Overview of the Male Reproductive System

1

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Abbreviations

HPG	Hypothalamic–pituitary–gonadal
SRY gene	Sex-determining region of the Y chromosome
ABP	Androgen-binding protein
GnRH	Gonadotropin-releasing hormone
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
DHT	Dihydrotestosterone
WHO	World Health Organization
PSA	Prostate-specific antigen

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Introduction

Humans are sexually dimorphic; however, both male and female reproductive systems consist of different sets of structures, that is, gonads, internal genitalia, and external genitalia. This chapter will specifically focus on the male reproductive system and its functions. Development and differentiation of the specialized cells, tissues, and structures that comprise the male reproductive system already start in utero but only initiate function during puberty. The male internal reproductive organs consist of the ducts (epididymis, vas deferens, and ejaculatory duct) and accessory sex glands (seminal vesicles, prostate, and bulbourethral glands), while the external genitalia consists of the testes, located inside the scrotum as well as the penis. The testes are located inside the scrotum. Each of these structures is well vascularized and innervated and is controlled by an intricate interplay with the endocrine system which plays a very important role in the successful production and delivery of the male gametes. The testes have both exocrine and endocrine functions in the sense that they not only produce spermatozoa but also synthesize and secrete hormones. The process of spermatogenesis is furthermore highly regulated by the hypothalamic–pituitary–gonadal (HPG) axis. The most important reproductive processes are the following: initiation and maintenance of spermatogenesis, sperm transport, sperm maturation, semen production, sperm secretion, sexual response, and androgen production. The first part of this

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chapter will emphasize the specific anatomy and histology of the male reproductive system, while the latter part will focus on the physiology and function of these structures.

Embryonic Development of the Male Reproductive System

Male reproductive development starts with gender determination. This occurs when the Y chromosome bearing spermatozoon fuses with the X chromosome bearing oocyte during the process of fertilization, creating a 46XY coded zygote. Thereafter, gonadal differentiation initiates as the foundation for testicular development. The bipotential gonads differentiate from the genital ridge which forms as a thickening of somatic cells on the inner surface of the mesonephros. Four structures are developed which later mature into the external genitalia: the genital tubercle, the urethral folds, the urethral groove, and the labioscrotal swellings. The sex-determining region of the Y chromosome (SRY gene) produces the SRY protein, which, in combination with other genes, promotes the development of the testis. After the gonadal differentiation process is completed, sexual differentiation starts. The testis develops steroidogenic cells, Sertoli cells, and cells responsible for completion of gonadal structural development from three bipotential cell lineages. The first fetal precursor cells are responsible for the formation of steroidogenic cells that are responsible for the secretion of sex hormones and subsequent onset of secondary sexual characteristics. The second cell lineage gives origin to Sertoli and mesenchymal cells. The Sertoli cells regulate the synthesis of the seminiferous tubules, while the mesenchymal cells differentiate into Leydig cells. Sertoli-cell and peritubular-cell secretions lead to the differentiation and migration of adult Leydig cells. The third cell lineage differentiates into the gonad structure. Development of the bipotential gonad is dependent on the anti-Mullerian hormone secreted by the Sertoli cells, with testosterone being secreted by interstitial cells and the insulin-like 3 hormone. The intermediate mesoderm is homologous for both male and female development and gives rise to the Wolffian ducts, Mullerian ducts, and the gonad precursors. During male development the Mullerian duct dissolves away, while the Wolffian duct gives rise to the epididymis, vas deferens, ductus deferens, ejaculatory duct, and the seminal vesicle. The development of the external male genitalia is dependent on dihydrotestosterone (DHT; secreted by Leydig cells) exposed to the fetus during the third trimester of pregnancy [1, 2].

The transfer of the testes from the genital ridge to the scrotum is a process of cardinal importance to sexual differentiation. Testosterone induces the relaxation of the cranial suspensory ligaments allowing the descent of the testes into the scrotum. The increased abdominal pressure due to the viscera growth and the elastic properties of the testes then cause the testes to be forced through the inguinal canal and into the scrotum. After the initial development of the essential male reproductive organs, the reproductive system lies dormant until puberty when the HPG axis becomes active and the process of spermatogenesis is initiated. The precursor cell development is of cardinal importance to spermatogenesis in the adult male. It is crucial that precursor cells proliferate unimpeded and give rise to an optimal amount of spermatogonia in later life [2, 3].

Anatomy and Histology of the Male Reproductive System

Testis

The two *testicles or* male gonads are responsible for spermatogenesis (the production of spermatozoa); simultaneously, they play a key role in the production of certain hormones, including testosterone, and can thus also be categorized as internal secretion glands (endocrine glands). The testes are housed within the *scrotum* (scrotal sac) below the penis, the left hanging a little lower than the right. The testis is oval shaped and slightly flat sided and has two smooth surfaces (internal and external), two poles (anterosuperior and posteroinferior), and two margins (anteroin-

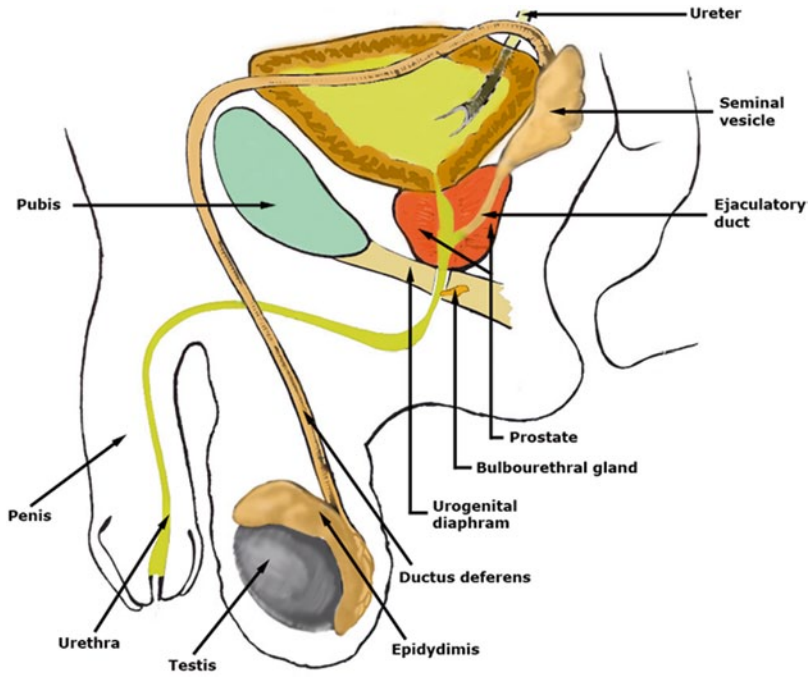

Fig. 1.1 Male genital system (scheme)

ferior and posterosuperior). It is covered by the *tunica vaginalis* (deriving from the peritoneum), which gives it its blue-white coloring. The adult testis is 40–50 mm long, 30 mm high, 25 mm wide, and weighs 16–20 g (Figs. 1.1 and 1.2).

The testis is surrounded by the *tunica albuginea,* a thick capsule of connective tissue and smooth muscle fibers. The innermost layer, known as the *tunica vasculosa,* is composed of loose connective tissue interspersed with numerous blood vessels. The tunica albuginea is thickest at the posterior margin, where it invaginates to form the *mediastinum testis*. The testis is secured to the scrotum by the *scrotal ligament*. Numerous connective-tissue septa arising from the mediastinum divide the testis into around 250 pyramid-shaped *lobules,* which are broad based at the surface of the capsule and become narrower as they converge to the mediastinum. Each lobule contains one to four highly-coiled *seminiferous tubules* (150–250 μm in diameter and 30–80 cm long). Towards the apex, straighter tubules known as *tubuli recti* connect the coiled tubules to the *rete testis* (rete of Haller) located in the mediastinum testis.

The *seminiferous tubules* are composed of a *seminiferous epithelium* lined by a *lamina propria* or peritubular tissue layer.

- *Lamina propria:* This layer is formed by connective tissue containing numerous fibroblasts and contractile myoid cells, whose rhythmic contraction facilitates the transport of spermatozoa.
- *Seminiferous epithelium:* This is a stratified epithelium composed of two main cell types: Sertoli cells and germ cells at different stages.

Sertoli cells are columnar cells that rest on the basement membrane and extend to the tubular lumen. They contain an oval nucleus, highly developed smooth endoplasmic reticulum, lysosomes, and Golgi complexes. Sertoli cells, which are bound to each other by tight junctions, have several functions:

- Promotion of nutrient exchange for germ cells
- Phagocytosis of degenerated germ cells and residual spermatid cytoplasm
- Production and secretion of testicular fluid

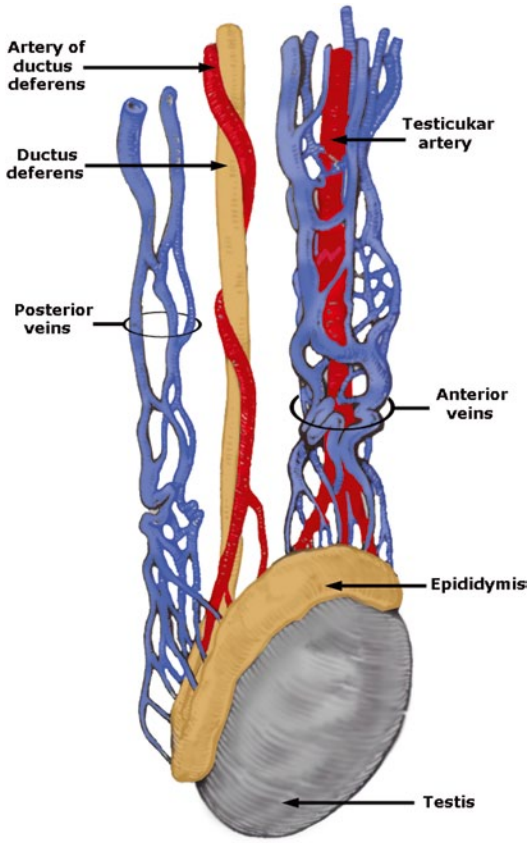

Fig. 1.2 Testis and epididymis (right lateral aspect)

- Production and secretion of *androgen-binding protein (ABP)* that binds specifically to the testosterone required for spermatogenesis
- Production and secretion of inhibin
- Regulation of germ cell movement in the epithelium, facilitating cell differentiation and the release of spermatozoa into the lumen
- Formation of the blood–testis barrier

Germ cells at various stages of maturity are found in the testis: *spermatogonia, spermatocytes, spermatids, and spermatozoa*.

- *Spermatogonia:*

These lie adjacent to the basement membrane of the tubular epithelium and are divided into two subtypes. *Type A* spermatogonia are stem cells which replicate and also divide by mitosis to produce *Type B* spermatogonia. The latter divide mitotically to produce primary spermatocytes. Due to incomplete cytokinesis during mitotic division, cells remain bound by cytoplasmic bridges during spermatogenesis.

- *Spermatocytes:*

Primary spermatocytes are the largest of the germ cells. They are formed in the *basal compartment* and migrate to the *adluminal compartment*. They are diploid cells which undergo meiosis I to produce secondary spermatocytes.

Secondary spermatocytes are haploid cells rarely seen under the microscope because they are present for only 8 h of the 64-day spermatogenic cycle. They divide by meiosis II to produce spermatids.

- *Spermatids:*

These are haploid cells found near the lumen of the seminiferous tubule. Rather than dividing, they undergo a process of differentiation to become spermatozoa.

- *Spermatozoa:*

These are fully mature haploid cells but are incapable of fertilization.

As referred to briefly above, the tight junctions between Sertoli cells form the histological basis of the blood–testis barrier, whose functions are to create a microenvironment for the correct development of spermatozoa and prevent contact between maturing (haploid) gametes and the immune system.

The barrier divides the tubule into two distinct sections:

1. Basal compartment: This compartment, which is in contact with the underlying connective vascular tissue, contains spermatogonia and primary spermatocytes.
2. Adluminal compartment: This compartment contains secondary spermatocytes, spermatids, and spermatozoa, and it is not in contact with underlying connective vascular tissue.

The final portion of the seminiferous tubules, containing a columnar epithelium composed entirely of Sertoli cells, opens into the rete testis, an anastomosing network of tubules lined by a cuboid epithelium, some of whose cells may

contain flagella. Seminiferous tubules are separated from each other by peritubular interstitial tissue composed of loose connective tissue containing blood vessels, lymph vessels, nerves, and *Leydig cells (also referred to as interstitial cells).*

Leydig cells may occur singly or in clusters and are characterized by a euchromatic nucleus and eosinophilic cytoplasm. Their appearance is typical of steroid-secreting cells, that is, abundant smooth endoplasmic reticulum, lipid vacuoles, and numerous mitochondria with tubular cristae. These are testosterone-producing cells [4–7].

Sperm Ducts

A whole set of tubular structures are involved in transporting spermatozoa from their origin in the testis to the urethra, through which both semen and urine are removed. These structures, to be subsequently described, are the epididymis, ductus deferens, and ejaculatory ducts.

Epididymis

The *epididymis* is an elongated organ located over the posterosuperior border of the testis. It is roughly 50 mm in length and contains a highly coiled tube known as the *epididymal duct,* which is around 4 m long and 0.3 mm in diameter. The epididymis can be divided into three portions: the *head* or *caput* (wider upper portion), the *body* or *corpus* (middle portion), and the *tail* or *cauda* (lower portion), which continues into the ductus deferens. The head of the epididymis is attached to the testis by *efferent ducts* and fibrous tissue and the tail by fibrous tissue alone; the middle portion of the epididymis is not attached to the testis (Figs. 1.1 and 1.2). The visceral layer of the tunica vaginalis forms a recess between the testis and the body of the epididymis, known as the *sinus of the epididymis*. The functions of the epididymis include sperm storage, resorption of most of the testicular fluid produced in the seminiferous tubules, and secretion of the enzymes required for the maturation of spermatozoa.

As indicated previously, the two main structures of the epididymis are the *efferent ducts* and the *epididymal duct:*

- *Efferent ducts:*

Around 15–20 ductules connect the rete testis with the epididymis, across the tunica albuginea. They are composed of a simple epithelium containing columnar ciliated cells which facilitate the transport of spermatozoa, and cuboid non-ciliated cells whose function is to absorb testicular fluid.

- *Epididymal duct:*

This is a single, coiled duct around 4 m long, located mainly in the body and tail of the epididymis. It is here that spermatozoa acquire motility and the ability to fertilize. The epididymal duct is surrounded by a layer of smooth muscle which becomes thicker towards the tail. The lumen is lined by a pseudostratified columnar epithelium containing stereocilia; the major cell types are principal cells and basal cells.

Principal cells:

These are columnar and contain a basal nucleus, with rough endoplasmic reticulum and abundant Golgi complexes, lysosomes, and micropinocytotic vesicles. The apical surface contains long, nonmotile microvilli (stereocilia).

Basal cells:

These are stem cells which serve to renew the principal-cell population [4–7].

Ductus (Vas) Deferens

The *ductus (vas) deferens,* a duct around 40 cm long, is the continuation of the tail of the epididymis. It traverses the scrotal sac, the inguinal canal, the pelvic cavity below the peritoneum, and the rear lateral portion of the bladder, where it enlarges to form the *ampulla*. It is cylindrical in shape, with a diameter of around 2 mm and a caliber of 0.5 mm; this thick wall ensures great consistency.

The ductus deferens is divided into various anatomical portions: *scrotal, funicular, inguinal, iliac,* and *pelvic* (Fig. 1.1).

- *Scrotal portion:* Here, the ductus deferens ascends along the medial side of the epididymis, from which it is separated by the testicular veins.

- *Funicular portion:* From the anterior surface of the body of the epididymis, the ductus deferens continues upwards to the superficial inguinal ring. Here, it is accompanied by blood vessels supplying the testis and epididymis, nerves, pampiniform and *testicular* venous plexuses, lymph vessels, and a vestige of the peritoneum known as the *processus vaginalis*. All these structures are sheathed by the *external spermatic fascia* and together form the *spermatic cord* (Fig. 1.2).
- *Inguinal portion:* This portion of the ductus deferens traverses the inguinal canal to the superficial inguinal ring. At this stage it is accompanied not only by the elements forming the spermatic cord but also by the genitofemoral and ilioinguinal nerves and the cremasteric artery.
- *Iliac portion:* After passing through the deep inguinal ring, it enters the pelvic cavity (below the peritoneum) and moves downwards across the internal iliac vein and artery. Here, it separates from the other structures of the spermatic cord except for the artery of ductus deferens.
- *Pelvic portion:* Here, the ductus deferens runs first to the side and later to the rear of the bladder. From the side of the bladder, it is directed backwards (below and adhering to the peritoneum) towards the rearmost portion of the lateral border of the bladder, where it crosses in front of and above the ureter. Thereafter, it descends along the posterior wall of the bladder and then changes direction, moving downwards, forwards, and inwards until it reaches the base of the prostate. Over this last stretch, the ductus deferens becomes enlarged and tortuous, forming the ampulla, which is separated from the fundus of the bladder first by the peritoneum and later by the *rectovesical septum* or *retroprostatic fascia*.

The *mucosa* of the ductus deferens is lined by an epithelium similar to that of the epididymal duct, surrounded by a slender *lamina propria* of dense connective tissue. The star-shaped cross-sectional appearance of the lumen is due to a number of longitudinal folds. The thick *muscularis* of the ductus deferens is formed by inner and outer layers of longitudinal fibers and a middle layer of circular fibers. The longitudinal fibers shorten and widen the ductus deferens immediately prior to ejaculation, drawing in the content of the epididymis and expelling it towards the urethra. These muscle fibers receive abundant innervation from the sympathetic nervous system [4–7].

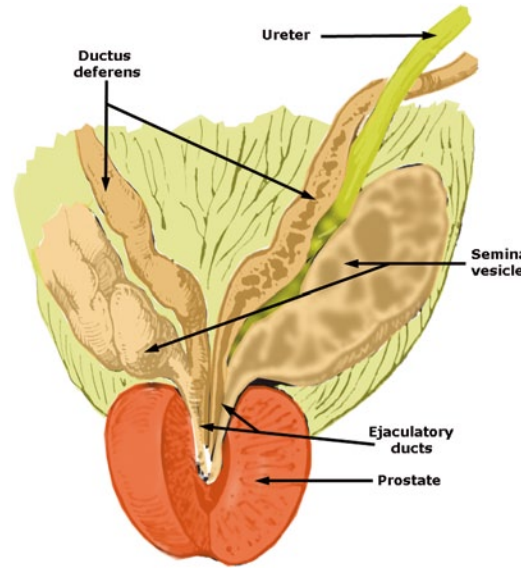

Fig. 1.3 Seminal vesicles, ejaculatory ducts, and prostate (posterior aspect)

Ejaculatory Ducts

The right and left *ejaculatory ducts,* tubes of around 25 mm in length, run from the terminal portion of the ampulla of the ductus deferens and the start of the seminal vesicles (Fig. 1.3), passing through the prostate and opening into the posterior portion of the prostatic urethra, to either side of the prostatic utricle, at the right and left *colliculi seminalis*. The ducts are lined by simple columnar epithelium and have no muscle layer [4–7].

Scrotum

The testes, epididymides, and a portion of the ductus deferens are sheathed in several layers of tissue which together form the *scrotum* or *scrotal sacs.* These sheaths derive from the abdominal wall, due to the descent of the testes from

the abdomen into the scrotum. The two sacs are separated by a central septum (median raphe); the left sac hangs lower than the right and the two are attached to the perineum by the *scrotal pedicle*.

Working inwards from the outside, the layers of the scrotum are as follows:

- *Scrotal skin:* The scrotal skin is thin, dark, and shows numerous folds.
- *Tunica dartos:* This layer is composed of smooth muscle fibers interspersed with connective tissue and elastic fibers; at the midline, it contributes to the formation of the central septum (median raphe).
- *Subcutaneous cell tissue layer*.
- *External spermatic fascia:* This thin membrane is the scrotal prolongation of the lining of the abdominal external oblique muscle.
- *Cremaster muscle:* This muscle is formed by inner and outer layers of striated muscle, derived from the internal oblique and transverse abdominal muscles, which eventually insert into the internal spermatic fascia.
- *Internal spermatic fascia:* This layer, deriving from the abdominal *fascia transversalis,* extends downwards to line the spermatic cord, the epididymis, and the testis.
- *Tunica vaginalis:* This serosa, deriving from the peritoneum, lines the anterior and lateral surfaces of the testis but not the posterior surface. It comprises two layers: the *superficial or parietal lamina* and the *deep or visceral lamina* (which lines the tunica albuginea of the testis). Both are composed of mesothelial cells and submesothelial connective tissue. The interval between the visceral and parietal laminae is known as the *serous cavity of the scrotum* [4–7].

Accessory Sex Glands

Seminal Vesicles

These two oval structures (50 mm long, 10 mm wide, and 10 mm thick) are located behind the urinary bladder at either side of the ampulla of the ductus deferens and are separated from the *rectum* by the *rectovesical septum*. The end of each seminal vesicle joins the end of each *ampulla* to form the ejaculatory duct (Figs. 1.1 and 1.3). The seminal vesicle consists of a coiled, glandular tube around 15 cm in length, covered by fibrous tissue. It produces a yellowish, gelatinous secretion which accounts for 60–80 % of seminal fluid or semen. This secretion is particularly rich in fructose, citrate, amino acids, and prostaglandins.

Seminal vesicles do not store sperm. Contraction of the smooth muscle during ejaculation pushes this secretion into the urethra. The single tube, of which each vesicle is composed, comprises three concentric layers. The outermost layer of loose connective tissue surrounds two layers of smooth muscle tissue, a longitudinal outer layer, and a circular inner layer.

The innermost layer of the vesicle is a mucosa arranged into numerous folds, giving the lumen a highly irregular appearance. The mucosa comprises a *pseudostratified columnar epithelium* and a *lamina propria* of connective tissue. Epithelial cells are of two types: principal and basal. *Principal cells* are columnar, and their cytoplasm contains secretion vesicles, lipofuchsin granules, and lipid droplets, while *basal cells* are stem cells (progenitors of principal cells) [4–7].

Prostate

This is a chestnut-shaped gland and resembles an inverted cone, its apex pointing downwards. It is located beneath the urinary bladder (the base of the prostate is fused to the fundus of the bladder) and therefore surrounds the initial portion of the urethra. The vertical, transverse, and anteroposterior diameters are 25–30, 40, and 25 mm, respectively. It consists of anterior and posterior surfaces, two lateral surfaces (down-facing and out-facing), a base, and an apex (Figs. 1.1 and 1.3).

Although there are no clear divisions within the prostate, it is traditionally divided into four lobes:

- *Anterior portion* (in front of the urethra)
- *Posterior portion* (behind the urethra and between the ejaculatory ducts)
- *Right and left lateral lobes* (rest of the gland)

The anterior portion of the prostate, including the apex, is surrounded by fibers of the external sphincter muscle of the urethra and by fibrous laminae deriving from the periprostatic fascia of the pelvic floor. The posterior portion is lined by the *rectovesical septum* (the *Denonvilliers prostatoperitoneal* membrane or fascia); as indicated earlier, this posterior fascia also sheathes the ductus deferens and the seminal vesicles. Laterally, the prostate is surrounded by the prostatic fascia, which contains periprostatic venous plexuses. These fibrous fascia are attached in the anterior portion to the pubis, laterally to the elevator muscle of the anus and posteriorly to the sacrum. The prostate secretes a colorless fluid which makes up between 15 and 30% of the volume of semen. This secretion contains acid phosphatase, citric acid for sperm nutrition, and fibrolysin for semen liquefaction. It should be noted that the prostate contains the prostatic urethra, the internal sphincter muscle of the urethra, the upper portion of the external sphincter muscle of the urethra, the ejaculatory ducts, and the prostatic utricle. The prostate is surrounded by a fibroelastic capsule containing bundles of smooth muscle fibers. It consists of 30–50 glands arranged in three concentric layers: an inner *mucosal* layer of glands surrounding the urethra, which is in fact invaginations of the urethral epithelium, an intermediate *submucosal* layer of tubuloalveolar glands, and a peripheral *principal* layer containing the main tubuloalveolar prostatic glands. The principal layer is the most susceptible to prostate cancer, while the mucosal and submucosal layers tend to be more affected by benign prostatic hyperplasia. The glandular parenchyma is surrounded by abundant connective tissue and bundles of smooth muscle fibers. During ejaculation, these muscles contract to expel the prostatic secretion into the urethra. The glandular mucosa is heavily folded, with a pseudostratified epithelium. It comprises *principal cells* containing numerous secretory granules and abundant acid phosphatase, and *basal cells* which are the precursors of principal cells. The alveoli of the prostatic glands often contain *corpora amylacea,* formed by precipitation of secretory material around cell fragments; over time, these may become calcified [4–7].

Bulbourethral Glands

These two lentil-sized glandular structures, also known as Cowper's glands, are located at the upper right and left of the urethral bulb, in the deep perineal pouch alongside the deep transverse perineal muscle. A duct, around 4 cm in length, arises from each gland to finish in the spongy urethra (Fig. 1.1). The glands produce a clear, viscous secretion which acts as a lubricant during sexual stimulation. They are surrounded by a capsule of connective tissue, with a simple epithelium comprising columnar mucus-secreting cells [4–7].

Penis

The penis is the male copulatory organ. It is located above the scrotum and in front of the symphysis pubis. The flaccid penis measures roughly 10 cm and is cylindrical in form, while the erect penis assumes the form of a triangular prism with rounded angles and measures around 16 cm (Fig. 1.1). Its anterior end is expanded in the form of an obtuse cone. This expansion, termed the *glans penis,* contains the external urethral orifice or *urinary meatus*. At the *neck* (the boundary between the glans and the body of the penis) the sheath of the penis folds in upon itself to form the *foreskin* or *prepuce*. The posterior portion of the penis, known as the *root,* is attached to the front of the symphysis pubis by the *suspensory ligament* and to the ischiopubic rami through the *corpora cavernosa penis*. The penis is formed by three blood-storing structures known *as erectile organs:* two dorsal tissue masses and one ventral tissue mass. The dorsal erectile organs, known as the *corpora cavernosa,* are capped by the glans. Behind, the corpora diverge, forming the *crura,* which attach to the ischiopubic rami, and terminate in a conical structure known as the *root of the penis*. The ventral erectile organ surrounding the urethra, termed the *corpus spongiosum,* is located in the lower longitudinal groove formed by the two corpora cavernosa. At its anterior end, the corpus spongiosum broadens out to form the *glans,* while the posterior end assumes a bulb shape to form the *bulb of corpus spongiosum*.

The integument of the penis is similar to that of the testis and comprises the following layers, working inwards from the outer layer:

- *Skin:* The skin is thin, mobile, and pigmented.
- *Dartos:* A layer of smooth muscle fibers underlying the skin.
- *Subcutaneous connective tissue:* It allows the skin to slide over the penis.
- *Deep fascia of the penis:* A layer of fibrous connective tissue covering the corpora cavernosa and the corpus spongiosum.

The skin surrounding the penis (dermis and epidermis) is very fine and contains small sebaceous glands. The hypodermis (superficial fascia) contains smooth muscle fibers but no adipose tissue, thus enabling the skin to slide freely over the underlying structures.

Inside the penis, the tunica albuginea is a layer of dense fibroelastic connective tissue surrounding the three erectile tissue masses. The erectile tissue is composed of highly irregular sinusoidal vascular structures, bounded by endothelium and surrounded by smooth muscle tissue. The corpora cavernosa are surrounded by a thick tunica albuginea, while that enveloping the corpus spongiosum is thinner [4–7].

Urethra

Although the urethra drains urine from the bladder and is thus part of the urinary apparatus, it is included here because it also carries semen out of the body.

The male urethra is divided into four portions, named after the location (Fig. 1.1):

- *Intramural:* This is the portion that traverses the bladder wall. It has a transitional epithelium *(urothelium)*.
- *Prostatic:* This portion, around 3 cm in length, crosses through the prostate gland, where it receives fluid from the seminal vesicles and the prostate (at the seminal colliculus). The epithelium is mostly transitional, although there are some areas of simple columnar epithelium.
- *Membranous:* This portion, measuring 1 cm in length, passes through the perineum. It is lined by a stratified columnar epithelium.
- *Spongy:* This portion, which is around 12 cm long, runs along the length of the penis, initially downwards and later forwards to the pubic symphysis; thereafter, it bends downwards in the flaccid penis or continues upwards in the erect penis. The distal portion has a pseudostratified columnar epithelium, while closer to the meatus the epithelium becomes squamous stratified.

The urethral lumen contains three dilations: the *prostatic sinus* (in the prostatic portion), the *intrabulbar fossa* (in the vicinity of the bulb of corpus spongiosum), and the *navicular fossa,* close to the *urinary meatus,* in which the urethra terminates [4–7].

Vessels and Nerves of the Male Reproductive System

Due to the importance of vascularization and innervation in the functioning of the male reproductive system, it is necessary to allude to the morphology and structure of these blood vessels, lymphatic vessels, and nerves.

Vascularization and Innervation of the Testis and Sperm Ducts

During embryonic development, the testis forms in the abdominal cavity, later descending into the scrotum. For that reason, the nerves and vessels of the testis originate or terminate in abdominal structures.

Arteries

- *Testicular artery* (Fig. 1.2): This is a branch of the abdominal aorta, which traverses the inguinal canal, where it forks to supply the epididymis *(epididymal artery)* and the testis; the latter then divides into two branches (internal and external), which give rise to the *interlobular arteries* of the testis.

- *Artery of ductus deferens* (Fig. 1.2): This is a branch of the superior vesical artery, which is in turn a branch of the internal iliac artery, alongside which the deferential artery runs throughout its course. It finally joins the epididymal branch of the testicular artery.
- *Cremasteric artery:* It is a branch of the inferior epigastric artery (which in turn arises from the external iliac artery). The cremasteric artery traverses the inguinal canal, where it supplies spermatic cord structures. It terminates in the tail of the epididymis, where it anastomoses with small arteries branching from the testicular artery and the epididymal artery.
- The *artery of ductus deferens,* the *prostatic branches of the inferior vesical artery,* the *inferior vesical artery,* and the *middle rectal (hemorrhoidal) artery* (all deriving from the internal iliac artery): These contribute to the vascularization of the seminal vesicles, the ampulla of ductus deferens, and the ejaculatory ducts.

Veins

- *Pampiniform plexus* (Fig. 1.2): This venous plexus, located in the anterior part of the spermatic cord, is a network of small veins originating in the testis and the anterior portion of the epididymis. Close to the *ductus deferens,* this plexus penetrates the abdomen and gives rise to the testicular veins. The right testicular vein empties into the inferior vena cava, while the left testicular vein drains into the left renal vein.

Some venous blood from the ductus deferens also drains into the pampiniform plexus.

- *Posterior spermatic plexus:* These are veins arising in the posterior half of the epididymis, which traverse the posterior portion of the spermatic cord and empty into the internal iliac vein system. Some venous blood from the ductus deferens also drains into the posterior spermatic plexus.
- *Prostatic, vesical, and seminal plexuses:* These are the networks in which the veins of the seminal vesicles and ejaculatory ducts terminate.

Lymph Vessels

The lymph vessels of the testis and epididymis terminate in the lumbar region, in lymph nodes close to the inferior pole of the right kidney and the anterior portion of the left renal vein. The lymph vessels of the ductus deferens and seminal vesicles lead to the external and internal iliac lymph nodes.

Nerves

The nerves of the testis and epididymis derive from the testicular plexus originating in the celiac plexus and from the deferential plexus originating in the inferior hypogastric plexus [4–7].

Vascularization and Innervation of the Scrotum

Arteries

- *Cremasteric artery:* As indicated earlier, this is a branch of the inferior epigastric artery. It supplies the cremaster muscle, the internal spermatic fascia, and the parietal lamina of testis.
- *Superficial arterial branches* of the *external pudendal arteries,* which derive from the femoral artery, and of the *perineal artery,* which arises from the internal pudendal artery.

Veins

- *Deep veins,* draining into the venous plexuses of the spermatic cord
- *Superficial veins,* draining into the external pudendal veins, which arise from the great saphenous vein

Lymph Vessels

The lymph vessels of the scrotum terminate in the internal inguinal lymph node groups.

Nerves

The scrotum is innervated by branches of the pudendal nerve, the perineal nerves, and genital branches of the ilioinguinal and genitofemoral nerves [4–7].

Vascularization and Innervation of the Prostate

Arteries

- *Prostatic branches of the inferior vesical artery* and the *middle rectal (hemorrhoidal) artery*

Veins

- *Prostatic veins:* These veins drain anteriorly and laterally into the *prostatic venous plexus,* and posteriorly into the *venous plexus of the seminal vesicles*. Blood from these two plexuses eventually empties into the internal iliac veins.

Lymph Vessels

The lymph vessels of the prostate terminate in the external iliac, internal iliac, lateral sacral, and internal pudendal lymph nodes.

Nerves

The nerves of the prostate arise in the inferior hypogastric plexus [4–7].

Vascularization and Innervation of the Penis

Arteries

- *Branches of the internal pudendal* and *perineal arteries,* located in the subcutaneous connective tissue layer, supply the integument and fibrous sheath of the penis.
- The *cavernosal arteries* (branches of the internal pudendal artery) supply the corpora cavernosa. Within the corpora, these branch off into numerous spirally arranged *helicine arteries*.
- The *arteries of bulb of penis, urethral arteries,* and *corpus spongiosum arteries* (all branches of the internal pudendal artery) supply the areas indicated by their name.
- The *dorsal arteries of the penis* (branches of the internal pudendal artery) flow from the dorsal aspect of the penis to the glans, passing through the corpora cavernosa and the corpus spongiosum.

Veins

- The *superficial dorsal vein of the penis,* located in the subcutaneous connective tissue layer, runs backwards to eventually drain into the left side of the great saphenous vein.
- The *deep dorsal vein of the penis,* located beneath the deep fascia and between the two dorsal arteries of the penis, arises through the merging of right and left venous plexuses in the neck region of the glans, formed by veins running from the glans. It is fed by lateral and superior venous branches from the corpora cavernosa and the corpus spongiosum and eventually drains into the prostatic venous plexus.

Lymph Vessels

- *Superficial lymph vessels* carry lymph from the integument and fibrous sheath of the penis to the inguinal lymph nodes.
- *Deep lymph vessels* carry lymph from the corpora cavernosa, corpus spongiosum, glans, and penile urethra. They run alongside the deep dorsal vein of the penis and terminate in the superficial and deep inguinal lymph nodes.

Nerves

- *Genital branch of the genitofemoral nerve*.
- *Dorsal nerve of the penis*.
- *Superficial branch of the perineal nerve*.
- The *cavernous nerves of the hypogastric plexus* provide vegetative innervation [4–7].

Physiology of the Male Reproductive System

Endocrine Regulation of the Male Reproductive System

The onset of puberty is associated with a rise in the cyclic secretion (peaking every 1.5 h) of the hypothalamic peptide hormone, gonadotropin-releasing hormone (GnRH). Factors that can

stimulate GnRH production are leptin and noradrenalin, while substances such as dopamine, serotonin, prolactin and certain interleukins can inhibit GnRH production. GnRH is released into the hypothalamic–hypophyseal portal system binding to membrane receptors of specific cells (gonadotropic cells) in the anterior pituitary, thereby activating a protein kinase C-mediated pathway. This in turn stimulates the synthesis and secretion of the gonadotropins. These glycoprotein hormones are central in the regulation of normal growth, sexual development, and reproductive function and include follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Both FSH and LH have similar α subunits but differ in their β subunit, which determines receptor-binding specificity. Low GnRH pulse frequency predominantly leads to FSH release, while higher GnRH frequencies are associated with preferential LH secretion [2, 3, 8, 9]. Once released from the anterior pituitary, they act on specific membrane receptors of their target tissue. LH is responsible for the stimulation of Leydig cells to produce mainly the steroidal hormone testosterone. FSH acts on Sertoli cells, which also have receptors for testosterone. The gonadotropins therefore initiate and support spermatogenesis. LH and FSH also promote the activation of ABP. The gonadal secretion of sex hormones also affects their own production by decreasing the release of GnRH, FSH, and LH in a negative-feedback manner. The gonads, furthermore, control the levels of FSH through testosterone secretion as well as by secreting a growth-factor-like peptide hormone, Inhibin B, from the Sertoli cells [10–14].

As previously mentioned, Leydig cells are responsible for the secretion of androgenic anabolic hormones. The primary androgen in the male reproductive system is testosterone, and its reduced form DHT binds to androgen receptors in Sertoli cells and modulates gene transcription. The endoplasmic reticulum and mitochondria of mature Leydig cells utilize cholesterol and acetate to produce testosterone. Testosterone and DHT are key to appropriate primary sexual characteristics of testicular development such as differentiation of male genitalia and pubertal growth in addition to initiating secondary sexual characteristics such as the characteristic male bodily and facial hair growth, body shape, muscular development, broadening of vocal chords, and development of libido. Testosterone is also a cardinal factor in the maintenance of spermatogenesis [15–17]. Maturation of the reproductive system is controlled by GnRH, the gonadotropins (LH and FSH), and the sex hormones. However, if thyroid hormone is not available in sufficient amounts, maturation of the reproductive system is delayed. Thyroid hormone cannot induce reproductive maturation and is thus regarded to have a permissive effect on reproductive maturation [18]. This system of combined hormonal interaction from various endocrine glands acting as a whole is referred to as the HPG axis and is illustrated in Fig. 1.4.

Spermatogenesis

Spermatogenesis is the process whereby the male gametes or spermatozoa are produced. Spermatogenesis is responsible for the production of haploid gametes from diploid spermatogonia and in so doing preserves the number of chromosomes in the offspring. This occurs in the seminiferous tubules of the testes through a complex and highly orchestrated process that initiates during puberty and continues throughout the rest of the male's lifetime. Spermatogenesis requires a combination of synchronized gene expression and cell division that takes place in the testes. Apart from the hormones necessary (FSH, LH, and testosterone), of fundamental importance to the normal occurrence of spermatogenesis are the Sertoli cells as they alter rates of spermatozoal production and produce factors essential to gamete development [19–22].

The whole process of spermatogenesis takes around 64–74 days during which mature spermatozoa (haploid cells) are produced from spermatogonia (diploid cells) and can be divided into three stages or phases (as seen in Fig. 1.5).

1. *Spermatocytogenesis:* This process includes division by mitosis and meiosis. Spermatogonia (diploid) divide in utero mitotically to

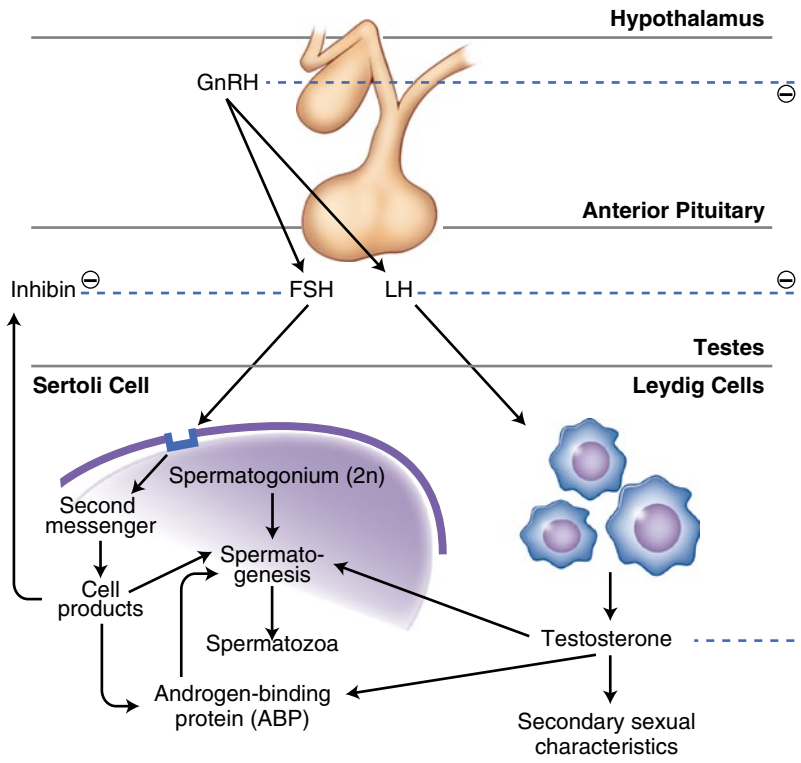

Fig. 1.4 Endocrine control and feedback of spermatogenesis and the hypothalamic–pituitary–gonadal axis *(HPG axis),* follicle-stimulating hormone *(FSH),* luteinizing hormone *(LH),* androgen-binding protein *(ABP)*

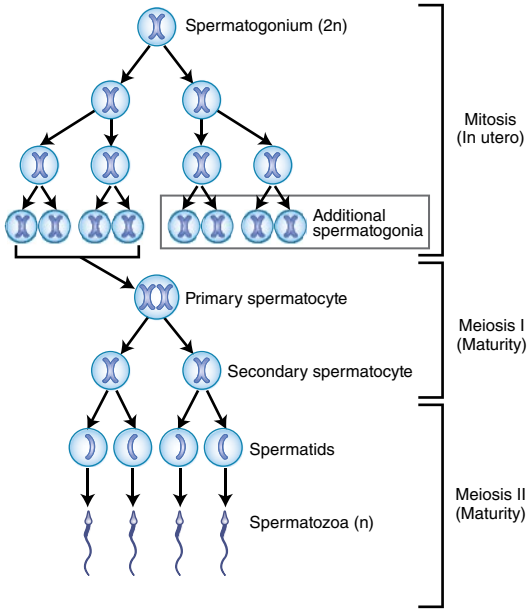

Fig. 1.5 Diagram representing three stages of spermatogenesis: mitosis, first meiotic division (meiosis I) and second meiotic division (meiosis II), and the development from diploid spermatogonia *(2n)* to haploid spermatozoa *(n)*

produce primary spermatocytes (diploid) and additional spermatogonia. After the onset of puberty, the first meiotic division takes place, and primary spermatocytes (which have replicated their DNA to two sets of chromosomes) give rise to secondary spermatocytes (diploid). During the second stage of meiosis, secondary spermatocytes (haploid) divide into spermatids (haploid). Sertoli cells nurture and support the developing spermatozoa throughout this process.

2. *Spermiogenesis:* This phase involves the differentiation of spermatids to produce spermatozoa (haploid). This process primarily entails maturation of the spermatozoon body and nuclear material. Maturation of the spermatozoon includes axoneme development via the thickening of the midpiece and microtubule congregation in addition to flagellum formation from one of the cell's centrioles. Nuclear maturation includes condensation of DNA and

packaging of the DNA, first with basic proteins and subsequently with protamines during spermatid elongation. The ensuing chromatin is not yet transcriptionally active. The chromatin is then enveloped by a Golgi apparatus which is then termed the acrosome. Testosterone is the main regulating factor with regards to spermatozoon maturation and results in the removal of excess organelles and cytoplasm, known as residual bodies, via phagocytosis by the neighboring Sertoli cells in the testicular tissue.

3. *Spermiation:* This is the process by which mature spermatids are released from the protective Sertoli cells into the lumen of the seminiferous tubule before their transition into the epididymis. Spermiation includes several steps including reorganization of the spermatid head and cytoplasm, disintegration of specialized adhesion structures, and the ultimate separation of the spermatid from the Sertoli cell. These processes take place at the apical edge of the seminiferous epithelium and take several days to complete. The newly matured and released spermatozoa are not yet motile and thus not yet able to penetrate the oocyte.

Due to the intricacy of the process, spermatogenesis is totally dependent on the existence of optimal conditions. It is extremely sensitive to changes in the external environment. Therefore, environmental and lifestyle insults that affect gonadal differentiation, Sertoli- or Leydig-cell proliferation, or spermatogenesis at any age could affect male reproductive development and thus lead to adverse reproductive pathologies such as oligozoospermia, asthenozoospermia, hypospadias, testicular cancer, and cryptorchidism [9–11, 20, 23].

Sperm Transport and Maturation

After production in the testes, immature spermatozoa are moved through the corpus and caput regions of the epididyma and are then stored in the proximal section of the cauda epididymis. The spermatozoa move a total of 6 m through the reproductive tract before leaving the urethra. The average transit time in the epididymis is estimated at 12 days. Sperm motion is driven by hydrostatic pressure that is created by the combination of fluids secreted by the seminiferous tubules and tubular peristalsis. Movement through the proximal epididymis is mediated by peripheral smooth muscle contractions, and movement through the epididymal head is mediated by contraction of the tunica albuginea. Fluidic rhythmic movements of the cilia, lining the walls of the ducts, and the cyclic contractions of contractile cells along the wall of the epididymal duct further propel seminal constituents. Epididymal duct contraction is believed to be regulated by cholinergic, adrenergic factors, and vasopressin [24–26].

Spermatozoa mature and acquire functional and motile characteristics during epididymal transit. These changes ensure that the sperm will be able to survive the female reproductive tract, capacitate, and fertilize the oocyte. Each epididymal section contains a unique gene expression profile of the epithelium that leads to specific and specialized secretion of proteins into the lumen. Maturational processes include changes in cell membrane, acrosome shape, and chromatin condensation and stabilization. Cell membrane changes primarily entail a reduction in cholesterol which leads to a downstream activation of kinases that promote capacitation. Chromatin condensation, structural changes to the acrosome and intracellular organelles, and migration of the cytoplasmic droplet, along the sperm tail, are all changes commonly observed during maturation. Lipids and proteins are also reorganized as signaling molecules in anticipation of fertilization. These changes are induced by the fluid milieu, secretions of the epithelium of the seminiferous tubules and epididymal lumen, which the cells are exposed to. This epididymal fluid contains many substances such as sodium, glutamate, albumin, bicarbonate, transferrin, immobulin, inositol, potassium, L-carnitine, sialic acid, lactate, metalloproteins, proenkephalin, taurine, clusterin

(SGP-2), glycerophosphorylcholine, and chloride. These substances are in part responsible for epididymal cell metabolism, activation of sperm motility, and regulation of fluid retention of sperm and epididymal cells [24, 25, 27–31].

Semen

Semen consists of cells suspended in fluid. Semen is generally observed to be a homogenous fluid opalescent to light greyish in color varying with difference in spermatozoal concentration. Semen coloration of reddish or yellow tints can be explained by red blood cells in the semen (hemospermia) or the influence of jaundice or drugs, respectively [32].

The bulk of the composition (99%) is made up of the fluids secreted by the male reproductive accessory glands (i.e., the prostate, the seminal vesicles, and the bulbourethral glands). These secretions join spermatozoa secreted from the vas deferens, during ejaculation, to form a mixture called semen. It is commonly believed that the seminal plasma provides a nutritive and protective medium for the spermatozoa during their journey through the female reproductive tract. The main constituents of semen are listed below along with their functions:

- Water: fluid mechanism of transport for sperm.
- Buffers: protect sperm in acidic vaginal environment.
- Nutrients: fructose, carnitine, vitamin C, and citric acid provide nourishment for spermatozoa.
- Mucus: acts as lubricant for sexual intercourse.
- Spermatozoa: fertilization of oocyte.
- Enzymes: semen clotting in vagina and further liquefaction of clot. Prostate-specific antigen (PSA) is a glycoprotein enzyme encoded by the KLK3 gene produced by the prostate for semen liquefaction and dissolving of the cervical mucus for sperm penetration.
- Prostaglandins: stimulate smooth muscle contraction and transport through both reproductive tracts and improve sperm motility.
- Immunity particles: lysozyme, immunoglobulins, and leukocytes act as antibacterial agents and wash out the urethra; zinc acts as antioxidant.
- Other cells: genitourinary tract epithelial cells and immature germ cells [32–36].

The lower reference limits for semen parameters as described by the World Health Organization (WHO) are as follows: semen volume (ml) = 1.5; total sperm number (10^6 per ejaculate) = 39; sperm concentration (10^6 per ml) = 15; total motility (progressive + nonprogressive, %) = 40; vitality (live spermatozoa, %) = 58; sperm morphology (normal forms, %) 4, and pH = 7.2 [32].

Sexual Response

Erection and ejaculation are two key phases of the male sexual response that are of absolute necessity for copulation and fertilization to take place and are under the control of parasympathetic stimuli (tactile or psychological). Erection takes place through relaxation of the smooth muscle in the penile arteries, as a result of which the sinusoidal spaces become engorged with blood, the corpora become distended and compress the tunica albuginea, which in turn compresses the venous drainage system and traps blood within the penis (as seen in Fig. 1.6). The penile urethra does not close as the tunica albuginea of the corpus spongiosum is thinner and more extensible, thus allowing sperm to be transported during ejaculation. The movement of sperm out of the vas deferens and into the urethra where it encounters secretions from the accessory glands is known as emission. Ejaculation refers to the rapid muscular contractions that dispel semen from the urethra to the external environment outside of the body. Once parasympathetic stimulation ceases, the penis returns to its flaccid state [37–41].

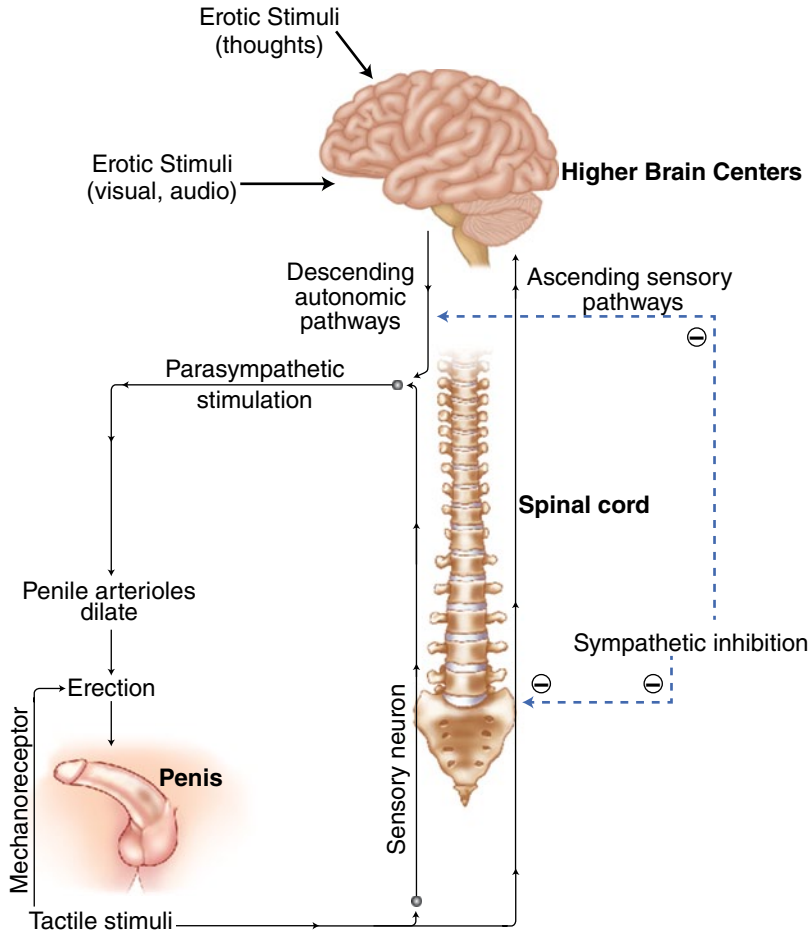

Fig. 1.6 Control, stimulation, and feedback pathways of the male sexual response

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