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THE SYNDROMES OF ANDROGEN RESISTANCE REVISITED

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Summary—A revisit to the existing complexities of the androgen resistance syndromes within the frame of our current knowledge was undertaken. Recent contributions of these and other laboratories are presented according to the topographic intracellular location of the underlying abnormalities causing these inherited disorders. Thus, the clinical spectrum, inherited pattern and biochemical features of defective androgen action at the pre-receptor, receptor, and post-receptor levels are examined. In addition, the effects of androgens on the development of gender role is discussed, with particular focus on patients with pre-receptor defects. It was concluded that a better understanding of the nature of the altered events in these syndromes has been achieved over recent years, although several important issues still remain unsolved.

INTRODUCTION

The building up of the male phenotype in mammalian embryos is a rather complex biological process under a precise endocrine regulation [1, 2]. Indeed, male phenotypic development is under the control of three fetal hormones which exert their effects on the genital primordium at early stages of intrauterine life. The first chronological event of this series is the Mullerian ducts regression, a process which occurs in human embryos between the 6th and 11th weeks of gestational age [3]. The Mullerian duct regression is dependent on the effect of the Sertoli cell-synthesized Mullerian inhibiting hormone (MIH) [4, 5]. Immediately after, the process of genitalia virilization begins under the hormonal regulation of androgens. First, the Wolffian ducts are androgen stimulated and as a result the epididymides, seminal vesicles, vas deferens, and ejaculatory ducts develop. Further actions of androgens result in virilization of external genitalia. Thus, the genital tubercle and genital fold elongate to form the penis; the urethral folds close over the groove to form the penile portion of the urethra and the urogenital swellings form the scrotum. The whole event of internal and external genitalia virilization is under the control of two fetal androgens: testosterone (T) and 5α-dihydrotestosterone (DHT) [6]. Fetal Leydig cell differentiation and T synthesis occur in a similar fashion as in the adult [7]; however, since fetal LH is not yet available at this point in time, throphoblastic-produced hCG takes over the LH actions [8]. hCG requires the presence of membrane-located LH–hCG receptors as well as the presence of a number of steroidogenic enzymes in order to accomplish Leydig cell differentiation and T production [9]. Formation of DHT requires the presence of an NADPH-dependent steroid 5α-reductase at the target cell level [10].

Abnormalities of the male phenotypic development could be the result of either impaired hormone biosynthesis or defective hormone action [11, 12]. Both types of defects result in a variety of inherited forms of male pseudohermaphroditism. Androgen resistance in mammals is constituted by a wide and heterogeneous group of different phenotypic and molecular inherited abnormalities which have been the target of extensive studies over the last few years. The spectrum of underlying molecular defects includes inability of the target cell to form DHT, intracellular failure to form androgen–receptor stable complexes, or lack of effectiveness of the androgen–receptor complexes to initiate androgen-dependent cellular responses.

This report summarizes the most recent studies from these and other laboratories on the biochemical and clinical aspects of the androgen resistance syndromes (ARS). The data are presented according to the nature of the inherited disorder: Defects at the pre-Receptor, Receptor, and post-Receptor levels.

ANDROGEN RESISTANCE AT THE PRE-RECEPTOR LEVEL

Following the original descriptions of Imperato-McGinley *et al.* [13] and Walsh *et al.* in 1974 [14], it was evident that the *in utero* deficiency of 5α-steroid reductase, the enzyme which converts T to DHT, resulted in a distinctive form of male pseudohermaphroditism. Since then, a number of cases sharing identical clinical features and enzyme defects have been reported [15].

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Patients bearing this inherited enzyme impairment exhibit severe external genital ambiguity with a bifid scrotum, small penis, perineoscrotal hypospadias and a urogenital sinus with separated vaginal and urethral openings. In some cases the blind-end vaginal pouch cannot be identified and the urethral opening is located in the perineum [6]. Bilateral testes are present and they are commonly cryptorchidic. Because of the phenotype presented by the affected individuals at birth, a female gender role is usually assigned. At the time of puberty, the hypothalamic–pituitary–testicular axis of these patients becomes active with a significant increase of the circulating T levels. As a result of this endocrine gonadal activity, they develop a masculine habitus at the expense of an important muscular mass growth, the appearance of male-type pubic hair and growth of the penis. In addition, they present hyperpigmentation and rugation of the scrotum, testicular descent and deepening of the voice. Despite the appearance of these pubertal virilizing features, the patients exhibit absence (or diminution) of facial hair and temporal hair-line recession.

Endocrine studies in postpubertal patients have revealed that the serum gonadotropin and T levels are slightly elevated, and the T/DHT ratio is consistently increased (above 20), a finding commonly used as a diagnostic clue (Fig. 1), although Horton [17] has recently shown that measurement of circulating 3α,5α-androstanediol glucuronide is a better marker of peripheral androgen production. In contrast, the T/DHT serum ratio in prepubertal patients is within normality and an exogenous hCG stimulus is needed to disclose the enzyme defect. The peripheral conversion of T to DHT is markedly decreased as it has been assessed by both *in vivo* and *in vitro* studies [13, 18–21]. The diminished DHT serum concentrations correlate well with a diminished urinary excretion of androsterone and androstanediol [19, 21]. The observation that the excretion of 5α-reduced metabolites of C-21 steroids (tetrahydrocortisol and tetrahydrocorticosterone) and C-19 steroids other than those of T (androstanedione and 11β-OH-androstanedione) is markedly reduced [19], indicates the lack of substrate specificity of the 5α-reductase enzyme involved in sexual differentiation. Studies conducted in genital skin-derived mutant fibroblasts have revealed 4 types of the enzyme defect: (a) the Dallas mutant, in which a decreased affinity for the steroid substrate was noticed [20], (b) the Dominican mutant, similar to the Dallas mutant except for the finding of slight heat instability and normal activity in monolayer assays [22], (c) the Los Angeles Mutant exhibited normal enzyme affinity for the steroid but instability with diminished affinity for NADPH [21], (d) the New York mutant resembles the combined mutations of the Dallas and Los Angeles cases [18]. Familial studies undertaken in large kindreds with 5α-reductase deficiency and the detection of decreased 5α-reductase urinary metabolites of C-19 and C-21 steroids in obligate carrier parents, have demonstrated the autosomal recessive pattern of inheritance of this entity [13].

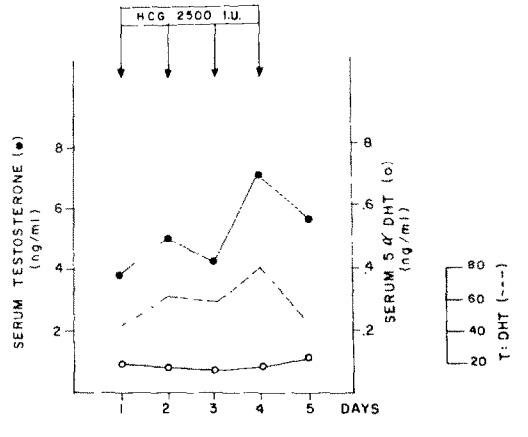


Fig. 1. Testicular responsiveness to exogenous hCG stimulation in a 16-yr-old XY male pseudohermaphrodite with a 5α-reductase deficiency. hCG was intramuscularly administered at a daily dose of 2500 IU for 4 consecutive days. Serum 5α-DHT levels remained unmodified throughout gonadotropin stimulation with a concomitant increase of the testosterone (T): 5α-DHT ratio.

One of the most fascinating aspects of this inherited disorders is related with the dynamics of the gender identity and psycho-sexual role exhibited throughout the life of the affected individuals. As described above, all subjects are reared, since birth, as females. However, at the time of puberty, coinciding with the striking increase on serum T and the development of a defined male external habitus, most of the patients have switched their gender identity and role from female to male [16]. Some variations within this pattern have been noticed. Thus, in some cases, a definitive male psycho-sexual role was adopted until adulthood [18, 23], even though a male gender identity had emerged at puberty; while other cases [24] do not clearly define their gender identity and role, in spite of the events of a male puberty. A recent case, evaluated by our group, adopted during adolescence an apparently definitive female role because of a defined intervening familial and social environment. However, 1 yr later, the patient manifested a clear shift toward a male role and identity and requested appropriate surgical corrections (complete data to be published elsewhere).

Although classical psychological studies have persistently neglected the role of sex steroid hormones in the establishment/development of gender identity in humans, the overall data derived from endocrine and psychological studies in patients with 5α-reductase deficiency strongly suggest that prenatal and peripubertal exposure to testosterone modulates, at a certain degree, the expression of male role and identity [15].

ANDROGEN RESISTANCE AT THE RECEPTOR AND POST-RECEPTOR LEVELS

Unresponsiveness of the target cell to the action of androgenic hormones (T, DHT) as the cause of male pseudohermaphroditism was first recognized by the pioneer work of Wilkins[25]. Recent advances in the understanding of the mechanisms of steroid hormones action have provided new insights into the altered molecular processes involved in the origin of these familial disorders. Thus, studies conducted in a number of laboratories have demonstrated that the underlying molecular abnormality can reside at either the androgen receptor or at a post-receptor level. Since defects at both sites usually lead to the development of identical phenotypes we will describe them together.

The clinical spectrum

The clinical expression of defects located at the receptor or at the post-receptor levels can be gathered in three main groups. The first is the complete androgen insensitivity syndrome (CAIS), also known as complete testicular feminization syndrome [26]. These 46, XY patients present a female habitus with normal breast development at puberty, lack of sexual hair, blind-ended vagina, and undescended testes. These clinical features reflect indeed a complete and universal lack of androgen action [27]. Because no Mullerian derivatives are usually found, it has been assumed that the function of the MIH has remained intact during embryonic life. Very recently, however, three sporadic cases [28–30] with CAIS who presented Mullerian remnants have been reported. Because human embryos carrying the X-linked mutation are refractory to androgen action, an exaggerated estrogenic cellular response in spite of the presence of normal serum androgen/estrogen ratio is what would be expected. Accordingly, we proposed [30] that the enhanced and unopposed estrogenic milieu in the CAIS-developing embryo might interfere with the MIH mode of action, resulting in the presence of Mullerian remnants.

The second group of androgen resistance disorders is represented by the incomplete form of the testicular feminization syndrome, which differs from the complete form in that although the patients exhibit a female habitus, they present certain signs which indicate limited androgen action such as pubic hair growth, acne and even moderate clitoral enlargement [31]. The finding of diminished cytosol T-DHT receptor binding sites [32], coupled with the different phenotypic expression and particularly the observation that no convincing pedigree has been reported in which the complete and incomplete forms coexist in the same family [33], suggests that these syndromes are indeed different entities. The third group of the androgen resistance includes a variety of entities in which a partial androgen insensitivity was demonstrated. These include the families or cases reported by Reifenstein[34], Lubs *et al.*[35], Gilbert-Dreyfus *et al.*[36, 37], Rosewater *et al.*[38], Larrea *et al.*[39] and Aiman *et al.*[40]. Although some of the early reports described them as distinctive entities, it has been demonstrated that they represent a clinical heterogenous group with similar molecular defects. In most of the affected individuals in this group, assignment of the gender role depends on the degree of genital ambiguity presented at birth. Bilateral gynecomastia is a common finding at the onset of puberty, although some cases only present infertility associated with azoospermia [40].

The inheritance pattern

The fact that androgen resistance syndromes are inherited as an X-linked recessive trait became evident after the genetic study of a number of large pedigrees of CAIS and partial androgen insensitivity [19, 41]. Even in the incomplete form of testicular feminization syndrome (the most uncommon variety of androgen insensitivity) in which the family history is usually uninformative, an X-linked inheritance pattern has been noticed [2]. Furthermore, the elegant studies of Meyer *et al.*[42] in cells from an obligated heterozygote, indicated that androgen insensitivity in humans results from a mutation of an X-linked gene specifying a DHT receptor. This locus corresponds to the tfm locus in the mouse, an observation that supports the hypothesis of homology between mammalian X chromosomes.

The molecular abnormalities

Throughout the route to ascertain whether the underlying defect of CAIS was located at the target cell level, advantage was taken from the finding that cultured genital skin-derived human fibroblasts are a suitable model for the study of the androgen mode of action. Indeed, the pioneer works of Keenan *et al.*[43] and Griffin *et al.*[44], later confirmed and extended by other groups [32, 45, 46], demonstrated a complete absence of cytosol-located androgen binding sites in cultured skin fibroblasts from androgen-resistant male pseudohermaphrodites. The observation made in our laboratory that CAIS mutant cell nuclei exhibited a normal uptake of DHT-labeled cytosol prepared from normal fibroblasts gave further support to the proposal that lack of androgen binding at the cytosol level was the primary molecular abnormality in this disorder [32]. Altogether, these data appeared to unveil the nature of the molecular abnormality causing inherited complete androgen insensitivity; however, more recent studies revealed that a significant number of CAIS patients have normal or even higher than normal concentrations of intracellular androgen receptors [47–53] indicating the wide molecular heterogeneity of this disorder. It must be stressed,

however, that most of the "receptor positive" CAIS patients exhibited qualitative receptor abnormalities including thermolability of the receptor [48, 50, 51], defective activation of androgen–receptor complexes [52], failure of sodium molybdate to stabilize the cytosol receptor [49], and a greater than normal binding affinity of the androgen receptor for progesterone [48]. In addition, we have reported [12] a familial CAIS aggregate in which two out of three affected members presented peculiar hormonal features characterized by markedly elevated serum gonadotropin and low T levels, inappropriate Leydig cell response to hCG stimulation, and a slight impairment of 17β-ol hydroxysteroid dehydrogenase. This unusual endocrine pattern resembled that exhibited by male pseudohermaphrodite rats and mice as it was described by Bardin *et al.*[54]. Furthermore, an even closer similarity between this family and the rodent mutation was evident by the presence of residual (diminished) androgen cytosol receptors in cultured skin fibroblasts (Fig. 2).

Very recently a new abnormality causing CAIS has been described by Hughes *et al.*[53], which is characterized by an increased concentration of androgen receptors that appear to be qualitatively normal. The observation in these patients' cells that androgens induced an augmentation of the receptor was interpreted as demonstrating that the gene coding for the androgen receptor was intact and therefore does not account for the androgen insensitivity. These cases represent a clear example of a post-receptor located molecular abnormality resulting in a complete impairment of androgen

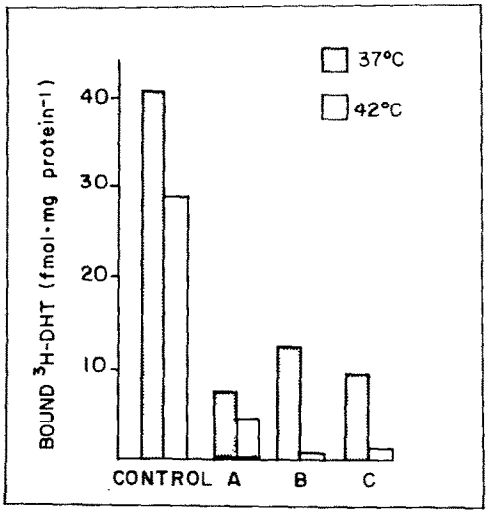


Fig. 2. Effect of elevated temperature on [^{3}H]DHT binding in fibroblasts from control strain and 3 patients with complete androgen resistance syndrome (A, B, C). The cells were incubated for 45 min with 1 nM [^{3}H]DHT at the indicated temperature. The results are the mean of 2 experiments in triplicate.

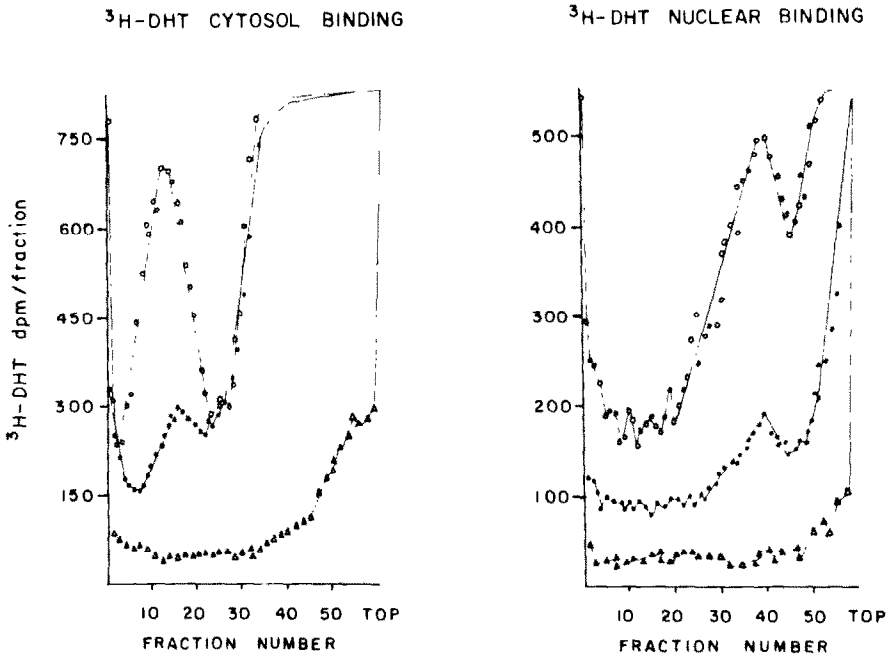
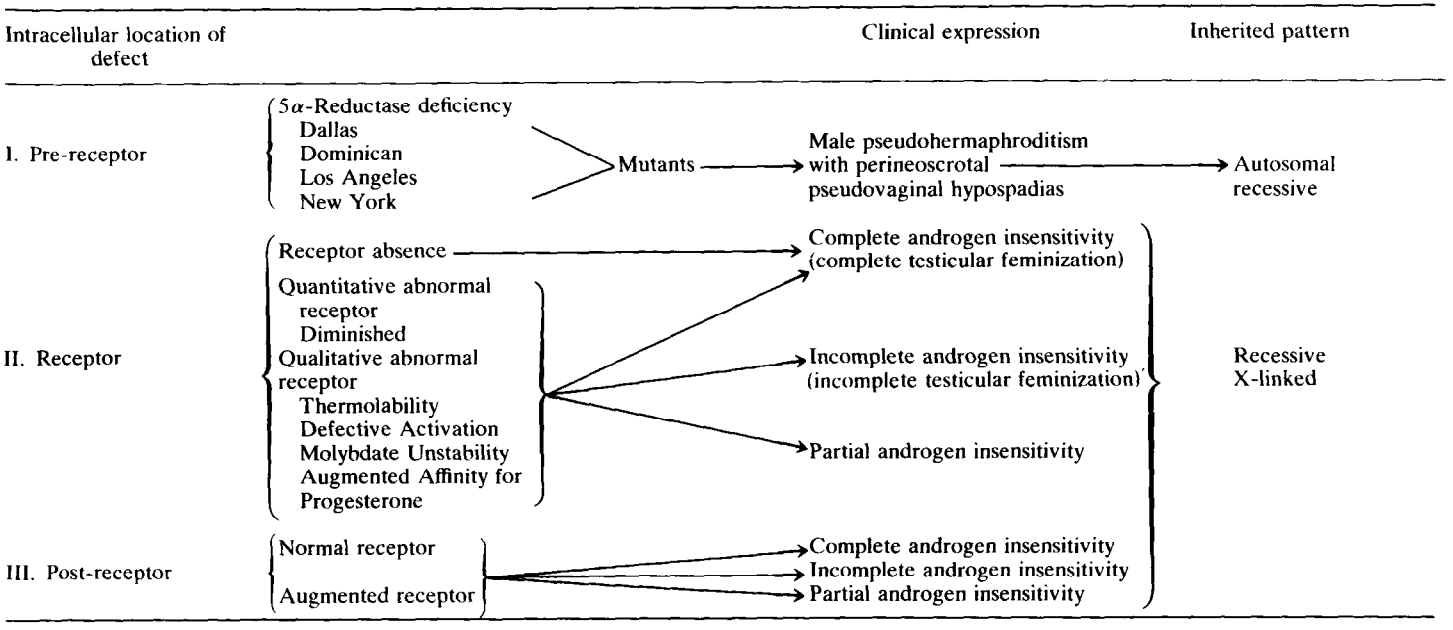


Fig. 3. [^{3}H]Dihydrotestosterone binding by genital skin derived fibroblasts from normal controls and patients with complete and incomplete androgen insensitivity syndromes as assessed by a linear sucrose gradient labeling technique. In the left panel [^{3}H]DHT 8-S cytosol binding is demonstrated, while in the right panel[^{3}H] DHT 3.5-S nuclear binding is shown. Lack of androgen receptor binding sites was evident in the patients with the complete form of the syndrome whereas a diminished DHT intracellular bindability was noticed in the patient with incomplete androgen insensitivity. Normal control (○), CAIS (△), incomplete androgen insensitivity (●). ^{14}C ovalbumin was used as internal marker.

Table 1. Androgen resistance syndromes



action. The nature of the defect cannot yet be ascertained and remains to be elucidated.

Studies on skin fibroblasts from patients with the incomplete form of testicular feminization syndrome [32, 49] have revealed in all of them the presence of intracellular androgen receptors (Fig. 3), albeit in most cases qualitative or quantitative receptor abnormalities have been noticed.

The results of studies undertaken in the heterogenous group of families bearing partial androgen insensitivity have invariably demonstrated the presence of intracellular androgen binding sites. However, in most of the patients, quantitative or qualitative alterations of the androgen receptor have been observed [44, 46, 49].

The overall data indicate that a given molecular abnormality on the mechanism of androgen action does not necessarily correlate with a defined phenotype. Thus, CAIS might be the result of either a complete absence of receptor bindability, or a defective androgen receptor, or even a post-receptor located defects, whereas the incomplete and partial types of androgen insensitivity are usually, if not exclusively, associated with the presence of defective androgen receptor (Table 1). However, in some cases a post-receptor abnormality cannot be excluded.

CONCLUSIONS

In summary, we can conclude that the work carried out by a number of laboratories has significantly contributed to a better understanding of the nature of altered molecular events in androgen resistance syndromes. However, several intriguing questions still remain unsolved and deserve further studies. It is envisaged that the application of current recombinant DNA technology [55] in this particular field will be instrumental in the final elucidation of these challenging problems.

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