Steroids and the Skin: A General Review

F. JOHN EBLING

Department of Zoology, University of Sheffield, Sheffield S10 2TN, U.K.

The skin is affected by a range of steroid hormones, including corticosteroids, oestrogens and androgens. Adrenocortical hormones have achieved prominence because of their effective use in dermatology. Their success as healing agents in a variety of conditions is only matched by our ignorance of how they work at the tissue level. In general it seems true that whatever can be measured, be it capillary blood flow in inflammation (Wilson, 1976), mitosis (Goodwin, 1976), epidermal thickness (Winter & Burton, 1976) or skin thickness (Kirby & Munro, 1976), is decreased by corticosteroids. Oestrogens pose an even greater puzzle, because there are conflicting views about their effects. The circumstantial evidence that appearance, texture and tone of skin are important sexual features of the female and that regressive changes occur after the menopause, favours the view that oestrogens stimulate the cutaneous tissues. Evidence that topical application of oestrogenic ointments to the backs of senile human subjects locally increased the size of the epidermal cells and accentuated the waviness of the basal layer (Eller & Eller, 1949) appeared to be reinforced by the claim that oestrogens stimulate epidermal cell division in mice (Bullough, 1953). Punnonen & Rauramo (1974) have revived the issue by the claim that, in women, epidermal thickness and thymidine-labelling index were decreased by ovariectomy, but could be restored by oral treatment with oestradiol succinate or oestradiol valerate. Against this must be set the failure to demonstrate any mitotic effects of systemically administered oestradiol in adult rats (Carter, 1953; Ebling, 1954, 1964), or any noticeable clinical improvement when oestrogen creams are applied to women's faces (Behrman, 1954). Moreover, oestrogens in pharmacological doses appear to decrease rather than stimulate sebaceous activity.

If the cutaneous effects of adrenocortical and oestrogenic steroids are ill-defined, the skin can, in contrast, be considered a specific androgen target. In particular, androgens stimulate sebaceous glands, whether distributed throughout the body or aggregated into specialized structures, and specialized apocrine glands in a range of animals (for review see Strauss & Ebling, 1970). They also affect hair follicles, particularly in man, where they stimulate hair growth on the body even if, in constitutionally deprived subjects, they promote hair loss on the scalp.

The responses of the sebaceous glands, in contrast to those of sexual hair, can be readily studied in animal models. However, discussion will be confined to experimental evidence from the rat and man, since specialized glands will be dealt with in this symposium (Johnson, 1976).

Sebaceous glands

At a simple level the facts are clear; androgens stimulate sebaceous activity. They have been shown to enlarge the sebaceous glands of rats and to increase sebaceous secretion, whether measured by the changes in the amount of fat in the hair of washed rats (for a review, see Ebling, 1974) or skin surface lipid removed by immersion in solvents (for a review, see Shuster & Thody, 1974). The action of testosterone as studied in the rat appears to involve a stimulation of cell division in the sebaceous glands. This is not surprising, since holocrine activity by definition implies that the secretion is formed by cellular disintegration and this must clearly be preceded by cell replication. However,
this is not the whole story. Oestrogens, administered systemically, will markedly inhibit sebum production, even in rats simultaneously given testosterone (Ebling, 1967). In such conditions, mitosis does not appear to be significantly decreased, so it must be concluded that the oestrogen acts not by antagonizing the effect of the androgen on cell division, but by inhibiting lipid synthesis within the sebaceous cells. It is reasonable to conclude, therefore, that sebaceous secretion can be influenced at two points, cell division and intracellular lipid synthesis, and that the processes may, to some extent, be disengageable. This view is reinforced by the finding that anti-androgenic steroids, such as 17α-methyl-β-nortestosterone (Ebling, 1967) or cyproterone acetate (Ebling, 1973) will also lower sebaceous secretion, and clearly do so in part at least by an effect in decreasing cell division. It should be added that oestrogen given in one-hundredth of the dosage of the administered testosterone is more effective in decreasing sebum production than is cyproterone acetate at ten times the dose of the androgen. Moreover, the effects of the anti-androgen and oestrogen have been shown to be additive. A final piece of evidence that the two steroids are entirely different in their modes of action is the finding that an anti-androgen, but not oestradiol, decreased the uptake in vivo of [3H]testosterone by rat skin and other androgen targets (Ebling, 1974).

The effects of androgens and oestrogens on sebaceous activity have been demonstrated in man. Strauss & Pochi (1961, 1963a,b), using a method in which sebum is absorbed from the forehead by pads of cigarette papers, showed that its secretion could be increased in a prepuberal boy or in adult eunuchs by oral administration of methyltestosterone. In contrast, no such effect could be shown in intact adult men, in whom the sebaceous glands are presumably stimulated to full capacity by endogenous androgens. Similarly, ethinyl oestradiol given orally reduces sebum secretion in adult men or women.

Apocrine glands

In addition to holocrine sebaceous glands, tubular glands also develop in association with hair follicles. In man, such glandular rudiments are ubiquitous in the foetus, but survive in the adult and become canalized only in the genital regions, the areolae and the axilla. Glands of this type are widespread in mammals and, often in association with sebaceous derivatives, make up specialized scent organs.

The rabbit possesses three such glandular masses, which have proved suitable models for testing the responses to steroids. Glands in the chin and anal regions appear to be concerned with scent marking to establish territory or social dominance; the inguinal glands, at least in the male, produce a sex attractant. All three pairs of glands are androgen-dependent and all, too, are highly susceptible to suppression by oestrogens (Wales & Ebling, 1971).

Hair

That some hair follicles, notably those of the beard, axilla, pubic region and to a lesser extent on the chest, abdomen and limbs, are under androgenic control is obvious. The sexual hair starts to grow at puberty. Hirsutism is seen in conditions associated with excessive androgen production, for example, Stein–Leventhal syndrome and adrenal tumour; conversely, hair growth is sparse when androgen is insufficient. What is paradoxical is why pattern alopecia in men, and the somewhat more diffuse, but nevertheless probable counterpart in women, is similarly androgen-dependent. Why should male hormones strengthen hair growth in some regions of the body, where it is often unwelcome, and decrease it to futility on the scalp, where it is highly desired?

Role of the pituitary

The response of the rat sebaceous glands to testosterone, whether measured by gland size (Lasher et al., 1954; Ebling, 1957) or by sebum production (Ebling et al., 1969) is greatly diminished by hypophysectomy. By comparison of a very large number of
treated animals with littermate controls it was possible to show a small significant response to testosterone of hypophysectomized castrated rats, but only about one-fifth of that produced in castrated rats with intact pituitaries (Ebling, 1974). The responses of the preputial glands and even the ventral prostate are also pituitary dependent, but to a lesser extent than the sebaceous glands (Ebling et al., 1975b).

The effective response to testosterone has been unequivocally restored by administration of a sheep prolactin (Ebling et al., 1969), a pig growth hormone (Ebling et al., 1969), a bovine growth hormone (Fig. 1) made by C. H. Li (Ebling et al., 1975a) and synthetic melanotropin (Ebling et al., 1975c; Thody & Shuster, 1975). The last two preparations were shown to have some independent actions, but to exert most of their effect as a synergism with testosterone. It is possible that thyrotropin also has a similar action (Ebling et al., 1970), but since it could exert an indirect effect by stimulation of thyroxin secretion, which also affects the sebaceous glands (Shuster & Thody, 1974), a direct synergistic effect has not been unequivocally demonstrated.

Metabolism of androgens

It is widely accepted that some, at least, of the effects of testosterone involve its transformation to active metabolites. The importance of 5α-dihydrotestosterone as an active metabolite was first established by studies on the prostate (Bruchovsky & Wilson, 1968), though both male and female human skin (Wilson & Walker, 1969) as well as rat skin are similarly capable of producing 5α-dihydrotestosterone from testosterone. However, this is not the only metabolite. Rat skin produces, both in vivo and in vitro, androstenedione and 5α-androstanediols (F. J. Ebling, unpublished work). That such compounds may be important in vivo in man is suggested by the finding that women with acne or idiopathic hirsutism excrete abnormally high amounts of androstanediol in the urine (Mauvais-Jarvis et al., 1973). The major pathways of androgen metabolism in skin are summarized in Scheme 1.

It is possible that peptide hormones have a role in these processes. The sebaceous glands of hypophysectomized-castrated rats, in spite of their insensitivity to testosterone

![Fig. 1. Sebum production in rats as measured by increase in hair fat](image)

Results are means ± s.e.m. for groups of 11 rats. [From Ebling et al. (1975a) by permission of the *British Journal of Dermatology.*] (a) and (e) untreated; (b) and (d) testosterone-treated; (c) growth-hormone-treated; (f) growth-hormone- and testosterone-treated.
itself, show a significant response not only to 5α-dihydrotestosterone, but to 5α-androstane-3β,17β-diol and to androstenedione (Ebling et al., 1971, 1973). There might therefore appear to be a prima facie case for supposing that pituitary peptides influence 5α-reduction of the testosterone. However, this would not explain the apparent effectiveness of androstenedione, which, since the effect of androstenedione is insignificant,
appears to give androstenedione the status of a tissue-active hormone. Moreover, experiments in vivo and in vitro have as yet failed to establish either an effect of hypophysectomy or a direct action of peptides on androgen metabolism. That peptides may have some other role, and that more than one androgen may be active at the tissue site, are possibilities that must remain open.

Clinical implications in man

Acne vulgaris, hirsutism and pattern alopecia are all androgen-dependent conditions. The etiology of acne is not as simple as it might seem, because in the male, at least, sufferers from acne do not appear to have more androgen than non-sufferers (Förström et al., 1974; Lim & James, 1974; Pochi et al., 1965). Moreover, if the sebaceous glands normally work at full capacity in adult males (Strauss & Pochi, 1961, 1963a,b), raised androgen concentrations could not in any case affect them. Nevertheless, statistically speaking, acne has been shown to be associated with abnormally high rates of sebum secretion (Burton & Shuster, 1971a,b; Pochi & Strauss, 1964). A possible explanation is that the glands in prone regions of subjects with acne have an abnormally high sensitivity to androgen stimulation with increased 5a-reductase activity (Hay & Hodgins, 1974; Sansone & Reisner, 1971). The further question might be asked whether this could be related to pituitary activity (Ebling, 1975).

In females the situation may be different, since their normal sebaceous secretion is less than that of males (Strauss & Pochi, 1963a,b) and the concentrations of plasma testosterone can be raised in women with acne (Förström et al., 1974). Similarly it now seems probable that much so-called idiopathic hirsutism is the result of abnormally high androgen production (Ismail et al., 1969, 1970). That this has only been demonstrated in the last decade was due to lack of adequate methods and the failure to appreciate that testosterone concentrations fluctuate throughout the menstrual cycle.

The question of pattern alopecia evades answer. That it is related to androgen metabolism is suggested by the finding that bald skin is more capable than non-bald skin of converting testosterone into 5α-dihydrotestosterone in vitro (Bingham & Shaw, 1973a,b). However, it has been pointed out that formation of dihydrotestosterone is an ubiquitous property of hair follicles irrespective of whether they are responsive to androgens, and that hair roots given labelled testosterone in vitro produce androstenedione as their major metabolite (Schweikert & Wilson, 1974). The high rate of dihydrotestosterone formation in balding might thus be its consequence rather than its cause.

Conclusions

The responses of skin to corticosteroids or oestrogens are relatively unspecific and difficult to quantify. In contrast, the hair follicle and its associated sebaceous and apocrine glands are specific targets for male hormones. Androgens stimulate sebaceous secretion, probably increasing intracellular lipid synthesis as well as sebaceous cell production. They also promote hair growth in some regions of the human body, even if they discourage it on the scalp. Animal experiments suggest that the action of testosterone may require the synergism of pituitary peptide hormones. The responses to testosterone may involve its transformation into metabolites such as the 5α-androstanediols and androstenedione as well as 5α-dihydrotestosterone. Acne vulgaris, hirsutism and pattern alopecia are all androgen-dependent, but the conditions could be promoted not simply, or not only, by increased androgen secretion, but from abnormal reactions of the target organ.

Steroids and Specialized Skin Secretions in Mammals

ELIZABETH JOHNSON

Department of Zoology, University of Reading, Whiteknights, Reading RG6 2AJ, U.K.

The majority of mammals have skin glands in particular regions of the body producing secretions important in social interaction. In small mammals the scent is usually produced by regions with enlarged sebaceous glands, such as the ventral gland of the gerbil (Mitchell, 1965; Glenn & Gray, 1965), the caudal or flank glands of microtine rodents (Quay, 1968) and the preputial glands of rodents (Clevedon-Brown & Williams, 1972). In larger mammals apocrine glands form an important component of the scent-producing regions. The chin glands of the rabbit are composed entirely of enlarged apocrine glands (Lyne et al., 1964), whereas the inguinal glands of rabbits (Mykytowycz &