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Hormonal influences on sexually differentiated behavior in nonhuman primates

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Abstract

Sexually dimorphic behavior in nonhuman primates results from behavioral predispositions organized by prenatal androgens. The rhesus monkey has been the primary primate model for understanding the hormonal organization of sexually dimorphic behavior. Historically, female fetuses have received high prenatal androgen doses to investigate the masculinizing and defeminizing effects of androgens. Such treatments masculinized juvenile and adult copulatory behavior and defeminized female-typical sexual initiation to adult estrogen treatment. Testosterone and the nonaromatizable androgen, 5α-dihydrotestosterone, produced similar effects suggesting that estrogenic metabolites of androgens are not critical for masculinization and defeminization in rhesus monkeys. Long duration androgen treatments masculinized both behavior and genitalia suggesting that socializing responses to the females' male-like appearance may have produced the behavioral changes. Treatments limited to 35 days early or late in gestation differentially affected behavioral and genital masculinization demonstrating direct organizing actions of prenatal androgens. Recent studies exposed fetal females to smaller doses of androgens and interfered with endogenous androgens using the anti-androgen flutamide. Low dose androgen treatment only significantly masculinized infant vocalizations and produced no behavioral defeminization. Females receiving late gestation flutamide showed masculinized infant vocalizations and defeminized interest in infants. Both late androgen and flutamide treatment hypermasculinized some male juvenile behaviors. Early flutamide treatment blocked full male genital masculinization, but did not alter their juvenile or adult behavior. The role of neuroendocrine feedback mechanisms in the flutamide effects is discussed. Sexually differentiated behavior ultimately reflects both hormonally organized behavioral predispositions and the social experience that converts these predispositions into behavior.

Keywords: Sexual differentiation; Primate; Rhesus monkey; Anti-androgen; Flutamide; Behavior; Aromatization; Genitalia; Copulatory behavior; Vocalization; Social behavior

1. Introduction

Nonhuman primates, like humans have a long developmental life span, live in complex social groups and exhibit striking sexually differentiated behavioral patterns both during development and in adulthood. Additionally, nonhuman primates have important biological similarities to humans, including a prenatal period of sexual differentiation, making them ideal for investigating basic mechanisms of sexual differentiation. Sexual differentiation of behavior has been investigated in few of the many nonhuman primate species, with the vast majority of studies using rhesus monkeys. While these studies have elucidated a great deal about sexual differentiation in a nonhuman primate, we know little if anything about the extent or the mechanisms of sexual differentiation of behavior in apes, new world primates, or nonmacaque species. However, the range of treatments investigated in rhesus monkeys and the diverse social conditions employed have revealed a number of important relationships that help frame research in other primate species, including humans. Thus this review primarily focuses on hormonal influences on sexual

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differentiation of behavior in rhesus monkeys, with other nonhuman primate species discussed where appropriate. Hormonal mechanisms of sexual differentiation in rhesus monkeys have been investigated in the context of a long history of studies on the role that hormones play in sexual differentiation.

The organizational hypothesis, the notion that androgens or their metabolites alter the developing nervous system during specific developmental periods permanently inducing behavioral characteristics of male and females, has become a central tenet of behavioral neuroendocrinology since the pioneering study of Phoenix et al. [78]. While specific details of hormonally induced organization continue to be debated [5,21], there is little doubt that exposure to steroid hormones during some period of developmental sensitivity permanently alters the responsivity of individuals to their environment. Most studies of the organizational effects of steroids on the sexual differentiation of behavior come from studies of altricial species who are born prior to complete neural differentiation, [101]; guinea pigs and nonhuman primates being the only precocial mammalian species whose sexual differentiation has been extensively studied. Whether this developmental distinction explains differences in sexual differentiation remains unresolved. There is little doubt, however, that these precocial species differ from the more typically studied altricial species in the timing of sexual differentiation and in the role of estrogenic metabolites of androgens in sexual differentiation [101]. This is of particular importance for considerations of human sexual differentiation, as the dominant rat and mouse models of sexual differentiation seem unlikely to apply to human sexual differentiation. In contrast, studies of nonhuman primates are likely to be more directly applicable to humans.

2. Basic processes of behavioral sexual differentiation

A cascade of physiological and cellular events leads to anatomical and psychological sexual differentiation of male and female mammals. Sex determination is the process by which the male or female pathway is selected and then sexual differentiation elaborates the chosen pathway [26]. Sexual differentiation is achieved through the processes of masculinization and defeminization that sculpt the developing fetus in a male or female direction. The sexual differentiation cascade is well understood, even if many molecular details remain to be elucidated. Similarly the evidence that sexual differentiation results from the processes of masculinization and defeminization is convincing.

Genes on the Y chromosome in males trigger a cascade of sexually differentiating events resulting from the expression of these genes, as well as autosomal genes [5]. A critical step in this process is the differentiation of the indifferent primordial gonad into testes as a result of products of the Sry gene on the Y chromosome interacting with products of the X chromosome genes, Sox9, and autosomal genes [54]. Without this system of genes, the gonad differentiates into an ovary. Testicular differentiation, and the activation of the hypothalamic–pituitary–gonadal axis (HPG), results in the production of testicular hormones which direct the differentiation of masculine and suppress feminine characteristics. This developmental cascade from gene expression to morphological and behavioral differentiation is the principle pathway for sexual differentiation, but nonhormonal pathways may also influence sexual differentiation [4]. Evidence from mice suggests that the Sry gene is transcribed in the developing male, but not female brain, raising the possibility of a direct effect of Sry transcripts on neural organization [55,67]. While these findings are intriguing and demonstrate that a full description of sexual differentiation will likely contain surprises, it is apparent that the actions of testicular hormones play a large and critical role. The role of steroid hormones on behavioral differentiation in primates is the focus of this chapter. This is preceded by a brief description of the cascade of differentiating events that testicular hormones influence.

Mammalian sexual differentiation is biased in a female direction [52], meaning that morphogenic processes produce female endpoints in sexual differentiation more easily than they produce male endpoints. This bias towards female endpoints in sexual differentiation has resulted in referring to the production of females as the "default" path, meaning this pattern occurs most easily. Unfortunately, others have equated default with passive or inactive and the term has become politicized and lost its original sense that masculine characteristics are imposed on an essentially female life-plan [52]. This concept is valuable as it implies that the failure of a process necessary to produce a male trait will lead to the creation of a female phenotypic trait instead. The converse is not true; that when a process necessary for full female sexual differentiation is blocked, a male characteristic arises. Thus, while there can be no doubt that female differentiation requires a suite of active morphogenic processes [21], it is also the case that male differentiation requires two specific processes that allow the male phenotype to emerge from what is essentially female-biased differentiation.

The nomenclature used to describe the processes through which sexual differentiation is achieved has been historically quite confusing. With little precision, terms like feminization and demasculinization have been used in descriptions of sexual differentiation even though there is little evidence to support their existence in mammals. Demasculinization, for example, would require the preexistence of a masculine characteristic that is eliminated or suppressed during sexual differentiation. While this term is appropriate in birds and other nonmamma-