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Age-specific changes in sex steroid biosynthesis and sex development

Nils Krone MD

Wellcome Trust Clinician Scientist Fellow

Division of Medical Sciences, Institute of Biomedical Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Neil A. Hanley PhD

Professor of Endocrinology

Centre for Human Development, Stem Cells & Regeneration, and Human Genetics Division, University of Southampton, Southampton, SO16 6YD, UK

Wiebke Arlt* MD, DSc, FRCP

Professor of Medicine, MRC Senior Clinical Fellow

Division of Medical Sciences, Institute of Biomedical Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Normal male sex development requires the SRY gene on the Y chromosome, the regression of Müllerian structures via anti-Müllerian hormone (AMH) signalling, the development of the Wolffian duct system into normal male internal genital structures consequent to testosterone secretion by the testicular Leydig cells, and finally, sufficient activation of testosterone to dihydrotestosterone by 5α-reductase. All these events take place during weeks 8–12 of gestation, a narrow window of sexual differentiation. Recent studies in human fetal development have demonstrated the early fetal expression of the adrenocorticotrophic hormone (ACTH) receptor and all steroidogenic components necessary for the biosynthesis of cortisol. These findings provide compelling evidence for the assumed pathogenesis of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency, diminished feedback to the pituitary due to glucocorticoid deficiency, subsequent ACTH excess, and up-regulation of adrenal androgen production with subsequent virilization. Another CAH variant, P450 oxidoreductase deficiency, manifests with 46,XX disorder of sex development (DSD), i.e., virilized female genitalia, despite concurrently low circulating androgens. This CAH variant illustrates the existence of an alternative pathway toward the biosynthesis of active androgens in humans which is active in human fetal

* Corresponding author. Tel.: +44 121 415 8716; Fax: +44 121 415 8712.
E-mail address: w.arlt@bham.ac.uk (W. Arlt).

life only. Thus CAH teaches important lessons from nature, providing privileged insights into the window of human sexual differentiation, and particularly highlighting the importance of steroidogenesis in the process of human sexual differentiation.

Key words: fetal adrenal; fetal gonad; sex development; urogenital ridge; bitpotent gonad; androgen; cortisol; testosterone; dehydroepiandrosterone; DHEA; CYP21A2; 21-hydroxylase; CYP17A1; 17alpha-hydroxylase; POR; P450 oxidoreductase; congenital adrenal hyperplasia; CAH; P450 oxidoreductase deficiency.

This review examines the impact of steroidogenesis: specifically, the impact of age-associated changes in steroidogenic enzyme expression on human fetal sex development. This will be done both in the context of normal human sexual differentiation and disordered sex development (DSD) as exemplified by variants of congenital adrenal hyperplasia (CAH). This will be done with a specific emphasis on 46, XX DSD, i.e. virilization of the female external genitalia, a characteristic feature observed in patients with CAH caused by 21-hydroxylase deficiency and in CAH due to P450 oxidoreductase deficiency.

MAJOR EVENTS IN HUMAN SEXUAL DIFFERENTIATION

After approximately 3 weeks of human embryonic development the gonad is visible for the first time. At this early stage, female and male gonads show the same morphology and present as a thickening on the inner surface of the mesonephros, the equivalent to the primitive kidney system. However, only 4 weeks later – i.e. during the 7th week of gestation – the differentiation of the indifferent gonad into either ovary or testis begins. A key event in this process is SRY gene expression in those cells destined to differentiate into testicular Sertoli cells, which collocate with the germ cells in the sex cord.[1–3] As a consequence of paracrine action of mediators secreted by the Sertoli cells, the development of the primordial germ cells arrests at the stage of prospermatogonia.[4] At the same time, anti-Müllerian hormone (AMH, also known as Müllerian-inhibiting substance, MIS), a member of the tumour growth factor β (TGF-β) family, elicits male sexual differentiation via signalling through two cell-surface receptors, AMH receptors 1 and 2.[5] AMH induces the regression of the mesonephric ducts, Müllerian structure precursors that would otherwise differentiate into oviducts, uterus and upper third of the vagina. Mutations in AMH[6] and AMHR2[7] provide impressive evidence for this chain of events as they lead to persistent Müllerian duct syndrome.[8,9] The next step towards male differentiation is the development of Leydig cells. Androgen secretion by the Leydig cells is a mandatory precondition for the development of a male genital phenotype, with the Wolffian structures developing into normal male internal genital structures under the influence of testosterone.[10] Androgen action results in a midline fusion of the urethral folds closing the urogenital sinus. The genital swelling differentiates into the scrotum, and the phallus extends into the penis. Testosterone is converted to dihydrotestosterone by 5α-reductase type 2 (SRD5A2), the androgen with the highest affinity for the androgen receptor. SRD5A2 deficiency[11] illustrates the importance of dihydrotestosterone for external virilization, as 46,XY individuals with this condition have normal male internal structures but their external genitalia are of female appearance.[12–14]

Thus, taken together, normal male sex determination and differentiation require the SRY gene on the Y chromosome, the regression of Müllerian structures via