Topical Antiandrogens

What Use in Dermatology?

The interaction between androgenic hormones and the skin has been a fascinating area of research that has tantalized dermatologists for several decades. Hirsutism, balding, and acne are all androgen-related disorders. Elevated levels of circulating androgens have recently been discovered in at least 80% of women suffering from hirsutism and, to a lesser extent, in women with female-pattern hair loss and acne. However, some obvious questions persist: Why do androgens cause hair to grow in some areas, such as the face, but cause it to regress to vellus hairs in other areas, such as the scalp? Why, with similar degrees of hyperandrogenemia, does severe acne develop in one woman and hirsutism in another? Answers to these questions seem to lie

within the skin itself. An understanding of the response of the skin and its appendages to circulating hormones requires innovative research. We would all like to see a topical antiandrogenic “weed killer” for hirsutism or a topical antiandrogenic “fertilizer” for balding. A new form of topical acne therapy might also be based on the blockage of androgenic action.

At the cellular level, androgens, like other steroid hormones, are transported into the cytoplasm, attach to a cytosol receptor, and are then translocated as a hormone-receptor complex to the nucleus. Here, a series of events results in the production of new messenger RNA. Testosterone and dihydrotestosterone (DHT) have been studied most frequently as the model androgens. Testosterone is converted into DHT in the target cell cytoplasm by the enzyme 5α-reductase. DHT appears to be a more potent androgen than testosterone. Antiandrogenic action can thus occur by several mechanisms: conversion of testosterone to DHT may be blocked by 5α-reductase inhibition; testosterone or DHT may be prevented from binding by competition for the cytosol or nuclear androgen receptor by a substance that has no androgenic activity, i.e., an antiandrogen; or androgens could be bound by larger molecules in the circulation and rendered unavailable for uptake into target tissues.

Ideal topical antiandrogens should act locally at the site of application, without producing undesired systemic side effects. Nondermatologic physicians have used the excellent transepidermal absorption properties of skin for the systemic administration of such diverse drugs as nitroglycerin and scopolamine. Finding drugs in appropriate vehicles that exert local action at the intended site, without producing systemic effects, is a challenge. Several mechanisms may produce such results: drugs could be rapidly converted into inert metabolites, drugs could be bound locally to the site of application and be unable to circulate, or drugs could be picked up by circulating molecules that render them systemically ineffective.

The easy accessibility of the Syrian hamster flank organ has made it an ideal model for studying antiandrogens. All hamsters, male and female, have a symmetrical pair of pigmented flank organs (also called costovertebral glands) on their backs that are made up of three androgen-dependent structures: pigment cells, hair follicles, and sebaceous glands.
Systemic and local effects of topical antiandrogens can both be studied using this model, and the presence of paired organs provides a built-in control for the study of topical applications to one side. Although it had been assumed that the three target tissues—pigment, hair, and sebaceous glands—were equally responsive to androgen, recent studies have shown that each may indeed be under separate androgenic control. Thus, a compound that inhibits sebaceous glands may not have the same effect on hair. Earlier studies of the hamster flank organ model used the size of the pigmented spot overlying the flank organ as a measure of androgen response, but we now know that this color change does not necessarily reflect sebaceous gland or hair follicle response.

The article by Weissmann et al in this issue of the Archives encourages the development of effective, local topical antiandrogens. Spironolactone acts as an antiandrogen by competing for the androgen cytosol receptor, and its systemic administration has been shown to inhibit sebaceous gland activity in the hamster, Weissmann et al show that the topical application of spironolactone to one flank organ of a mature male hamster results in the unilateral diminution of sebaceous gland size on the treated side only. They carefully assessed sebaceous gland rather than pigment response. In this hamster model, the contralateral side served as a control for systemic absorption.

The local effectiveness of spironolactone may be due to a rapid degradation of the drug to an inert compound so that the absorbed portion is no longer effective as it moves away from the site of application. The results reported in the hamster study showing sebaceous gland inhibition are in agreement with a few rather anecdotal clinical observations on the effectiveness of systemic spironolactone in acne. The effect of spironolactone on hair growth was not addressed in the study performed by Weissmann et al. Hair growth should also be investigated because of encouraging reports of the systemic use of this drug for hirsutism.

Surprisingly, few antiandrogens have been studied to date. In contrast to spironolactone, cyproterone acetate, which is an even more potent competitor for the androgen receptor, was found by Weissmann et al to cause diminution of the flank organ size on both the treated and untreated side, indicating a systemic rather than local antiandrogenic effect and confirming results of previous studies. Thus, it is not only the potency of an antiandrogen but also its metabolic fate that may render it a successful topical drug. The most frequently studied topical antiandrogen has been progesterone, which acts as an inhibitor of 5α-reductase. It appeared to function well as a local antiandrogen in early studies using the hamster flank organ model, but human studies measuring 5α-reductase directly in scalp hair showed a bilateral effect, indicating systemic rather than local action.

Studies using animal models should stimulate our interest in the mechanism of action of steroid hormone effects on the skin. Although the potential for a new drug is exciting, translation to human use must be made with caution. Animal studies screen the myriad of compounds that are potentially antiandrogenic and shed some light on their mechanisms of action. However, antiandrogenic activity in the hamster, for example, would not necessarily imply equal efficacy in humans. In addition, the success or failure may not be in the selection of the antiandrogen but in the selection of the vehicle in which it is delivered. In our laboratories, for example, we have performed studies using the same concentrations of spironolactone in a different vehicle from that used by Weissmann et al and have found no antiandrogenic effect in a similar flank organ model (unpublished data, 1983). Finally, the antiandrogenic effect on one skin structure, such as the sebaceous gland, is not necessarily equivalent to the effect on another, such as the hair follicle. Thus, a topical antiandrogen that may be effective in acne therapy may not work in treating hirsutism or balding. Studies like those of Weissmann et al should encourage additional animal trials of new antiandrogenic compounds and should result in carefully controlled clinical trials applied to disorders of end-organ response to androgen in humans. With a sound scientific basis, the “weed killer” for hirsutism, the “fertilizer” for balding, and the new topical “miracle cure” for acne may be within our grasp.

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References

56 Arch Dermatol—Vol 121, Jan 1985

Printed and Published in the United States of America

Editorial