Editorial

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Commentary on "Classic and backdoor pathways of androgen biosynthesis in human sexual development"

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Steroidogenesis is the process by which cholesterol is converted into biologically active steroid hormones.[1] Sex steroids are hormones that determine human sexual development and affect the quality of life. In particular, androgen and dihydrotestosterone (DHT) are essential for male sexual differentiation. DHT is a more potent androgen that virilizes the male external genitalia and urethra[2]; it is the end-product of the classical and backdoor pathways of androgen synthesis.

The classical pathway is widely regarded as the only androgen synthesis pathway. The process is initiated in mitochondria, where cholesterol is converted to pregnenolone by the P450scc cholesterol side-chain cleavage enzyme. Pregnenolone is converted to 17OH-pregnenolone by the P450c17 17α-hydroxylase. Then, 17OH-pregnenolone is converted to dehydroepiandrosterone by 17,20 lyase. Dehydroepiandrosterone is converted to androstenedione by 3β-hydroxysteroid dehydrogenase type 2 in the adrenal gland and testis. Androstenedione is converted to testosterone by 17β-hydroxysteroid dehydrogenase type 3, mainly in the testes. Testosterone is converted to DHT by 5α-reductase type 2 in the genital skin.[3] Therefore, the testis is indispensable for male sexual differentiation.

The androgen backdoor pathway bypasses the usual intermediate steroids of dehydroepiandrosterone, androstenedione, and testosterone.[4] 17OH-Pregnenolone is usually converted to 17OH-progesterone, which is 5α-reduced by 5α-reductase type 1 to 5α-pregnan-17α-ol-3,20-dione; this is 3α-reduced by AKR1C2 or AKR1C4 to yield 17OH-allopregnanolone. 17OH-Allopregnanolone is converted to androsterone by 17,20 lyase. 17β-Hydroxysteroid dehydrogenase type 3/5 converts androsterone to androstenediol, which is 3α-oxidized to produce DHT.[3]

O'Shaughnessy et al.[5] measured plasma and tissue levels of endogenous steroids in second-trimester human fetuses. They reported that androsterone is the principal backdoor androgen in the human fetus; moreover, placental progesterone is a major substrate for backdoor androgen synthesis, which occurs in the placenta, fetal liver, and adrenal gland. This means that the testis is no longer the supreme organ responsible for fetal male sexual development—it is necessary but not sufficient to produce androgenic steroids.[3] Both the testis and backdoor androgens are needed for sexual development of the male fetus. Thus, both classical and backdoor pathways are required for normal human male genital development.[6]

Lee and Kim[7] described the classical and backdoor pathways of androgen biosynthesis; they reported that the backdoor pathway has a role in hyperandrogenic disorders. Approximately 20 years have passed since the human androgen backdoor pathway was revealed, but there remain many processes to investigate. In addition to hyperandrogenism, undervirilization may be related to unexpected pathological conditions in backdoor pathway. The identification of normal backdoor androgen synthesis at the molecular level and elucidation of enzymes that function during each step may be the cornerstones for identification of diagnostic markers and therapeutic targets for pathological conditions.

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