Physiology, Male Reproductive System

Gurung P, Jialal I.

Introduction

The male reproductive system consists of the internal structures: the testes, epididymis, vas deferens, prostate, and the external structures: the scrotum and penis. These structures are well-vascularized with many glands and ducts to promote the formation, storage, and ejaculation of sperm for fertilization, and to produce important androgens for male development. [1] The major male androgen is testosterone, which is produced from Leydig cells in the testes. Testosterone can be converted in the periphery to a more active form, dihydrotestosterone via 5-alpha-reductase, or estradiol via aromatase. Other key hormones include inhibin B and Mullerian inhibiting substance (MIS) hormone, both produced by the Sertoli cells in the testes. Important hormones that modulate these include follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are released from the anterior pituitary gland and are regulated by gonadotropin-releasing hormone (GnRH), produced by the hypothalamus. Together, these hormones form the hypothalamic-pituitary-gonadal axis that promotes and maintains sexual development and function in the male.[2]

Issues of Concern

It is important to note that testosterone can be converted peripherally to estradiol via aromatase from adipose tissue. Estradiol can go on to be converted to estrogen peripherally. Estradiol/estrogen can play a role in bone resorption, epiphyseal closure, gynecomastia, and vascular effects, and exert an inhibitory effect on the hypothalamus and anterior pituitary similar to testosterone. When levels of estradiol increase in males, this can lead to pathological changes such as weak bones, development of breasts and loss of libido or infertility.

Cellular

Functional cells of the male reproductive system primarily consist of Leydig and Sertoli cells found in the testes. Leydig cells are found in the interstitium of the testes adjacent to the seminiferous tubules. On histology, they have pink cytoplasm and can be identified by pink crystals of Reinke. They produce testosterone, a steroid hormone that exerts its effects by binding intracellular receptors of different tissues and regulating protein expression.[3] Sertoli cells are found in the periphery of the seminiferous tubules. They promote spermatogenesis, which begins at the periphery of the tubules. They bind together to form a blood-testis barrier to keep germ cells contained in the seminiferous tubules and connect with each other through tight junctions. These cells are characterized by their relation to germ cells or primitive spermatogonia. Sertoli cells are much larger than germ cells, which are found nearby, and have less prominent nuclei. Germ cells line the interior of the seminiferous tubules and progress toward the lumen as they mature. These cells feature prominent, dark and dense nuclei.[4]

Development

In human embryos, the default sexual differentiation is female. However, having the Y chromosome defines differentiation into the male phenotype and the male reproductive system. The Y chromosome contains the sex-determining region (SRY) gene, which encodes for development of the testes. The testes descend from the posterior abdominal wall during development to lie in the scrotum at maturity. The testes develop Sertoli cells, which produce MIS to induce regression of the Mullerian ducts, which form the female reproductive tract. The testes also develop Leydig cells that produce testosterone, the major driver of male reproductive development.

Testosterone plays an important role in stimulating the development of the Wolffian ducts in the male fetus, which become the testes, epididymis, vas deferens and seminal vesicles. Testosterone is also responsible for erythropoiesis, pubertal growth

spurt, bone density, closure of epiphyseal plates, deepening of the voice, increase in muscle mass, male physique development and libido. Additionally, testosterone can be converted to dihydrotestosterone (DHT) via 5-alpha-reductase, an enzyme produced by the prostate peripherally. Both DHT and testosterone bind to the same androgen receptors intracellularly, but DHT has a higher affinity. DHT stimulates the development of the prostate, scrotum, and penis. DHT is also responsible for male hair pattern (facial, axial, and pubic hair), including the pathology of male pattern balding, increased sebaceous gland secretion and acne. Together, these hormones promote puberty and subsequent maintenance of the male reproductive system. [5]

Typically, the growth of the testes marks the beginning of puberty in males, which occur between 11 to 13 years of age. This is stimulated by a sudden rise in GnRH from the hypothalamus, which stimulates FSH and LH release from the anterior pituitary. LH stimulates Leydig cells to increase testosterone, which causes growth and pigmentation of the scrotum and penis. Secondary sexual characteristics such as facial, axillary, chest and pubic hair growth, deepening of the voice and growth spurt occur next. At this stage, first fertile ejaculations appear, marking mature reproductive function. Eventually, the epiphyseal growth plates close, marking the end of pubertal development. Pubertal development can continue into a male's 20s.

Organ Systems Involved

The hypothalamic-pituitary-gonadal axis plays a major role in promoting sexual maturity, sperm production and the development of secondary sex characteristics. It maintains spermatogenesis and sexual function throughout the male’s lifetime. The hypothalamus secretes GnRH into the hypothalamo-hypophyseal portal system to stimulate the anterior pituitary. GnRH is a peptide hormone released by hypothalamic neurons in a pulsatile fashion. It acts on the gonadotrophs of the anterior pituitary via the binding and activation of a G protein receptor, which stimulates the anterior pituitary through inositol 1,4,5-triphosphate (IP3) activation (which increases intracellular calcium) to release FSH and LH. GnRH is inhibited by testosterone, estrogen, estradiol, and prolactin.[2]

In response, the anterior pituitary secretes LH and FSH into the blood. These gonadotropic hormones act on membrane receptors in the Leydig and Sertoli cells of the testes respectively. Both hormones come from the same glycoprotein family and consist of identical alpha subunits, but their different beta-subunit differentiates their functions. Both exert their physiologic effects by binding and activating a G protein receptor, which activates adenylyl cyclase and increases cellular cAMP levels, to stimulate Sertoli and Leydig cells. LH stimulates Leydig cells in the interstitium of the testes to produce testosterone from cholesterol. LH promotes desmolase, which is the initial rate-limiting enzyme that converts cholesterol into pregnenolone. This goes on to produce two key weak androgen intermediates: dehydroepiandrosterone (DHEA) and androstenedione. The enzyme 17-beta-hydroxysteroid dehydrogenase completes the conversion of androstenedione to testosterone. Testosterone acts on the hypothalamus and anterior pituitary via negative feedback to decrease the secretion of LH and FSH. Testosterone can also exert some effect on Sertoli cells, found in the periphery of the seminiferous tubules of testes. FSH and testosterone can stimulate Sertoli cells to release androgen-binding protein (ABP), which provides testosterone to germ cells during spermatogenesis. FSH stimulates Sertoli cells to promote sperm production and release inhibin B and MIS. Inhibin serves as the negative feedback control that Sertoli cells exert on the hypothalamic-pituitary system to decrease FSH release.[6]

Before puberty, the levels of androgens and gonadotropins typically remain low and constant. Once puberty occurs, the hypothalamus releases GnRH in a pulsatile fashion every one to two hours to maintain amounts of FSH, LH and plasma testosterone, all of which regulate each other to maintain hormonal balance. In the third decade of life, testosterone levels are found to decline.[2][5][7]

Although a majority of testosterone production in men come from the Leydig cells in testes, the adrenal cortex contributes some androgen production. Similar to the hypothalamic-pituitary-gonadal axis, the adrenal glands are also controlled by the hypothalamus and anterior pituitary to form the hypothalamic-pituitary-adrenal axis. The hypothalamus release corticotrophin-releasing hormone (CRH), which stimulates the release of adrenocorticotropic hormone (ACTH) from the

anterior pituitary. ACTH stimulates the enzyme desmolase to convert cholesterol into pregnenolone in the adrenals, similar to testosterone synthesis in the testes. Specifically, the zona reticularis of the adrenal medulla is responsible for generating the weak androgens DHEA and androstenedione, which go on to be converted to testosterone or estradiol peripherally.[2]

Function

The function of the male reproductive system is to produce androgens such as testosterone that maintain male reproductive function and to promote spermatogenesis and transport into the female reproductive system for fertilization. The testes act as both endocrine and exocrine organs in that they are responsible for androgen production and sperm production and transport.

Mechanism

Spermatogenesis starts at puberty with the germ cells found in the basement membrane of the seminiferous tubules of the testes. Sertoli cells stimulated by FSH help regulate spermatogenesis. One cycle of spermatogenesis begins approximately every 13 days; however, spermatogenesis is not consistently synchronous throughout all seminiferous tubules. The first stage of spermatogenesis begins with mitosis of diploid spermatogonia into primary spermatocytes. These spermatocytes undergo meiosis I to produce haploid secondary spermatocytes, which undergo meiosis II to form haploid spermatids. The most primitive spermatocytes are found peripherally in the seminiferous tubules and mature by migrating towards the lumen. Spermatids transform into spermatozoa by reducing cytoplasm. These spermatozoa are still immotile and are released into the tubules to travel to the epididymis for maturation. The epididymis is a coiled structure consisting of a head, body, and tail. The tail eventually joins with the vas deferens, providing an outlet for mature sperms to ejaculate. In the epididymis, the sperm takes about twelve days to mature and develop motility. They are then stored in the tail of the epididymis until ejaculation occurs. A mature sperm consists of a head, midpiece, and tail. The head contains the nucleus with very little cytoplasm. An acrosome or cap covers the head and is filled with lysosomes, which aids with fertilization. The midpiece contains abundant mitochondria to provide energy for the flagellum or tail of the sperm.

During sexual arousal (physical or psychological), vasodilation brings blood to the penis. The penis contains corpora cavernosa and a corpus spongiosum where blood flows along to enlarge and erect the penis. As sexual stimulation continues, blood continues to flow to the genitals, and the testes enlarge in preparation of ejaculation.

When ejaculation occurs, smooth muscle contractions of the epididymis pushes sperm into the ductus deferens (vas deferens), which sits in the spermatic cord. The ductus deferens delivers the sperm to ejaculatory duct by joining with the seminal vesicle duct near the prostate. The seminal vesicles produce fructose, which provides the energy for sperm motility. It is released within a fluid that mixes with the sperm to form semen. Once in the ejaculatory duct, the semen passes through the prostate, which secretes an alkaline fluid that helps thicken the semen so sperm can better stay within the female reproductive system. The semen then passes the bulbourethral glands or Cowper's glands, which release a thick fluid that lubricates the urethral opening and clears the urethra of any urine residue. The semen then can enter the female vaginal canal, allowing the sperm to travel to and fertilize a potential egg within the female reproductive system.[2][6][8]

Related Testing

Common tests of male reproductive function include a blood test to measure testosterone levels. A majority of testosterone is bound to plasma proteins, particularly sex-hormone-binding globulins (SHBGs), which serve as storage. Some testosterone is also bound to albumin, which serves as a transporter. Only a small amount of testosterone circulates freely in plasma (normal range: 50 to 210 pg/mL). Total testosterone ranges from 300 to 1000 ng/mL.[9] Other tests include semen analysis, which establishes fertility status and function of the seminiferous tubules, epididymis, and accessory sex glands.[10] A sperm sample is collected and examined microscopically for count, motility, and shape. It can be useful in diagnosing cases of infertility or success of a vasectomy. Normal sperm counts are typically greater than 15 million/mL and motility greater than 40%. Other tests include blood prostate-specific antigen test (PSA), which screens for prostate cancer. The prostate produces PSA

typically, and levels can rise in prostatic carcinoma.[11] Recommendations for screening vary but typically screening should start around 50 years of age. A PSA greater than 4 ng/mL may prompt prostatic biopsy to rule out prostatic carcinoma. Physical exams include the digital rectal examination, which helps identify structural changes in prostate size such as benign prostatic hyperplasia, which is common in older men and can lead to urinary difficulties.

Pathophysiology

An imbalance in the hypothalamic-pituitary-gonadal axis can result in infertility and hypogonadism. Primary hypogonadism (also referred to as hypergonadotropic hypogonadism) results from a gonadal failure to produce adequate testosterone or spermatogenesis despite high LH and FSH levels. Congenital causes of primary hypogonadism include Klinefelter syndrome, androgen synthesis disorder, or cryptorchidism. Acquired causes include hepatic cirrhosis, renal failure, drugs, autoimmune disease, irradiation, infections, trauma or commonly, age. These result in failure of the testes to develop properly, injury to the testes or impaired function. Hence, loss of testicular function results in damaged or underdeveloped Leydig or Sertoli cells that cannot respond to stimuli to maintain reproductive function.

Secondary hypogonadism results from a disruption in the hypothalamic-pituitary axis where low GnRH, LH or FSH leads to low testosterone and spermatogenesis. These disorders can arise from congenital isolated GnRH, LH or FSH deficiency (such as in Kallmann's, Prader-Willi, Lawrence-Moon, GnRH receptor mutations, beta-subunit mutations in LH or FSH, or the kisspeptin/G protein-coupled receptor fifty-four mutations, which play a role in GnRH release). Acquired causes notably include hyperprolactinemia, panhypopituitarism, drugs (i.e., steroid use or opiates), systemic diseases, tumors, infection, trauma or irradiation. Notably, hyperprolactinemia can suppress GnRH release and is commonly due to prolactinomas, but can also result from hypothalamic-pituitary stalk lesions, drugs (dopamine antagonists, psychotropic agents, etc.) or systemic diseases.[8][12][13][14] These diseases result in loss of the primary stimuli to the testes. Without the proper stimuli (GnRH, LH, or FSH), the Leydig and Sertoli cells, which are functional and intact, cannot exert their effects. This results in low testosterone levels or loss of spermatogenesis.

Other causes of infertility in men include defects in androgen action, hyper/hypothyroidism, adrenal insufficiency, congenital adrenal hyperplasia, disordered sperm transport (i.e., ductal obstruction), and systemic disease. Defects in androgen action, such as androgen insensitivity syndrome, result in a female phenotype despite male genotype due to an inability of the body's tissues to respond to testosterone. Hence, despite high testosterone levels in circulation, the clinical presentation is that of a patient with low testosterone and typically female as the disorder arises from birth.

Clinical Significance

Disorders of the male reproductive system typically result from decreased testosterone levels or insensitivity to testosterone, which lead to low libido, failure to ejaculate, decrease in bone density, muscle loss, infertility, loss of body hair and, importantly, incomplete sexual development if the disorder is congenital or acquired before puberty. Other less specific symptoms of low testosterone include low energy/depressed mood, anemia or increased body fat. Other comorbidities associated with low testosterone include metabolic syndrome, insulin resistance, and atherosclerosis,[14][9]

Questions

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Publication Details

Author Information

Authors

Purnima Gurung[1]; Ishwarlal Jialal[2].

Affiliations

[1] California Northstate University
[2] VA MEDICAL CENTER, MATHER, CA

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