THE INFLUENCE OF SEX HORMONES ON ACNE

Lars Förström

Department of Dermatology, University Central Hospital, Helsinki

Abstract. The sebaceous glands are stimulated by androgens produced in the skin itself. This explains why elevated androgen levels are seldom found in blood and urine from patients with acne. The most potent androgen is dihydrotestosterone (DHT), which is formed in the target cells, i.e. in the sebaceous glands, by a 5α-reduction of testosterone. DHT is then bound to a specific receptor protein and translocated into the cell nucleus. In young persons genetically predisposed to acne a temporarily increased local DHT-formation has been postulated. In women androstenedione appears to be the major pre-hormone for DHT-formation. Adrenal androgens may account for prepubertal acne. Estrogens and progesterone influence acne only in high, unphysiological doses. Therapeutically we are waiting for a safe, effective anti-androgen for topical use.

It has been known for many years that sebaceous gland activity is regulated by hormones, and thereby these hormones may have an influence on acne. Although sex steroid metabolism is very complex, the simple facts are that androgens stimulate and estrogens suppress sebaceous activity. The determination of urinary total 17-ketosteroids has not turned out to be a useful measurement technique in patients with acne. Recently elevated urinary excretion of specific androgens has been reported in acne (1), but studies of urinary steroids have in general provided little if any evicence of a hormonal disturbance in acne. The same statement can be applied to determinations of the plasma testosterone levels, at least in males. Since the sebaceous glands normally are fully stimulated in adult men, a further increase in androgen concentrations could not in any case affect them. In women the situation may be somewhat different, since sebaceous secretion is usually lower than that of males and the glands may be responsive to androgen stimulation. Elevated plasma testosterone levels have been reported in some women with acne (2).

In general then, there is scanty correlation between plasma and urinary concentrations of androgens and the presence of acne. This is not surprising, since although acne sometimes occurs in disorders due to hormonal abberrations, most cases of acne are unaccompanied by other signs of hormonal malfunction. Neither is there any correlation between plasma level and the quantitative function of other androgen-sensitive target organs, i.e. spermatogenesis (3). Therefore it represented a remarkable step forward, when it was recognized that the skin itself is a major site for androgen conversion, similar to the prostate gland and the male genitalia. Under certain conditions the androgen effect can be influenced by estrogens and progesterone.

MECHANISM OF ACTION OF THE SEX STEROID HORMONES

The mechanism of action is principally the same for all sex steroid hormones (Fig. 1). On entry of the hormone into the target cell, it is bound to a hormone receptor protein. All sex steroid hormones have their own highly specific receptors. This cytoplasmic hormone-receptor complex is then transferred to the nucleus in an "activated" form. Within the nucleus the hormone is bound to the chromatin and initiates transcription and translation of the stored genetic information (4). The intracellular concentration of receptors, the stability of the hormone-receptor complex and the half-life of the chromatinbound complex appear to be important factors determining tissue responsiveness to the hormone. However, there is the possibility that sex steroid hormones may also work through mechanisms not involving receptor molecules.

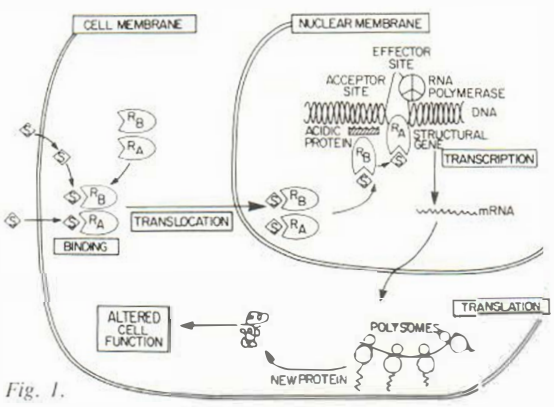

Fig. 1.

The effect of androgens

Various elegant studies have been performed on experimental animals to obtain a clearer understanding of the target tissue response to androgens. Animal models are not ideal for this work, but unfortunately studies with human target organs are complicated by the invariable contamination of cytosols by extracellular fluids containing serum sex hormone-binding globulin, itself a protein with high binding affinity for androgens. Furthermore, absence of detectable androgen receptors in *in vivo* studies may only reflect saturation of receptor binding sites by endogenous androgens. However, recent studies have provided evidence that human skin also contains specific androgen receptors, and there is reason to believe that part of them are located in the sebaceous glands (5). These findings were preceded by two further discoveries in testosterone metabolism (6). First, dihydrotestosterone (DHT) rather than testosterone was found to be the most potent androgen end-organ effector. Second (Fig. 2), DHT is formed mostly in the target cells themselves by the 5α-reduction of testosterone (7). After conversion the DHT-receptor protein complex translocates into the cell nucleus. In predisposed young persons a temporarily increased local DHT formation, due to increased 5α-reductase activity and resulting in acne has been postulated. The pattern and duration of this sebaceous hyperactivity might be determined by genetic factors. In fact, it has been shown that acne-bearing skin produces 2 to 20 times more DHT than normal skin from corresponding areas (8). If this finding does not merely reflect greater sebaceous gland size in acne, it must be due to increased enzymatic activity in the skin, as previously postulated. In women, androstenedione appears to be the major pre-hormone for DHT formation (9). Sebaceous gland activity does not depend entirely upon gonadal androgens; adrenal androgens may contribute significantly in this regard. Urinary excretion of weak androgens, presumably of adrenocortical origin, has been demonstrated in prepubertal children with increased sebum secretion and acne (10). Such weak androgens can easily be converted into more potent ones. Finally, hydroxysteroid dehydrogenase, found in rich amounts in skin regions prone to acne, can influence the action of several sex steroids.

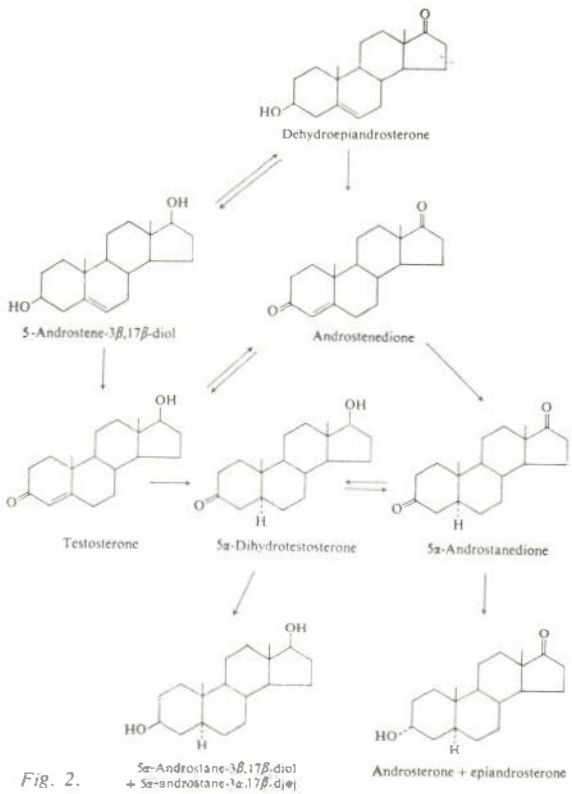

Fig. 2.

It has to be emphasized, that although the severity of acne is related to the sebum excretion rate, seborrhoea cannot be the only causative factor, since it persists long after the acne lesions have cleared. It is possible, as Prince (11) has pointed out, that DHT can mediate changes in the thickness and quality of the keratin, in the permeability of the pilosebaceous duct epithelium and in sebum composition quite as well as in sebum production.

The effect of estrogens

Inhibition of sebaceous gland activity can problably be achieved only with dosages of estrogens that exceed the physiological requirement of women. Estrogens do not seem to act by antagonizing the effect of androgens on cell division, but large pharmacological doses inhibit lipid synthesis within the sebaceous cells. In men, some testosterone is converted to estrogens by peripheral tissues. DHT, on the other hand, can never serve as an estrogen precursor.

The effect of progesterone

Studies concerning the cutaneous effects of progesterone have given conflicting results. This is not surprising, since progesterone is not only an active hormone but also a precursor for several other sex steroid hormones, i.e. for testosterone (12). Progesterone has long been considered an estrogen antagonist, and high doses seem to stimulate sebum secretion in rats.

On the other hand, progesterone also has anti-androgenic activity (13). Progesterone in physiological amounts hardly has any effect on the activity of she sebaceous glands. However, several synthetically produced progestins derived from testosterone and used as components of oral contraceptives, retain considerable androgenicity in appropriate dosages.

PITUITARY HORMONES

Gonadotropins stimulate testicular and ovarian tissues to synthesize and release sex hormones, and in this way influence the activity of the sebaceous glands. On the basis of animal experiments it has also been postulated that the conversion of testosterone to DHT and other 5α-reduced metabolites in sebaceous glands is pituitary-dependent (6). Accordingly, the response of the rat sebaceous glands to testosterone is markedly diminished after hypophysectomy. Administration of certain pituitary hormone fractions can restore this response (14). Some of the synthetical progestins also may cause marked gonadotropin inhibition.

THERAPEUTICAL CONSEQUENSES

Estrogens are useful for treatment of acne in females, particularly in cases with premenstrual exacerbations. The most physiological form of estrogen therapy available involves the use of contraceptive pills. Tablets containing derivates of 17-hydroxy-progesterone can be used either sequentially or in combined form. Because of their androgenicity the 19-nor-testosterone derivates are unsuitable for patients with acne. In the newer oral contraceptives the estrogen content has been greatly reduced, and the effect on acne is not as clear cut. Therefore this form of therapy is nowadays used less frequently. Unfortunately, topically applied estrogens will work only in concentrations which give systemic effects. Testosterone has certain essential functions and is not solely a prehormone for DHT. Many pubertal events are mediated by testosterone. Moreover, testosterone, and not DHT, appears to be the important behavioral regulator. This gives us — at least theoretically — an opportunity to block DHT at a given target site without interfering with the psychologic and other important effects of testosterone. The action of DHT can be blocked by competitive inhibition with steroids with close structural resemblance to testosterone. Another way of blocking DHT is through a decrease in the androgen-receptor protein. Of the anti-androgens available cyproterone and its 17α-acetate are considered the most potent ones. These substances have been used in combination with ethinyl estradiol in small series of women with acne. Such a treatment regimen is principally a form of contraception and the results and side-effects mimic those seen with oral contraceptives. It is hardly likely that systemic antiandrogens will be used in general for the treatment of acne. What we are all waiting for is a safe and effective anti-androgen for topical use. This local approach should be free of systemic effects and the important roles of testosterone in the body itself should not be affected. Several anti-androgens have been tried clinically. Some of the failures encountered (15) may be due to inadequate absorption. Some probably are not. Laboratories throughout the world are still working on the development of new anti-androgens. If our theories are valid the next really remarkable therapeutical approach in acne may take place within this field.

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DISCUSSION

Kentsch, Berlin: I have been asked to summarize our data on the topical application of cyproterone and cyproterone acetate.

For the treatment of acne, the availability of an anti-androgen which is not only effective by oral administration but also by topical application without any effect on feedback mechanisms would be very helpful. Cyproterone and its acetate are potent anti-androgens, but topical application of cyproterone acetate has not led to the desired effect, i.e. reduction of sebum levels. One of the reasons for the lack of any effect might have been the use of an ointment base that was not optimal. Therefore we have investigated the penetration rates of cyproterone and cyproterone acetate from different ointment bases. The anti-androgens, which were applied in a 0.1% concentration were tritium-labelled. The penetration rates of cyproterone were the highest from lipophilic ointment (Vaseline) while the penetration rate of cyproterone acetate was highest from a hydrophilic ointment (Polyethyleneglycol DAB 7).

A clinical trial has now been conducted using cyproterone and cyproterone acetate in a Polyethyleneglycol DAB 7 ointment base, for cyproterone too because of clinical considerations. The concentration of 0.1% cyproterone should have been great enough to expect an effect on the sebaceous glands.

The 0.1% ointment was rubbed onto the forehead twice daily for a four week period. Measurements of refatting two hours after defatting have been carried out by the rough glass platelets method at weekly intervals. Neither cyproterone, nor cyproterone acetate, nor Polyethyleneglycol DAB 7 had any influence on the skin surface lipids. When the concentration of cyproterone acetate was raised to 1% sebum production remained unchanged.

Based on these results our conclusion is that competition between androgen and anti-androgen at the target organ, sebaceous gland, is not very probable.

Shuster, Newcastle-upon-Tyne: Could I just make a brief comment about the cyproterone? We have also looked at cyproterone acetate, topically as well as systemically. The topical material gets through adequately, but it does not work. We also have some evidence, which I did not show, which casts a doubt on the idea that 5α-reductase activity is necessary to androgen action on the sebaceous glands and I do not believe that dihydrotestosterone is the active androgen at the sebaceous target organ.

Furthermore, it works well when it is given systemically. When it is administered to ordinary acne patients for a period of two months without any antibiotic therapy you get a reduction in sebum excretion and about 50 per cent get moderate or considerable clinical improvement. If you give it topically, you do not get a reduction in sebum production although the material appears to go through the skin.

Plewig, Munich: Then you feel that this is not the active drug to block the site locally?

Shuster, Newcastle: Since it works systemically but not locally this raises very interesting theoretical problems. One suggestion is that the active agent is not cyproterone acetate but a metabolite. Another is that cyproterone acetate or its metabolite blocks androgens other than dihydrotestosterone, since we have evidence that 5α-reductase is not the determining factor in androgen response in the human sebaceous gland.

Schaefer, Berlin: I would like to further clarify the status of cyproterone acetate. Years ago we measured the effect of cyproterone acetate on sebaceous gland activity. In female patients who improved with this treatment, sebum secretion went down. However, after topical treatment we saw no effect either on sebum excretion or on the clinical status of the patients.

Then we changed the application so as to push more material into the skin and again we did not observe any improvement in acne and there was no effect on sebaceous gland activity. The point is that the theory that there is local antagonism of androgens and this anti-androgen obviously is not true.

Strauss, Iowa: Dr. Förström, I think you mentioned that there was some evidence that the 5α-reductase activity in the skin might be elevated in patients with acne. Is this based on the studies conducted in Reisner's laboratories or do you have direct evidence for this?

Förström, Helsinki: I think that there is no direct evidence; it is just a theory.

Strauss, Iowa: To expand on the question of anti-androgens, I am not convinced that any of the experimentally used anti-androgens, including A-norprogesterone that we used extensively several years ago, have been demonstrated to have a local effect. I think that all of them are acting through a systemic mechanism.

Shuster, Newcastle: Can I just add that I agree with you in man, but not in the experimental animal where you can apply the anti-androgen topically and block an androgen effect on one side of the animal.

Plewig, Munich: We have used sebaceous glands of the ventral side of ear lobes on the Syrian hamster as an experimental model using radioautography and planimetry after application of cyproterone acetate. There is a clear topical effect on one side and no effect on the contralateral side. However, when we applied the same drug in a 1% concentration in humans we did not observe any effect. So there probably are differences between animals and humans.

Cunliffe, Leeds: I wondered if Dr. Strauss will comment on possible local effect of estrogens? As I remember, I think you have shown that estrogens might have some local effect as well as obviously systemic effects.

Strauss, Iowa: We have not shown any local effect of estrogen that can be separated from a systemic effect in man. However, it is quite clear that in the rat, local effects have been demonstrated. In man we have applied estrogens in concentrations that still show evidence of systemic absorption as manifested by gynecomastia or loss of libido in a male, yet there is no separate local effect.

Schaefer, Berlin: May I just reinforce this. We have measured percutaneous absorption of estrogens. The absorption is so great that you never will succeed in having only a local effect. The penetration rate is sufficiently high that you get a systemic effect in the same range as with estrogen-containing oral contraceptives.