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Androgens, Androgen Receptors, and Male Gender Role Behavior

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Studies of genetic males with single gene mutations that impair testosterone formation or action and consequently prevent development of the normal male phenotype provide unique insight into the control of gender role behavior. 46,XY individuals with either of two autosomal recessive mutations [17β-hydroxysteroid dehydrogenase 3 (17β-HSD3) deficiency or steroid 5α-reductase 2 (5α-R2) deficiency] have a female phenotype at birth and are raised as females but frequently change gender role behavior to male after the expected time of puberty. In contrast, genetic males with mutations that impair profoundly the function of the androgen receptor are also raised as females and have consistent female behavior as adults. Furthermore, the rare men with mutations that impair estrogen synthesis or the estrogen receptor have male gender role behavior. These findings indicate that androgens are important determinants of gender role behavior (and probably of gender identity) and that this action is mediated by the androgen receptor and not the result of conversion of androgen to estrogen. The fact that all genetic males with 17β-HSD3 or 5α-R2 deficiency do not change gender role behavior indicates that other factors are also important determinants of this process.

Gonadal steroids are responsible for phenotypic sexual differentiation, sexual maturation at the time of puberty, and control of libido and potentia in adults. Human sexual behavior also involves gender identity, the perception of oneself as male or female, and gender role behavior (also termed social sex or social identity), the various processes by which gender identity is communicated to others. These two aspects of behavior are normally in accord, but most studies focus on gender role behavior because the change of legal registration of sex from one gender to another is unambiguous, whereas gender identity can be difficult to quantify. It is obviously not possible to devise definitive experiments to examine the role of hormones in human behavior, but on the basis of studies of subjects with a variety of forms of intersex and/or endocrine abnormalities it was for many years the predominant view that human gender identity and gender role behavior are determined primarily, if not exclusively, by psychological and social forces.

In the past 20 years, however, a growing body of evidence has accumulated to indicate that androgens play an important role in human male gender identity/behavior (Wilson, 1999). This evidence stems largely from the work of Imperato-McGinley and her colleagues (1979a,b), who showed that genetic males with either of two autosomal recessive mutations that impair androgen synthesis or androgen metabolism during embryogenesis, and hence result in formation of female external genitalia and female sex of rearing, frequently change gender role behavior to male at or after the time of expected puberty.

The molecular biology of these two autosomal recessive disorders has been explored in some detail. The cDNAs and genes that encode the two critical enzymes involved—17β-hydroxysteroid dehydrogenase-3 and steroid 5α-reductase-2—have been cloned, and a great deal has been learned about the underlying pathophysiology. This article is designed to review the studies of these two conditions and of other single-gene mutations that impair steroid hormone formation and/or action and to summarize the implications of these studies for understanding human behavior.

GENDER IDENTITY/ROLE BEHAVIOR

Some of the ambiguities in the definition and understanding of gender identity and gender role behav-

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ior are due to difficulties in quantifying these parameters and to the fact that gender role behavior is influenced by cultural and social variables, as evidenced by the different actions and activities of the two sexes in different societies. Since many studies of human sexual behavior have involved analysis of gender role behavior in subjects with endocrine disorders, particularly abnormalities of sexual development, it is necessary to consider briefly how such disorders arise.

NORMAL AND ABNORMAL SEXUAL DEVELOPMENT

The embryos of both sexes develop in an identical fashion until the 7th week of gestation. Thereafter, the anatomic and physiological development in the two sexes diverge. As formulated by Jost (1972) normal sexual development in the mammal depends on three sequential processes. The first involves the establishment of *genetic sex* at the time of conception, the heterogametic sex (XY) being male and the homogametic sex (XX) female. In the second phase information encoded on the sex chromosomes causes the establishment of *gonadal sex,* in which the indifferent gonad develops into either an ovary or a testis. The final stage involves the translation of gonadal sex into *phenotypic sex.* In the presence of an ovary or in the absence of a functional gonad the phenotypic sex is female. Masculinization of the urogenital tract and the external genitalia, in contrast, requires the action of three hormones of the fetal testes, antimullerian hormone, testosterone, and dihydrotestosterone, the 5α-reduced metabolite of testosterone. Antimullerian hormone is essential for suppression of the mullerian ducts and hence for preventing formation of a uterus and fallopian tubes in the male. Testosterone, the principal androgen in the testes and in the plasma, converts the wolffian ducts into the epididymis, vasa deferentia, and seminal vesicles, and dihydrotestosterone, which is formed predominately in the target cells themselves, induces formation of the male urethra and prostate and the male external genitalia.

Derangement of any of the processes involved in sexual differentiation can cause abnormal sexual development. The pathogenesis, manifestations, endocrine pathology, and functional disturbances in these disorders have been reviewed extensively, but certain aspects of abnormal sexual development are relevant to the analysis of human sexual behavior.

First, the phenotypic effects of the various abnormalities differ markedly. For example, men with 47,XXY Klinefelter syndrome or with the 46,XX male syndrome develop as men (albeit infertile) and have endocrine abnormalities only in later life. Likewise, women with 45,X gonadal dysgenesis or with 46,XX or 46,XY pure gonadal dysgenesis have a female phenotype, and most subjects with true hermaphroditism have unequivocal male or female phenotypes. In brief, most individuals with abnormalities of sexual differentiation end up with unambiguous male or female phenotypes, either because the formation of testicular hormones was sufficient to induce a male phenotype or because the failure of formation / action of testicular hormones was so complete as to allow formation of a female phenotype. Since sex assignment and the sex of rearing are determined by the anatomical development, any direct hormonal effects on behavior in most such individuals would not be apparent because behavior would correspond to the anatomical development and hence to the gender assignment and sex of rearing.

Second, phenotypically similar disorders can arise by different mechanisms. For example, men with 45,X / 46,XY mixed gonadal dysgenesis can have phenotypes similar to those of men with 5α-R2 deficiency or with partial loss-of-function mutations of the androgen receptor. Since these disorders have different pathophysiologies, it is essential that diagnoses be established before attempting to draw interpretations as to the behavioral consequences of a given abnormality.

Third, genital ambiguity occurs in relatively few disorders of human intersex and is due to one of three mechanisms: (1) The testes do not produce sufficient hormones to virilize a male embryo completely, either because of developmental abnormality of the testes or a defect in testosterone biosynthesis; (2) sufficient testosterone is synthesized by the testes, but the hormone cannot virilize the embryo normally because of an abnormal androgen receptor); or (3) androgen is overproduced in the female embryo, as in congenital adrenal hyperplasia, due to deficiency of steroid 21-hydroxylase (CYP21). In newborns with ambiguous genitalia gender assignment usually corresponds to the predominant or apparent anatomy. If hormones participate directly or indirectly in gender identity it follows that gender identity and gender behavior would be more likely to be discordant or uncertain in subjects with ambiguous genitalia. Nevertheless, all types of ambiguous genitalia vary in severity among affected individuals and can cause variable phenotypes. For example, the external phenotypes of males