

Chapter 1

Physiology of Erection

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Introduction and Background

Penile erection is a complex process involving anatomic, vascular, neurologic, hormonal, molecular, and psychological factors [1]. A thorough understanding of erectile anatomy and physiology is essential for fertility specialists as erectile dysfunction (ED) is common in infertile men; it is estimated that some degree of ED is present in 11–28 % of male partners of infertile couples [2–4]. ED and other sexual dysfunctions may pose serious barriers to conception in infertile couples. Aside from compromising a couple's ability to conceive, sexual dysfunction may add to the already substantial psychological toll of an infertility diagnosis [2, 5].

Penile Anatomy

Penile tumescence occurs by the expansion of three chambers of the spongy erectile tissue in the penis (Fig. 1.1) [6]. The paired dorsal corpora cavernosa function as a single unit due to an incomplete septum and extensive vascular communications. Each corpus cavernosum is surrounded by a bilayered collagenous sheath called the tunica albuginea [7]. The tunica provides rigidity and strength to the penis during erection by limiting the degree of corporal expansion and compressing the emissary veins to restrict the outflow of blood from the corporal bodies [6, 8, 9]. The tunica also contains internal fibrous struts that provide additional support. The thickness and strength of the tunica varies over its length; it is weakest on the ventral sides at

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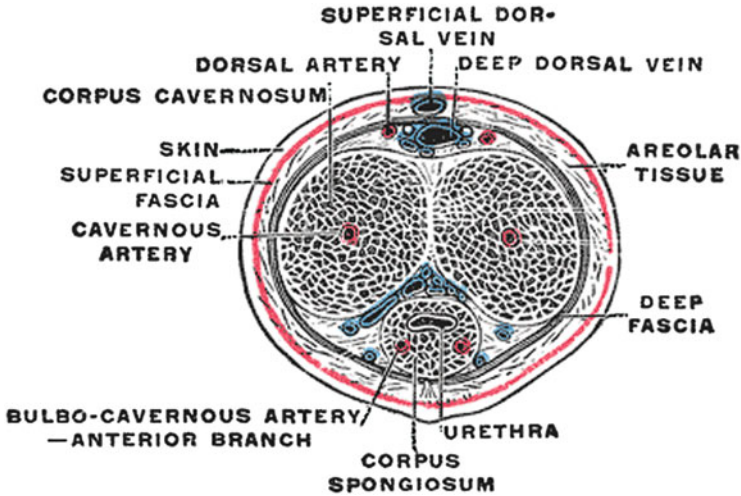


Fig. 1.1 Cross-sectional anatomy of the penis (adapted from Gray's anatomy)

the 5 and 7 o'clock positions and it is in this vicinity that most penile fractures occur [7].

The third erectile chamber of the penis is the ventrally located corpus spongiosum. The corpus spongiosum surrounds the urethra and enlarges distally as the glans penis, the most sensitive portion of the male phallus. The spongiosum lacks a dense tunica sheath and therefore does not become erect in the same fashion as the corpora cavernosa [6]. However, during rigid (maximal) erection the spongiosum and the corpora cavernosa are engorged by contraction of the bulbospongiosus and ischiocavernosus muscles; this forces additional blood into all three erectile chambers [6]. During this phase of the erectile response, intrapenile pressure may exceed systolic blood pressure [6].

All three erectile bodies are surrounded by Buck's fascia. External support of the penis is provided by the fundiform ligament laterally. Medially and dorsally, the suspensory ligament of the penis helps anchor the phallus to the pubic bone [10]. Testosterone appears to play an important role in maintenance of corporal tissue integrity; androgen ablation has been associated with penile tissue atrophy, decreased smooth muscle content, and nerve changes [11]

Vascular Anatomy

The blood supply to the penis is derived from the internal iliac artery via the internal pudendal artery, which gives rise to the common penile artery. The common penile artery also supplies the scrotum and portions of the urethra. The common penile artery bifurcates into the dorsal artery of the penis and the deep penile artery; the

latter supplies the corpora cavernosa via the cavernous and helicine arteries [12]. Branches of the deep penile arteries are given off throughout the length of each corporal body and flow in a radial fashion towards the tunica albuginea and the emissary venous network [12]. Variations in this anatomy do exist. Common variants include unilateral arterial dominance and/or the presence of accessory pudendal arteries [13].

The venous outflow from the penis is primarily via the internal pudendal veins. Emissary veins within the cavernous bodies join to form cavernous and crural veins; these veins either lead to the internal pudendal veins or communicate with circumflex veins which converge on the deep dorsal vein of the penis and eventually the periprostatic plexus. Proximal drainage also flows from Santorini's plexus [12, 14]. Drainage of the skin and subcutaneous tissues of the penis is typically via the saphenous veins. Communication occurs between all the venous systems of the penis and can be highly variable between patients [14].

Neural Anatomy

Central Nervous System

The nervous system regulates penile erection at multiple levels and acts to coordinate the overall process of erection and detumescence. Many of the central nervous system effects may relate to sexual drive (libido) more than penile tumescence; however, the intimate relationship between sexual drive and penile erection makes an understanding of these effects relevant when discussing erectile physiology.

Brain Centers Involved in Penile Erection

The brain has a modulatory effect on the spinal pathways of erection and serves to integrate various sensory inputs. Several supraspinal regions have been implicated including the hypothalamus, limbic system, amygdale, thalamus, substantia nigra, periaqueductal gray, and tegmentum. Additional brainstem and medullary centers are also thought to be involved. The paraventricular and preoptic nuclei found near the hypothalamus in the brain are believed to be specifically associated with facilitation of erection [6, 15].

Neurotransmitters and Neurohormonal Regulation of Sexual Function in the Brain

The modulation of sexual function in the brain is affected by a number of neurotransmitters and hormones; these pathways are incompletely understood and therefore will be considered only briefly here.

Dopaminergic, adrenergic, oxytocin, and melanocortin pathways appear to promote sexual function, while the 5-HT serotonin pathway and prolactin generally appear to inhibit sexual function [1, 16, 17]. Oxytocin is a hormone and neurotransmitter that can act centrally or peripherally. The release of oxytocin tends to promote sexual function and orgasm and may influence nitric oxide production [18]. Norepinephrine from locus ceruleus and in the pons and medulla act on the paraventricular and supraoptic nuclei of the hypothalamus and appear to have a positive effect on sexual function [15]. Finally, the melanocortins additionally modulate sexual behavior and, at the level of the spinal cord, possibly erectile function as well [19]. Less clear are the roles of GABA and opioids, both of which appear to oppose erectile response [20].

Androgens appear to play a role in modulating erectile function in the brain. Testosterone receptors are present in the medial preoptic area and paraventricular nucleus and the medial amygdala [21]. Studies in rats have demonstrated that testosterone appears to prime the central neurologic response to dopamine release [22, 23]. Castrated rats very quickly lose the pro-erectogenic effects of dopamine release; the administration of exogenous testosterone prevents this loss of dopamine sensitivity [21, 22]. Testosterone thus appears to bias sensorimotor integration to elicit pro-sexual effects in response to stimulation in the central nervous system, possibly by the production of nitric oxide [22–24].

5-HT is believed to have a central inhibitory effect in the brain on sexual drive by action on the hypothalamus and limbic system [1]. 5-HT may affect spinal reflexes involved with erection, though some supraspinal facilitator effects may exist as well [25]. Prolactin generally decreases sexual arousal, and this is likely via its negative action on dopaminergic activity. Higher serum prolactin levels have been linked to decreased sexual activity and libido [17].

Spinal Cord and Peripheral Nerves

The penis is innervated by somatic and autonomic nerves. The somatic representation is provided by the pudendal nerve, mediating sensation of the penis, and motor control over striated musculature (e.g., contraction of the ischiocavernosus muscle at rigid erection). The somatic motor nerves arise from the ventral horn of S2–S4 [6, 12]. Somatic sensation is derived from highly concentrated free nerve endings and unique structured corpuscular sensory receptors in the corona, glans, and penile skin [26]. These fibers culminate in bundles which eventually converge

to form the dorsal nerve of the penis. The dorsal nerve of the penis carries afferent sensory input to the pudendal nerve to enter the spinal cord at the S2–S4 roots at which point they terminate on the spinal neuron tracts [27]. Pain and temperature are carried towards brain via the spinothalamic tract [27]. Complex touch and stimulatory input is carried primarily by the ascending spinoreticular tract, proceeding towards the sensory cortex of the CNS [27]. From there, in conjunction with visual, auditory, and additional sensory inputs, they undergo a more complex processing; it is thought that this process modulates perceptions of arousal and sexual stimulation [21, 27]. Efferent innervations to the pudendal nerve are derived from Onuf's nucleus in the ventral sacral spinal cord, which provides motor input to the perineal striated muscles (bulbospongiosus and ischiocavernosus) important for ejaculation [21].

The autonomic component of the cavernous nerves consists of both sympathetic and parasympathetic fibers. The terminal branches of the cavernous nerves (including sympathetic and parasympathetic fibers) innervate the helicine arteries and trabecular smooth muscle, governing the vascular events of erection [6].

Sympathetic innervation to the vascular smooth muscle of the penis is derived from the sympathetic chain ganglia at the T11–L2 levels [6]. These fibers exit the spinal cord as the superior hypogastric plexus or paravertebral sympathetic chain [21], which sits in close proximity to the aorta and is vulnerable to injury during retroperitoneal surgery [28]. Injury to these nerves may have a very substantial effect on seminal emission during ejaculation [29]. Peripherally, these nerves terminate as the pelvic plexus and cavernous nerves [21]. These fibers also mediate baseline sympathetic tone to the penis by action of adrenergic fibers, which release norepinephrine. This maintains the penis in its flaccid state. Adrenergic tone to the penis may be overridden by inhibition from cortical centers, facilitating penile erection by removing inhibitory sympathetic tone [6].

Pro-erectogenic parasympathetic innervation to the penis is provided by the parasympathetic nuclei of the spinal cord at the S2–4 level [6]. Descending parasympathetic neural pathways involved with erection originate in the intermediolateral nuclei of the sacral spinal cord and course peripherally to form the pelvic nerves and join the cavernous nerves. Along their course, they travel intimately close to the prostate and rectum, making them vulnerable to injury during radical pelvic surgery [30].

The specific contributions of the sympathetic and parasympathetic nerve systems to penile erection explain the variation in erectile response observed in men with spinal cord injuries. Psychogenic erections tend to be preserved in men with lower spinal cord injuries (below T12); these erections appear to be mediated by the central nervous system suppression of sympathetic (vasoconstrictive) tone to the penile circulation [6]. The proposed proximal source of this erectogenic efferent modulation is from the medial preoptic area which in its propagation inhibits the sympathetic pathway and facilitates parasympathetic firing [21]. Reflex erections in response to tactile stimulation may be preserved in men with upper cord lesions (above T12). These erections appear to be mediated by the sacral reflex arc which is not interrupted in men with upper spinal cord lesions [6]. It is apparent that partial

preservation of erection is possible in spinal cord injury patients; however, for a complete erectile response it is clear that both the cerebral inhibition of sympathetic stimulation and activation of the parasympathetic response at the level of the sacral spinal cord are required [6].

The Physiology of Penile Erection

Fundamentally, penile erection is a vascular event [6, 8, 9, 12]. There are two components to this vascular process; cavernosal and arterial smooth muscle relaxation/dilation and synergistic restriction of venous outflow [6, 9]. Detumescence occurs following smooth muscle contraction of penile arteries with resultant decreased inflow and drainage of blood trapped within the cavernous spaces [6, 31].

Arterial Dilation

In the flaccid state, there is little blood flow to the penis, and the smooth muscle is in a state of general contraction [6, 31]. Relaxation of the cavernosal arteries increases blood flow 20–40-fold. Within the tunica of the corporal bodies, there are endothelial-lined sinusoids between layers of the trabecular smooth muscle. These lacunar spaces are filled with blood during erection [9].

Venous Occlusion

As the penis expands, pressure increases at the outer circumference of the corpora near the tunica albuginea; this is the primary site of the venous outflow from the corporal bodies. As filling continues, the peripherally located subtunical venous plexus and the emissary veins are compressed between the relatively inelastic outer layer of tunica albuginea and the corporal sinusoids. This veno-occlusive mechanism enhances tumescence by impeding the outflow of blood [8, 9]. This blood-trapping phenomenon accounts for the rise in cavernous pressure seen at full erection, which typically averages around 100 mm Hg in healthy men [6]. Pressure in the corpus spongiosum is usually a third of what is observed in the corpora cavernosa during this phase of erection because the thinner tunica albuginea of the spongiosum does not permit tight coaptation [6].

The vascular component of erection is further enhanced by the bulbocavernosal reflex brought on by repetitive penile stimulation (e.g., intercourse). During this response, the bases of the corporal bodies (crura) are compressed by a strong sustained contraction of the ischiocavernosus and bulbospongiosus muscles. This contraction forces additional blood into the erectile chambers and increases rigidity

of the corpus spongiosum and glans penis. This leads to the rigid erection phase in which intrapenile pressure may exceed systolic blood pressure [6].

Molecular Mechanisms of Penile Erection

Smooth Muscle Activity and Calcium Metabolism

Smooth muscle contraction, in penile vasculature and elsewhere, is modulated by the binding of calcium ion to calmodulin. The calcium–calmodulin complex binds to myosin light chain kinase, creating a calcium–calmodulin–myosin light chain kinase complex (MLCK). The formation of this complex triggers phosphorylation of ATP on myosin light chains, providing energy for actin cross bridging and cycling of myosin attachments to actin. The end result is smooth muscle contraction [32].

Thus, intracellular concentrations of calcium play a role in regulating smooth muscle contraction [33]. There are a number of mechanisms by which intracellular levels of calcium are regulated; the most well understood of these are outlined below.

NO/cGMP

The major neurochemical cascade controlling smooth muscle relaxation in the penis is the nitric oxide-cyclic GMP (NO/cGMP) pathway (Fig. 1.2) [34, 35]. NO is generated by cleavage of its precursor L-arginine by the enzyme nitric oxide synthase (NOS).

NOS is found in the terminals of non-cholinergic, non-adrenergic, nitrergic cavernous nerves (neuronal NOS, nNOS) and in the endothelium (endothelial NOS, eNOS) of vascular structures including the penis [36]. Neuronal-derived NO is thought to initiate erection, while endothelial-derived NO is thought to help maintain it [36, 37]. eNOS activity is modulated in part by release of Acetylcholine (Ach) from parasympathetic nerves; Ach acts on muscarinic receptors in the cavernous tissue and promotes release of nitric oxide from the endothelium via eNOS [36, 38].

In smooth muscle cells, NO activates the membrane bound enzyme guanylyl cyclase which converts GTP to cyclic GMP (cGMP) [36]. cGMP interacts with protein kinase G. Protein kinase G has numerous downstream effects, the most important of which is the activation of various cell and sarcoplasmic reticulum membrane protein and ion channels [6]. Activation of these channels sequesters calcium ions in the sarcoplasmic reticulum and expels calcium ions from the cell [6, 33]. The flow of calcium is tightly linked to the activity of potassium channels

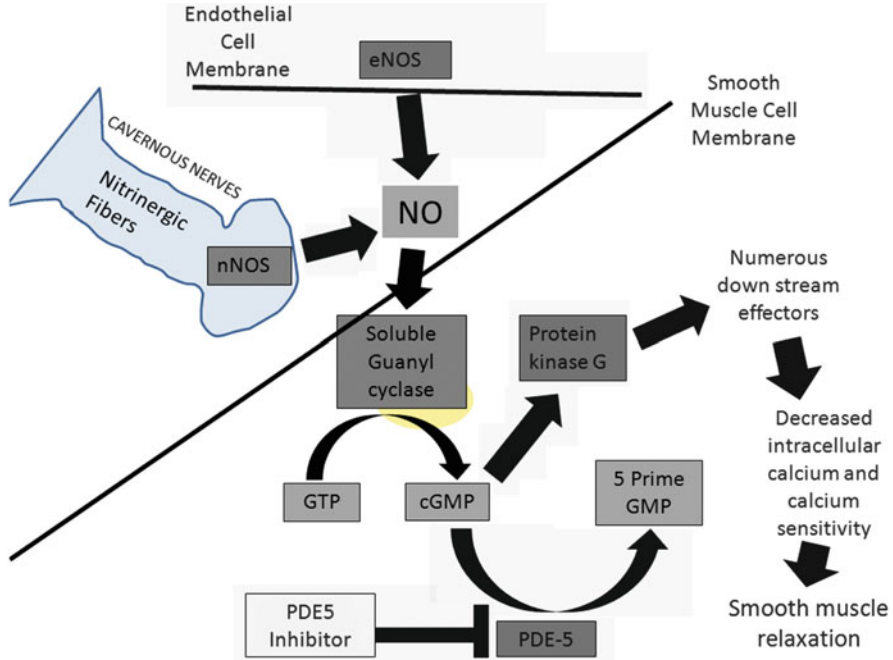


Fig. 1.2 The NO/cGMP pathway in erectile physiology. Molecules are presented in *light gray boxes*, enzymes in *dark gray boxes*, pathways in *black arrows*

which hyperpolarize the smooth muscle cells in turn causing closure of voltage-dependent calcium channels. This activity between adjacent cells is synchronized by the presence of gap junctions which allow for rapid communication of signaling [6]. The net effect of these various processes is at least the transient reduction in intracellular calcium [33].

NO release in smooth muscle also has effects on the activity of inositol triphosphate (IP₃), phospholipase C, endothelin, and the Rho kinase pathways [33, 36]. These pathways (partially detailed below) are also important in erectile physiology.

PDE5

The phosphodiesterases are a class of enzymes that degrade cyclic nucleotides such as cGMP and cAMP. There are at least 11 known isoforms encoded on 21 different genes found in different tissues throughout the body [39]. Within the penile tissues, the most important isoform is PDE type 5 (PDE5), which acts exclusively on cGMP [40]. PDE5 is composed of two domains, a regulatory domain and a catalytic domain, the latter of which degrades cGMP by hydrolysis to 5 prime GMP

[39]. PDE5 breaks down cGMP continuously as the molecule is produced, providing constant negative regulation on the erectile process [39]. As PDE5 reduces the amount of available cGMP, intracellular calcium concentration tends to increase, which promotes smooth muscle contraction. Detumescence is thus driven in a large part by PDE5 activity.

PDE5 is the target molecule of the class of drugs known as PDE5 inhibitors (PDE5I) which includes sildenafil, vardenafil, tadalafil, udenafil, avanafil, mirodenafil, and lodenafil [41, 42]. These drugs are competitive inhibitors of PDE5 and thus tend to elevate cytosolic levels of cGMP [41]. The net result of increased cGMP activity is decreased intracellular calcium and subsequent smooth muscle relaxation, leading to prolongation of vasodilation. Because PDE5I act to maintain preexisting levels of cGMP, it is clear that these drugs cannot act without some form of sexual stimulation and/or an intact means to generate cGMP in penile tissues.

Other Mediators

A number of other molecular agents have been shown to have roles in the erection process. Many of these are areas of active research and will thus be mentioned briefly here.

The cyclic AMP, another cyclic nucleotide, is shown to have a similar action as cGMP on the smooth muscle cells of the penile vasculature. Like cGMP, cAMP is degraded by PDEs and promotes a decrease in intracellular calcium levels by its action on protein kinase A. Cyclic AMP is upregulated by a family of eicosanoides, the prostaglandins, specifically PGE1 [43]. The prostaglandins have widespread effects throughout the body; however, a few subtypes including PGE1 have been shown to act on various penile tissues. PGE1 has been utilized as therapeutic injection or intraurethral suppository in the treatment of ED [1].

Inositol triphosphate (IP3) levels are increased in response to the neurologic stimulation of protein phospholipase C. IP3 in turn stimulates the release of calcium from the sarcoplasmic reticulum, tending to promote smooth muscle contraction [44]. Carbon monoxide (CO) is a gaseous second messenger compound with activity somewhat similar to NO [45]. CO has an effect on vascular tone and may stimulate production of cAMP and cGMP [45, 46]. The natriuretic peptides (atrial, brain, and c-type natriuretic peptides) function in the regulation of the cardiovascular system and seem to have relaxing effects in the cavernous smooth muscle; their role in physiological erection in vivo is unclear [47].

The Rho A/Rho kinase calcium sensitization pathway has been a topic of some interest in recent years [48]. Rho A is a molecule that activates Rho kinase. Rho kinase in turn phosphorylates myosin light chain phosphorylase (MLCP); this has the net effect of decreasing MLCP activity [48, 49]. MLCP is responsible for removing phosphate groups from the myosin light chain. The increased phosphorylation of myosin light chain tends to increase the actin–myosin cross bridge

formation in response to intracellular calcium and hence promotes smooth muscle contraction [49].

Endothelin, which is present within smooth muscle, is also felt to potentiate the effects of the catecholamines in promoting smooth muscle contraction [50]. Prostaglandin F₂-alpha and angiotensin II have also been shown to play a role in the maintenance of smooth muscle tone in response to sympathetic input. These factors together are thought to maintain baseline penile flaccidity [51].

Conclusions

Erectile physiology is of great importance to the fertility specialist as ED is common in infertile men and may pose a substantial barrier to conception. Penile erection is fundamentally dependent on the actions of neural and vascular pathways both centrally and peripherally. An understanding of the complex physiology of penile erection enables the infertility practitioner to address issues of sexual dysfunction in their patients.

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