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## Distal-opening-proximal-closing double zipper model of guinea pig tubular urethra and penile formation, a better model for human hypospadias

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Hypospadias is one of the most common congenital anomalies, occurring in approximately 1 in 250 live births, roughly 1 in 125 live male births. Tubular urethra formation in humans was described as distal-opening and proximal-closing “double zippers”, but similar process has never been shown in any other published animal models. After studying the embryology and sexual differentiation of the guinea pig external genitalia, we revealed the penile masculinization process is similar to humans. Canalization and dorsal-to-ventral movement of the urethral canal develops the urethral groove (UG) in both sexes. UG formation is an important step in external genitalia development and penile formation, but the cellular and molecular mechanisms of UG formation have never been discovered for being lack of appropriate animal models. We found differential cell proliferation and cell death in developing urethral epithelium led to UG formation and Shh expression in ventral surface epithelium of genital tubercle plays important roles. When exposed to androgen, the UG of males performed distal-opening and proximal-closing to form tubular urethra. More nuclear localized androgen receptors were found in genital tubercles of males than females at developing external genitalia. Antiandrogen treatment at E26-30 could induce severe hypospadias, but only reduced penile size when treated after E30. Methyl-testosterone administration at E27-31 can cause penile formation in females. Our data suggest guinea pig is an appropriate model for further study of cellular and molecular mechanisms involved in distal-opening-proximal-closing in tubular urethra formation and the evaluation of the etiology and pathophysiological processes of hypospadias.

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