Chapter 34

Antiandrogens and Hair Growth: Basic Concepts and Experimental Research

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1 Introduction

The term antiandrogen had already appeared several times over the years up to 1963. Estrogens, for instance, were thought to have antiandrogenic properties because they could inhibit the growth of the comb in chicks and roosters – a classical parameter of androgenic action (Gley and Delor 1937a, b; Mühlenbock 1938a, b, c, d). Mammals, however, do not display any direct antagonism between androgens and estrogens (Neumann et al. 1968). Other substances, so-called partial agonists/antagonists, displayed antiandrogenic properties only within a certain dose range – at high doses they were androgenic. This phenomenon, i.e., that a weak hormone at an appropriate dosage can to some extent suppress the action of a strong hormone, can be explained by the mechanism of action of sex hormones working via steroid receptor binding. Naturally, such weak androgens with only limited antiandrogenic properties had not found any particular interest. These substances were in any case unsuitable for clinical application.

A number of compounds thought to have antiandrogenic qualities were found to be toxic. A mitosis-inhibiting cytostatic drug of course impairs the androgen-mediated response by inhibiting proliferation of the target organs. Glucocorticoids exert similar effects through their protein-catabolic properties. The action of these compounds can be mistaken for antiandrogenic effects, but because these substances are nonspecific, they cannot be called antiandrogens.

The real era of antiandrogens started in 1962 with the discovery of the marked antiandrogenic properties of cyproterone acetate. This was the first compound suitable for clinical studies. Also, the chemists and pharmacologists had a lead structure for the first time, and it became possible to vary the molecule of cyproterone acetate in the search for even more powerful antiandrogens – the classical method of pharmaceutical research.
2 General Observations on Antiandrogens

2.1 Definition of Antiandrogen

The definition given by Dorfman (1970) greatly limited the term antiandrogen:

Antiandrogens are substances which prevent androgens from expressing their activity at target sites. The inhibitory effect of these substances, therefore, would be differentiated from compounds which decrease the synthesis and/or release of hypothalamic (releasing factors) and anterior pituitary hormones (gonadotrophins, particularly luteinizing hormone) and materials which act directly on the gonads to inhibit biosynthesis and/or secretion of androgens.

According to this very narrow definition, only those substances may be classified as antiandrogens which competitively inhibit the action of androgens at the receptor. It is remarkable that, up to now all antiandrogens which have become of any importance exert their action at least partly by this mechanism (see Sect. 2.3).

This definition of antiandrogen is, however, of only theoretical interest. It is unimportant to the clinician how the antiandrogenic effect comes about. It is conceivable, for example, that an inhibitor of androgen or gonadotropin biosynthesis or secretion could also have antiandrogenic effects. In fact, some antiandrogens, e.g., cyproterone acetate and \( \Delta^1 \)-chlormadinone acetate, are not pure antiandrogens within the definition of Dorfman (1970), since they also have antigonadotropic properties. Thus, the effects at the target organs for androgens following administration of such substances are, in the final analysis, the result of peripheral competitive antagonism and of the antigonadotropic effect. Which of the two mechanisms dominates depends, among other factors, on the dosage administered and also on the sex (for review see Neumann and Steinbeck 1974). However, some consequences for clinical application do arise from this (see Sect. 2.6).

2.2 Chemistry of Antiandrogens

Most substances – steroidal and nonsteroidal – with antiandrogenic properties which were reported before 1965 did not achieve any significance either experimentally or clinically (Neumann et al. 1967). We have tested some of these compounds in the classical antiandrogen test on castrated rats under androgen replacement. In this test, substances such as \( \Delta \)-norprogesterone and \( \Delta^1 \)-testolactone, for example, were less effective than progesterone, which has only very weak antiandrogenic properties (Junkmann and Neumann 1964).

The first antiandrogen which was of interest for clinical use was cyproterone acetate, a hydroxyprogesterone derivative. A number of chemically very similar compounds likewise displayed antiandrogenic properties, e.g., chlormadinone acetate and \( \Delta^1 \)-chlormadinone acetate (Neumann et al. 1967; Wiechert et al. 1967; Fig. 1). The relative antiandrogenic potencies of a number of derivatives of cyproterone acetate are shown in Fig. 2. It can be seen that none of these derivatives is superior to cyproterone acetate as regards their potency (Neumann and Wiechert 1974). Most of the antiandrogens shown in Fig. 2, especially the substances