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Steroidogenesis of the testis – new genes and pathways

Stéroïdogenèse testiculaire – nouveaux gènes et nouvelles voies

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Abstract

Defects of androgen biosynthesis cause 46,XY disorder of sexual development (DSD). All steroids are produced from cholesterol and the early steps of steroidogenesis are common to mineralocorticoid, glucocorticoid and sex steroid production. Genetic mutations in enzymes and proteins supporting the early biosynthesis pathways cause adrenal insufficiency (AI), DSD and gonadal insufficiency. The classic androgen biosynthesis defects with AI are lipoid CAH, *CYP11A1* and *HSD3B2* deficiencies. Deficiency of *CYP17A1* rarely causes AI, and HSD17B3 or *SRD5A2* deficiencies only cause 46,XY DSD and gonadal insufficiency. All androgen biosynthesis depends on 17,20 lyase activity of *CYP17A1* which is supported by P450 oxidoreductase (*POR*) and cytochrome b5 (*CYB5*). Therefore 46,XY DSD with apparent 17,20 lyase deficiency may be due to mutations in *CYP17A1*, *POR* or *CYB5*. Illustrated by patients harboring mutations in *SRD5A2*, normal development of the male external genitalia depends largely on dihydrotestosterone (DHT) which is converted from circulating testicular testosterone (T) through *SRD5A2* in the genital skin. In the classic androgen biosynthetic pathway, T is produced from DHEA and androstenedione/-diol in the testis. However, recently found mutations in *AKR1C2/4* genes in undervirilized 46,XY individuals have established a role for a novel, alternative, backdoor pathway for fetal testicular DHT synthesis. In this pathway, which has been first elucidated for the tammar wallaby pouch young, 17-hydroxyprogesterone is converted directly to DHT by 5α-3α reductive steps without going through the androgens of the classic pathway. Enzymes *AKR1C2/4* catalyse the critical 3αHSD reductive reaction which feeds 17OH-DHP into the backdoor pathway. In conclusion, androgen production in the fetal testis seems to utilize two pathways but their exact interplay remains to be elucidated.

Keywords: Disorder of sexual development; Lipoid congenital adrenal hyperplasia; *CYP11A1*; *HSD3B2*; *CYP17A1*; *HSD17B3*; *SRD5A2*; *POR* and *CYB5* deficiencies; *AKR1C2/4* genes

Résumé

Les défauts de la biosynthèse des androgènes entraînent des troubles du développement sexuel de type 46 XY. Tous les stéroïdes sont produits à partir du cholestérol et les étapes précoces de la stéroïdogenèse sont communes aux axes minéralo-corticoïde, gluco-corticoïde et à la production de stéroïdes sexuels. Les mutations des gènes codant pour les enzymes et les protéines impliqués dans les étapes précoces de la biosynthèse entraînent une insuffisance surrénale (AI), des troubles du développement sexuel et une insuffisance gonadique. Les anomalies classiques de la biosynthèse des androgènes associées à une insuffisance surrénale sont l'hyperplasie congénitale lipoïde des surrénales et les déficits en *CYP11A1* et *HSD3B2* (hydroxy-stéroïde-déshydrgogénase 3B2). Les déficits en *CYP17A1* entraînent rarement une insuffisance surrénale et les déficits en *HSD17B3* (hydroxyl-stéroïde-déshydrogénase 17B3) ou en *SRD5A2* induisent seulement un trouble du développement sexuel de type 46 XY et une insuffisance gonadique. Toute la biosynthèse des androgènes dépend de l'activité 17, 20 lyase du gène *CYP17A1* porté par le complexe

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oxydoréductase P450 (*POR*) et le cytochrome B5 (CYB5). Ainsi, les troubles du développement de type 46 XY avec des déficits apparents en 17, 20 lyase peuvent être liés à des mutations de *CYP17A1*, de *POR* ou de *CYB5*. Comme le montrent les patients qui présentent une mutation de *SRD5A2*, le développement normal des organes génitaux externes masculins dépend largement de la dihydrotestérone (DHT) convertie à partir de la testostérone testiculaire circulante (T) par l'intermédiaire de *SRD5A2* dans le revêtement cutané testiculaire. Au cours de la biosynthèse classique des androgènes, la testostérone est produite à partir de la DHEA et de l'androsténédione/-diol dans le testicule. Cependant, des mutations récemment identifiées dans les gènes *AKR1C2/4* chez des individus 46 XY peu virilisés, ont montré le rôle d'une nouvelle voie de biosynthèse alternative de recours permettant la production de dihydrotestostérone testiculaire fœtale. Par cette voie, d'abord identifiée chez le jeune Wallaby Tammar lorsqu'il vit encore dans la poche de sa mere, la 17 OH progesterone est convertie directement en dihydrotestostérone par une étape de reduction 5α-3α qui court-circuite la biosynthèse classique des androgènes. Les enzymes *AKR1C2/4* catalysent l'étape de réduction critique passant par la 3α hydroxy-stéroïde-déshydrogénase (3αHSD) qui oriente la 17 hydroxy-dihydroxyprogestérone vers la voie de recours. En conclusion, la production d'androgènes dans le testicule fœtal semble utiliser 2 voies de biosynthèse mais leurs inter-relations exactes demeurent à élucider.

Mots clés : Troubles du développement sexuel ; Hyperplasie congénitale lipoide des surrénales ; Déficits en *CYP11A1* ; *HSD3B2* ; *CYP17A1* ; *HSD17B3* ; *SRD5A2* ; *POR* ; *CYB5* ; Gène *AKR1C2/4*

1. Introduction

The human testis is a complex organ comprised of two distinct units, the androgen biosynthesis unit in the Leydig cells of the interstitial compartment and the sperm producing unit nourished by the Sertoli cells of the seminiferous tubule compartment which makes around 90% of the testis volume [1]. Testosterone (T) production of the testis plays a critical role in sex development, sexual function and reproduction. Early in fetal life (4–5 weeks gestation), the neutral anlage is determined by 46,XY chromosomes to become a testis (Fig. 1). From then on T production together with Anti-Müllerian hormone and sex differentiating factors will lead to normal male sex differentiation. In this process T and more so dihydrotestosterone (DHT) are particularly crucial for the formation of the normal male external genitalia. Soon after birth, minipuberty is observed in the first 6 months of life with elevated testosterone production [2]. This phenomenon is of unknown function but offers a window of opportunity for functional testing of the testis before it becomes hormonally quiescent till puberty. Stimulated by the hypothalamic-pituitary hormones, the testis resumes androgen biosynthesis at puberty to prompt the development of secondary male sex characteristics and initiate sexual function and spermatogenesis for reproduction in adult life. Thus it is easy to understand that abnormalities in androgen biosynthesis cause disorders of sex development (DSD) and function.

The biochemical pathway for T synthesis is long known. But recently, an alternative, so-called "backdoor" pathway for the production of DHT, not using DHEA, androstenedione and T as precursors (Fig. 2), has been described first in the tammar wallaby pouch young [3,4]. We have found mutations in genes of this backdoor pathway (*AKR1C2/4*/3αHSDs) in subjects manifesting with moderate to severe forms of 46,XY DSD [5,6]. However, the role of this novel pathway in human androgen biosynthesis is largely unknown.

2. Normal steroid biosynthesis

All steroid hormones are produced from cholesterol through a cascade of enzymes which are encoded by genes that are common to all steroid producing organs [7]. In most cases the organ specific gene expression determines the steroid profile of each specialized organ. For instance, the testis is determined to produce androgens from cholesterol (Fig. 2). The cholesterol molecule is transported to the inner mitochondrial membrane by the steroidogenic acute regulatory protein (StAR) where cholesterol is the substrate for the first step of steroidogenesis. In the mitochondria cholesterol is converted to pregnenolone by the side chain cleavage system comprised of *CYP11A1* (P450scc), ferrodoxin (FDX1) and ferrodoxin-reductase (FDXR). In the classic pathway, pregnenolone is then converted through the delta 5 pathway by *CYP17A1* (P450c17) to 17α-hydroxypregnenolone (17OHPreg) and dehydroepiandrosterone (DHEA) with the first reaction catalysed by its 17α-hydroxylase activity supported by P450 oxidoreductase (*POR*) and the second reaction by the 17,20 lyase activity supported by *POR* and cytochrome b5 (*CYB5*). DHEA is then turned over to testosterone through androstenedione or androstenediol catalyzed by 3β-hydroxysteroid dehydrogenase type II (HSD3B2/3βHSDII) and 17β-hydroxysteroid dehydrogenase 3 (HSD17B3/17βHSD3). Testosterone may be converted to DHT which has about 10-times more affinity for the androgen receptor. This conversion is catalyzed by 5α-reductase type II (*SRD5A2*/5αRed2) which is expressed in genital skin and the prostate. In humans, only little conversion to androstenedione occurs through the delta 4 pathway coming from progesterone (Prog) and 17-hydroxyprogesterone (17OHP) because 17,20 lyase activity is poor on the substrate 17OHP compared to 17OHPreg [8].

By contrast, the human adrenal cortex produces from cholesterol not only androgens, but also mineralocorticoids and glucocorticoids through the expression of steroidogenic enzymes 21-hydroxylase (CYP21A2/P450c21) and 11β-hydroxylase, aldosterone synthase (CYP11B1/2/P450c11β, P450c11AS) as well as mainly differential expression of *CYP17A1*. In principal, non-expression of *CYP17A1* leads to mineralocorticoid production in the zona glomerulosa, expression of *CYP17A1* and activity of 17α-hydroxlyase in the zona fasciculata leads to glucocorticoid production, while additional CYP17's lyase activity in the zona reticularis leads to the production of adrenal C19 steroids, namely DHEA and