Gonadal Hormone Influences on Human Neurobehavioral Development: Outcomes and Mechanisms

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Abstract Testosterone exposure during early development has enduring influences on mammalian behavior, increasing male-typical characteristics and decreasing female-typical characteristics. Research in non-human mammals indicates that testosterone also influences development of the mammalian brain, affecting programmed cell death, anatomical connectivity and neurochemical specification, and these neural changes, which occur during early development, are thought to explain the subsequent behavioral changes. The strongest evidence linking prenatal testosterone exposure to human behavioral sexual differentiation has come from studies of children's sex-typed play. There also is substantial evidence linking early testosterone exposure to sexual orientation and to core gender identity and some evidence linking such hormone exposure to physically aggressive behavior and to empathy. However, for most, perhaps all, human behaviors that show sex differences, other factors, including socialization, also play a role, and the magnitude of this role appears to vary across behavioral outcomes. In addition, in contrast to other species, the acquisition of sex-typical behavior in humans involves social-cognitive mechanisms related to gender identification. This chapter will suggest that these social-cognitive mechanisms could be involved in the developmental cascade of processes linking early testosterone exposure to sexual differentiation of human behavior.

Introduction

Thousands of experiments in non-human species indicate that exposure to testosterone prenatally or neonatally has enduring influences on behavior, increasing male-typical characteristics and decreasing female-typical characteristics (Arnold

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2009; Goy and McEwen 1980). Testosterone also influences the development of the mammalian brain, affecting programmed cell death, anatomical connectivity and neurochemical specification, and these neural changes, set in place during early development, are thought to underlie the subsequent behavioral changes (Arnold 2009; Goy and McEwen 1980; McCarthy et al. 2009). This chapter will describe evidence that testosterone has similar effects on human neurobehavioral development to those documented in other mammals. In addition, it will attempt to integrate a unique aspect of human gender development—cognitive understanding of gender—along with these hormonal influences and processes of socialization into our understanding of human gender development. Finally, it will suggest that the impact of hormones on the developing human brain could include secondary influences on gender identification and processes related to cognitive understanding of gender, and that these alterations in cognitive processes could represent an additional mechanism by which the early hormone environment alters human gender-related behavior.

Human Gender Development

Human gender development begins at conception, when the 23rd pair of chromosomes is determined as either XX or XY. Genetic information on these chromosomes then causes the primordial gonads, which are initially identical in males and females, to develop as testes or as ovaries (Wilson et al. 1981). By week 8 of human gestation, the testes in the XY fetus are producing testosterone, resulting in higher levels of testosterone in male than in female fetuses. Although testosterone appears to be elevated in male compared to female fetuses throughout gestation, the sex difference appears to be particularly pronounced from about gestational week 8 to about gestational week 24 (Abramovich and Rowe 1973; Abramovich 1974; Carson et al. 1982; Nagamani et al. 1979; Reyes et al. 1973; Robinson et al. 1977; Rodeck et al. 1985).

The prenatal elevation of testicular hormones in male fetuses causes the external genitalia to develop as penis and scrotum, whereas, in the absence of testicular hormones, they develop in the female pattern – clitoris and labia (Wilson et al. 1981). Testosterone, and its five alpha reduced metabolite, act through androgen receptors on the external genitalia to promote male-typical development of these tissues. A somewhat different mechanism produces male-typical development of the internal genitalia (Wilson et al. 1981). In this case, both male and female fetuses begin with two sets of structures: Müllerian ducts and Wolffian ducts. Testosterone causes the Wolffian ducts to develop, and a separate testicular hormone, Müllerian Inhibiting Factor, causes the Müllerian ducts to regress in the male fetus. The female fetus has no testes and so no Müllerian hormone; as a consequence, the Müllerian ducts persist. In addition, because the female fetus has no testicular testosterone, the Wolffian ducts are not stimulated, and they regress. Thus, slightly different processes lead to sexual differentiation of the internal and external genitalia.

There is extensive evidence that processes similar to those that promote male-typical development of the external genitalia also promote male-typical development of the brain and of behavior. Treatment of female animals with testosterone during early development causes masculinization of the external genitalia, as well as masculinization of regions of the brain that have the appropriate receptors and masculinization of behavior. The mechanisms involved in this gonadal steroid induction of neural virilization include influences on programmed cell death, neurite outgrowth, anatomical connectivity, and neurochemical specification (Arnold 2009; Goy and McEwen 1980; McCarthy et al. 2009). These virilizing effects of testosterone and its metabolites on brain development have been documented particularly extensively in the hypothalamic and limbic regions.

A growing body of research suggests that testosterone influences human neural and behavioral development in a manner similar to that documented in experimental studies of other species (Hines 2011). Much of this evidence has come from studies of girls and women exposed to high levels of testosterone and other androgens prenatally, because they have the autosomal, recessive disorder of sex development, congenital adrenal hyperplasia (CAH; Cohen-Bendahan et al. 2005; Hines 2004, 2009). CAH usually involves a deficiency in the enzyme, 21 hydroxylase, and a consequent inability to produce cortisol (New 1998). Because the pathway to cortisol is disabled, hormones that would normally be used for this purpose are shunted into the androgen pathway, producing high levels of testosterone and other androgens, beginning early in gestation (New 1998; Pang et al. 1980; Wudy et al. 1999). For affected girls, this high level of androgen exposure typically results in partial masculinization of the external genitalia (fused labia, penile enlargement) at birth, and the diagnosis is usually made soon thereafter. The diagnosis of CAH is generally followed by female sex assignment and rearing and lifelong treatment with corticosteroids to regulate hormone levels postnatally. Girls and women with CAH have female internal genitalia and reproductive potential.

Androgen and the Development of the Human Brain and Human Behavior

The masculinizing influences of elevated androgens during early life in girls with CAH are not limited to the external genitalia. Girls with CAH show increased male-typical toy, playmate and activity preferences and decreased interest in toys and activities usually preferred by girls. This outcome has been reported in numerous studies from different research groups, in different countries and using a range of assessment tools (Berenbaum and Hines 1992; Dittmann et al. 1990; Ehrhardt et al. 1968; Ehrhardt and Baker 1974; Hines et al. 2004; Nordenstrom et al. 2002; Pasterski et al. 2005, 2011; Slijper 1984; Zucker et al. 1996). It has been suggested that the increased male-typical behavior in girls with CAH might not reflect a masculinizing effect of androgen on the developing brain and behavior but rather

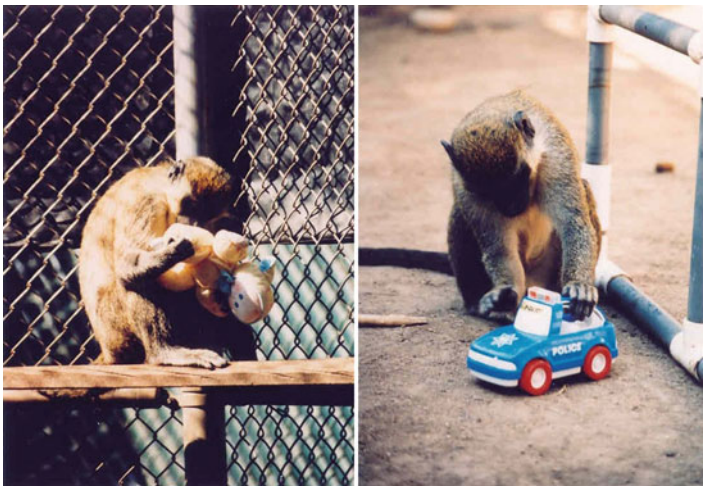

Fig. 1 Sex-typical toy play in female and male vervet monkeys resembles that of children. *Left*: A female vervet with a doll. *Right*: A male vervet with a toy car (Reprinted with permission from Alexander and Hines 2002)

consequences of other aspects of the CAH disorder, or even processes set into motion by the knowledge of genital virilization at birth (Fausto-Sterling 1992; Jordan-Young 2010). It is therefore important to see if normal variability in testosterone exposure prenatally relates to normal variability in sex-typed behavior in children with no disorder and no genital virilization. For childhood toy and activity interests, this evidence exists. For instance, testosterone measured in maternal blood during pregnancy (Hines et al. 2002) or in amniotic fluid (Auyeung et al. 2009) has been linked to male-typical childhood play behavior. In addition, there is evidence that non-human primates show sex-typed toy interests similar to those seen in children (Alexander and Hines 2002; Hassett et al. 2008), suggesting an inborn, probably hormonal, contribution to this behavior (Fig. 1).

This evidence of prenatal androgenic influences on children's toy preferences and the observation of sex-typed object preferences in non-human primates has led to a reconceptualization of the origins of children's sex-typed toy preferences. These preferences were widely assumed to result from socialization, intended to provide rehearsal for the sex-typed social roles of women and men. The existence of inborn influences has led to investigations of the object features that might make certain toys more or less interesting to brains exposed prenatally to different amounts of testosterone. Girls' and boys' toys differ in shape, with girls' toys tending to be rounded and boys' toys tending to be angular. They also differ in color, with girls' toys tending to be pink whereas boys' toys are not and may be any number of stronger colors, including blue. Sex differences in toy preferences have been documented in infants as young as 12–24 months of age (Campbell et al. 2000; Jadva et al. 2010; Serbin et al. 2001), before sex differences in preferences for pink or rounded shapes emerge (Jadva et al. 2010; Lo Bue and De Loache 2011),

Table 1 Human psychological and behavioral sex differences: evidence of relationship to prenatal androgen exposure

Characteristic	Altered in females with CAH?	Related to normal variability?
Juvenile play interests	YES	yes
Sexual orientation	YES	insufficient information
Core gender identity	YES	insufficient information
Physical aggression	yes	insufficient information
Empathy	yes	yes

YES independent replication exists, *yes* a study or studies from one research group exist, *maybe* results from different research groups are contradictory, *no* the existing evidence does not support an association, *insufficient information* the relevant studies are not available

suggesting that the toy preferences do not result from the color or shape preferences. An alternative suggestion is that the toys that boys like tend to be those that can be moved through space and that prenatal androgen exposure increases interest in watching things move in space (Alexander and Hines 2002; Alexander 2003; Hines 2004), perhaps by altering the development of visual or motor systems (Alexander 2003; Hines 2004, 2011).

Although the strongest evidence linking prenatal testosterone exposure to human behavior comes from studies of children's sex-typed play, there is also evidence linking early testosterone concentrations to other behaviors (Cohen-Bendahan et al. 2005; Hines 2009, 2011; Table 1). For some outcomes, like core gender identity or the sense of self as male or female, the evidence comes from a number of studies from several independent researchers investigating CAH (Dessens et al. 2005; Meyer-Bahlburg et al. 1996; Zucker et al. 1996), as well as research on other disorders of sex development that involve atypical androgen exposure during early development (Cohen-Kettenis 2005; Meyer-Bahlburg 2005), but not, at least as yet, from studies of normal variability. The situation is similar for sexual orientation, in regard to which several independent studies of women with CAH have reported reduced heterosexual orientation (Dittmann et al. 1992; Frisén et al. 2009; Hines et al. 2004; Meyer-Bahlburg et al. 2008; Money et al. 1984), but evidence of a link to normal variability in testosterone is lacking. For other characteristics, such as empathy and tendencies to physically aggressive behavior, there is evidence from one or more studies of individuals with CAH (Berenbaum and Resnick 1997; Mathews et al. 2009; Pasterski et al. 2007) and from studies of normal variability in testosterone, or hormonal treatment (Chapman et al. 2006; Reinisch 1981) but, as yet, limited or no consistent independent replication of either of these types of finding.

In addition, although there is evidence supporting a role for the early hormone environment in the development of human gender-related behavior, other factors, including socialization and cognitive developmental processes, also play a role, and the magnitude of this role appears to vary across behavioral outcomes (Hines 2004). In addition, the development of human sex-typical behavior involves mechanisms

related to cognitive understanding of gender—mechanisms that are unlikely to operate in other species. The next section of this chapter describes the socialization and cognitive developmental processes that are thought to influence the development of gender-related behavior in human beings.

Socialization and Cognitive Developmental Influences on Human Gender Development

After birth, the human infant encounters processes of socialization, and these are thought to influence the development of gender-related behavior. For instance, parents decorate rooms differently and dress children differently, depending on their gender (Maccoby and Jacklin 1974; Rheingold and Cook 1975). Parents also are more likely to respond positively to their children's gender-typical behavior than to their gender-atypical behavior; boys, in particular, are discouraged from engaging in play with girls' toys or girls' activities (Fagot 1978; Lytton and Romney 1991; Pasterski et al. 2005). Children also sex segregate, spending much of their time with other children of the same sex (Maccoby and Jacklin 1987; Maccoby 1998), and children, like parents, encourage girl-typical play in girls and boy-typical play in boys (Fagot and Patterson 1969; Fagot 1977), as do teachers (Fagot and Patterson 1969; Fagot 1977) and strangers (Seavey et al. 1975; Stern and Karraker 1989). Perhaps as a consequence, children's behavior becomes more sex stereotyped as they progress through early and middle childhood (Golombok et al. 2008; Maccoby 1998). Very little direct evidence is available as to whether or not the widespread encouragement of sex-typical play increases children's subsequent sex-typical behavior. One study has found that the amount of parental encouragement of sex-typical toy play correlates positively with the sex-typical toy choices of their typically developing children (Pasterski et al. 2005), but in general this question has not been studied. Perhaps investigations directly examining the effect of reinforcement of sex-typical play on subsequent behavior are lacking because of the extensive evidence documenting the effects of reinforcement on behavior in general.

Humans are perhaps unique among animals in having a cognitive understanding of their own gender. There is no evidence, for instance, that individuals of any other species sort the world into males and females and know the group to which they themselves belong, much less that they have an identity related to their belonging to that group.

Children can accurately sort pictures of males and females and can add their picture to the correct pile by about the age of two (Slaby and Frey 1975; Stagnor and Ruble 1987). In subsequent years, they come to understand that their gender will not change over time and that their gender will not change if they change their appearance or the activities in which they engage (Slaby and Frey 1975; Stagnor and Ruble 1987). This developing gender understanding is thought to contribute to children's gender-related behavior, beginning with the first stage of understanding at about age 2. As evidence of this, children's behavior becomes increasingly

gender typed across the ages when their gender understanding is increasing (Golombok et al. 2008; Maccoby 1998). In addition, the sophistication of children's gender understanding has been found to relate to some aspects of their gender-typed behavior (Leinbach and Fagot 1986), and children who have gender identity disorder, and engage in extensive cross-gendered behavior including sex-atypical play, show delayed gender understanding (Zucker et al. 1999).

Boys and girls also engage in processes related to gender identification that contribute to their acquisition of sex-typical behavior. For instance, once they understand that they are male or female, they preferentially model the behavior of others of their own sex and prefer items that have been labelled as for their own sex. For example, if shown men consistently choosing items such as bananas, and women consistently choosing items such as apples, or vice versa, they are later more likely to show a preference for the items that they saw chosen by individuals of their own sex (Perry and Bussey 1979; Masters et al. 1979). Similarly, children respond to labels that tell them that certain toys or activities are "for girls" or "for boys." For example, if told that white balloons are for girls and green balloons are for boys, or vice versa, they are later more likely to indicate a preference for the balloons of the color that they were told was for their own sex (Masters et al. 1979).

Cascading Effects of Early Androgen Exposure on Cognitive Understanding of Gender and on Other Aspects of Gender Development

Women exposed to high levels of androgens prenatally, because they have CAH, are at increased risk of dissatisfaction with the female sex of assignment and of gender dysphoria, and gender change. Although most girls with CAH develop a female gender identity, about 2–5 % of individuals with CAH, who were raised as girls, choose to live as men in adulthood (Dessens et al. 2005; Meyer-Bahlburg et al. 1996; Zucker et al. 1996). In addition, even among women with CAH who identify as female, this identification is not as strong as it is in women without CAH (Hines et al. 2004). Other disorders of sex development that involve androgen abnormality in either XX or XY individuals also are associated with an increased likelihood of gender dysphoria and change from the assigned sex (Cohen-Kettenis 2005; Meyer-Bahlburg 2005). In childhood as well, girls with CAH, or girls exposed to high levels of androgens prenatally or other disorders of sex development, are at increased risk of gender identity problems (Slijper et al. 1998) and are more likely than other girls are to express satisfaction with being a girl (Ehrhardt et al. 1968) and to say that they might not have chosen to be a girl if given the choice (Ehrhardt and Baker 1974).

This reduced gender identification could contribute to increased male-typical behavior in girls with CAH. This may also be the case for girls exposed to relatively high levels of androgens for other reasons, including genetic variability in androgen

production or sensitivity within the normal range. How might these cognitive processes influence the acquisition of sex-typed behavior? Sex-typed toy preferences are apparent before the age of 2 (Campbell et al. 2000; Jadva et al. 2010; Serbin et al. 2001), before the age at which children can be shown to have even an initial understanding that they are a girl or a boy. In addition, the evidence of sex-typed toy preferences in non-human primates (Alexander and Hines 2002; Hassett et al. 2008), similar to those seen in children, argues for some inborn component to these preferences. It is possible that the development of a range of gendered behaviors starts with prenatal hormone influences on neural systems regulating object preferences, as evidenced in sex-typed toy preferences. Later, when children have come to understand that the world includes males and females, and that they are male or female, they will also have learned that they like the toys that other children of their own, or of the other sex, typically like, and this may further influence gender-typical or -atypical behavior. For instance, if a girl has cross-gendered toy interests because she was exposed to relatively high levels of testosterone prenatally, she may anticipate that she would like other toys and activities that are for boys and so seek these out. In addition, her interest in, engagement with, and enjoyment of boys' toys and activities could reduce her identification with and enjoyment of the female role, which could in turn lead to reduced modeling of individuals of the female sex and reduced interest in objects and activities that are labeled as for girls, accompanied by increased modeling of males and increased interest in objects and activities that are labeled as for boys. These mechanisms could then lead to further changes in behavior, including changes in behaviors other than object (e.g., toy) interests. Thus, social-cognitive mechanisms, such as gender identification and responses to models and labels related to gender, may be part of the cascade of processes involved in the influence of testosterone on sexual differentiation of human behavior, and, indeed, may be unique to human beings. Thus, human beings may share one mechanism of neurobehavioral sexual differentiation with other species, a mechanism involving prenatal actions of testosterone and its metabolites on basic processes of neural development. In addition, these effects may be compounded in humans by an additional mechanism set into motion by these prenatal hormone effects but involving the uniquely human cognitive understanding of gender and the acquisition of sex-typed behavior through processes such as modelling of sex-typical behavior and responses to labels as to what is and is not associated with one's own sex.

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