



Published in final edited form as:

*Early Hum Dev.* 2008 December ; 84(12): 805–807. doi:10.1016/j.earlhumdev.2008.09.006.

## Early androgen influences on human neural and behavioural development

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### Abstract

Gonadal hormones, particularly androgens, influence sexual differentiation of the body, as well as the brain and behaviour. Ante-natal exposure to atypical hormone environments leads to alterations in human behaviours that show sex differences. These include childhood play, sexual orientation, gender identity, and personality characteristics, such as empathy and aggression. Individual variability among healthy children in antenatal hormone exposure show similar relationships to individual variability in postnatal behaviour. As in studies of atypical exposure, higher levels of androgen predict more male-typical, and less female-typical, behaviour. Hormone-induced alterations in brain development are thought to underlie these behavioural outcomes, although there is little information on specific neural differences associated with early hormone differences. Notable, however, is evidence relating early androgen exposure to activation of the medial amygdaloid nucleus in women. Other emerging research areas include the role of neonatal hormones in infant development and interactions between hormone-induced predispositions and postnatal experience in producing behavioural outcomes.

### Keywords

testosterone; androgen; behaviour; prenatal; antenatal; development; brain; human; sex; gender

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Gonadal hormones play an important role in early human development, influencing not only physical characteristics, but also behaviour. The fetal testes are active as early as week 8 of gestation, and produce testosterone prenatally in amounts similar to those seen in adulthood. As a consequence, male fetuses are exposed to higher levels of testosterone than are female fetuses.

### A1: Sex differences in gonadal hormones during early human development

There appear to be two peaks in testosterone production in males early in life. The first is thought to occur from about week 8 to week 24 of gestation, and the second from about the first to the sixth month of infancy. The first surge influences behavioural development, as well as physical development, but little is known about the role of the second surge. The fetal ovaries are thought to produce little or no estrogen or progesterone prenatally, but there is a neonatal surge of estrogen in female infants. Again, little is known about the importance of this neonatal

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hormone surge for physical, neural or behavioural development. Although female fetuses are thought not to produce gonadal steroids, the adrenal gland is active in both male and female fetuses, and, as will be detailed below, individual variability in androgen exposure prenatally influences human behaviour postnatally, in both girls and boys. (See 1 for a more extensive discussion of gonadal hormones during early human development and their behavioural consequences).

## **A2: Gonadal hormone influences on neural and behavioural development in non-human mammals**

The rationale for hypothesizing that hormones influence human behavioural development comes from experimental research in other species. Treating female rodents or non-human primates with testosterone during early development increases behaviours that are more common in males than in females, and decreases behaviours that are more common in females than in males. The behaviours that are subject to these early influences of hormones include reproductive behaviours, as well as others that differ on the average for male and female animals. For example, treating pregnant female rhesus monkeys with testosterone produces female offspring who show increased levels of male-typical rough-and-tumble play as juveniles, as well as increased male-typical sexual behaviour and decreased female-typical sexual behaviour in adulthood.

The behavioural effects of early exposure to gonadal steroids are thought to occur because testosterone, and hormones produced from it, play an important role in brain development, directing some aspects of neural development during early life and thus influencing the underlying organization of the brain<sup>2</sup>. Perhaps the best-known example of the neural influences of gonadal steroids involves a sub-region of the anterior hypothalamic/preoptic area (AH/POA) called the sexually dimorphic nucleus of the preoptic area (SDN-POA). This nucleus is several times larger in male than in female rats, and treating female animals with testicular hormones during early life enlarges the nucleus, whereas withdrawing these hormones from developing males reduces it<sup>2</sup>. Additional research on the SDN-POA and other neural regions that show sex differences has demonstrated that the early hormone environment can influence brain development by determining which cells live and die, what other neural regions they connect to anatomically and which neurotransmitters they use<sup>3</sup>.

## **A3: Gonadal hormone influences on human development**

Ethical constraints generally preclude experimental manipulations of gonadal hormones during human development. Consequently, information about the early influences of testosterone on human brain and behaviour has come largely from clinical syndromes that cause hormonal abnormality during early life, particularly the autosomal recessive disorder, classical congenital adrenal hyperplasia (CAH). Some information also has come from studies relating normal variability in hormones early in life to subsequent behaviour.

### **B1: Classical CAH**

Classical CAH is an autosomal recessive disorder that occurs in approximately 1 in 10,000 live births in North America; in about 90% of cases, the underlying problem is a deficiency in the enzyme, 21-hydroxylase (21-OH)<sup>4</sup>. Because 21-OH is needed to produce cortisol, precursors to cortisol are shunted into the androgen pathway, and testosterone and other androgens are overproduced. In male fetuses, sexual development appears to progress normally, perhaps because feedback mechanisms allow reduction in testicular androgens to compensate for adrenal overproduction. In female fetuses, however, testosterone is elevated dramatically, and this elevation produces alterations in the external genitalia that are apparent at birth. Typically,

the external genitalia of affected girls are masculinised by the prenatal androgen exposure, with some degree of clitoral enlargement and labial fusion. In rare cases, the virilisation is so extreme that the girls are mistakenly assigned at birth as boys, but, typically, the genitalia are ambiguous and the diagnosis of CAH is made within days. Corticosteroid treatment is then initiated to regulate cortisol and androgen levels postnatally and the girl is assigned and reared in the female sex. In many cases, the external genitalia are also surgically corrected in infancy. There are two primary types of classical CAH, salt-losing and simple virilising, with the salt-losing form being the more severe.

Studies of girls with classical CAH suggest that their prenatal androgen exposure has influenced not only their external genitalia, but also their brains and their behaviour. The most consistent evidence of altered behaviour comes from studies of childhood play. Girls with classical CAH show increased interest in toys usually preferred by boys, such as vehicles and weapons, and reduced interest in toys usually preferred by girls, such as dolls and tea sets. They also show increased preferences for boys as playmates and for rough, active play styles. These results have been reported in studies from several research groups in North America and Western Europe, and are seen when the girls with CAH are compared to controls matched for sex and age or to unaffected female relatives of similar age 5. The size of the behavioural change has also been related to the specific genetic problem underlying the disorder and to the type of CAH (salt-losing versus simple virilizing), with more severe disorder associated with more male-typical childhood behaviour and toy interests 6,7.

The findings of altered toy preferences in girls with CAH challenge the view that differences in the toy preferences of girls and boys result solely from socialization, such as exposure to sex-typed advertisements or encouragement by parents, peers and others to play in sex-appropriate ways. Augmenting the data from children with CAH, however, is evidence that non-human primates show sex differences in toy preferences similar to those seen in children 8,9. These findings suggest that the different toy preferences shown by girls and boys are not wholly caused by socialization, but are, to some extent, part of our evolutionary heritage. It is likely that the early hormone environment provides a proximal mechanism for transmitting this heritage.

Although other behaviours have not been studied as extensively as has childhood play, there also is evidence linking antenatal androgen to sexual orientation. For instance, although the majority of females with CAH are heterosexual, as a group they are more likely than their unaffected female relatives or matched controls to be bisexual or homosexual in orientation, and this effect, like the effect on childhood play, is more marked in women who have the more severe, salt-losing, form of CAH than in those with the less severe, simple virilizing, form 10. There also is evidence of increased physical aggression and activity level in girls with CAH 11 and of enhanced ability to throw darts and balls at targets with accuracy 12, decreased empathy and interest in infants, along with increased physical aggression 13 and reduced satisfaction with the female sex of assignment 14 in adolescent females and women with CAH.

## **B2: Normal variability in hormones**

Studies relating normal variability in prenatal hormone exposure to postnatal behaviour also support a prenatal influence of testosterone on human development. One study, of a longitudinal, general population sample of pregnant women and their children, looked at testosterone in blood samples taken during pregnancy from mothers of girls who were extremely masculine, extremely feminine or typical in their gender-related behaviour at age 3.5 years. The study found a significant linear relationship between the mother's total and free testosterone during pregnancy and the daughter's sex-typical behaviour, with mothers of extremely masculine girls having the most testosterone, mothers of typical girls having the next most, and mothers of extremely feminine girls having the least 15. Another study found

that testosterone measured prenatally in amniotic fluid related positively and linearly to masculine sex-typed childhood behaviour in boys and in girls from the general population 16. Amniotic fluid testosterone also has been related to vocabulary scores in infants and to empathy in children 17,18.

#### A4: Neural changes underlying behavioural changes

The behavioural consequences of early variability in gonadal hormones are assumed to result from neural changes similar to those documented in other species, but surprisingly few studies have looked at neural differences related to the prenatal hormone environment in humans. One report found that females with CAH show masculinized function of the medial amygdaloid nucleus (MA) while viewing emotional faces 19. This finding fits well with evidence that the MA is involved in emotion regulation, as well as aggression, and is sensitive to androgen exposure during early life in other species 3.

#### A5: Research directions

An area that merits future investigation is elucidating the role of the postnatal surge in androgen in males and estrogen in females for behavioural development. The human brain continues to undergo extensive restructuring during the first two years of postnatal life and these neonatal surges in gonadal hormones could regulate some of this neural development, much as it appears to do during the prenatal period. These neonatal influences could be particularly important for cognitive sex differences, given that the cerebral cortex is undergoing rapid development during this period of early life. A second area that promises to produce important new information involves identifying the precise neural changes that are induced by variability in the prenatal hormone environment in humans. Research in other species points to several sub cortical regions, including the medial preoptic area and the bed nucleus of the stria terminalis, as well as the MA. In addition, the human cerebral cortex differs more dramatically from other species than do sub cortical regions, and hormones may alter cortical development as well. A third missing link is evidence regarding hormone-related behaviour during infancy, and information on how hormone-induced behavioural predispositions in infancy might interact with the early social environment to determine individual differences in subsequent behaviour. We know, for instance, that by three years of age girls and boys show clear preferences for different types of toys, with girls tending to choose dolls and tea sets and boys tending to choose vehicles and weapons. Hormone-related differences in toy choices also are seen in children beginning at about this age. However, we know little about how hormones relate to behaviours earlier in life and how hormone-related differences between girls and boys, or between children of the same sex who were exposed to different hormone environments early in life, might elicit different behaviors from parents or other caretakers. These are three exciting areas for future research.

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