussed in a subsequent article.

SWEAT GLANDS : Apocrine glands are poorly developed in childhood and begin to enlarge with the approach of puberty. The activity of the glands is androgen dependent and the glands show marked 5 alpha reductase activity.[63]

The response of the eccrine sweat glands to cholinergic stimulation is greater after puberty and is greater in males than in females. The concentration of potassium in the sweat of males is lower than in that of females. Burton et al[64] found that the eccrine sweat gland response to cholinergic stimulation is increased, towards male levels, in females with idiopathic hirsutism.

OTHER ACTIONS : Androgens are responsible for an increase in the total collagen in the skin and probably in other tissues.[65] In both man and rat, testosterone stimulates the dermal fibroblasts.[66]

Testosterone also stimulates epidermal mitosis in experimental animals.[67] The effect of androgens on melanogenesis is less elucidated. The skin of face, chest and the areola of the nipple darken more in boys than in girls.[68] Tanning is potentiated by the administration of androgens to castrates.[69] The mode of action on the epidermal cell melanocyte unit is not clear.

In addition to the skin, androgens have many other physiological functions especially at puberty. These include development of the external genitalis, the adolescent growth spurt, hypertrophy of the larynx with the change of voice and the increased muscular development.

The pathological aspects of androgen metabolism and the use of antiandrogens in dermatology will be discussed in a separate article in a forthcoming issue of the journal.

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