Chapter 36

Molecular Biology and Physiology of Erectile Function and Dysfunction

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36.1 Introduction

Erectile dysfunction (ED) refers to the inability to achieve or maintain an erection for satisfactory sexual performance. It is highly prevalent among aging men and can have significant impact on quality of life and interpersonal relationships [1]. It was estimated in 2000 that as many as 18 million Americans aged 40–70 have some degree of ED with a growing incidence rate of 26 new cases per 1,000 annually [1]. Similar projections suggest that by the year 2025, global prevalence may be as high as 322 million [2]. ED has well-established associations with poor general health including cardiovascular disease and diabetes, lifestyle factors, and even low socioeconomic status [3]. Therefore, identification of ED offers a glimpse into men's health, illuminating underlying illness and providing opportunities to intervene in otherwise asymptomatic men.

Over the last several decades there have been major advances in our understanding of erection physiology from the neural pathways of the sympathetic and parasympathetic nervous system down to the biochemical effectors such as nitric oxide (NO), Ras homologue A (RhoA), and cyclic adenosine monophosphate (cAMP). These discoveries have helped us better understand pathophysiology and develop a number of effective pharmacotherapies. The aim of this chapter is to summarize the anatomical and molecular biology of erectile function, highlighting the dynamic interplay of multiple neurochemical pathways that enable male potency.

36.2 Physiology of Erectile Function

Penile erection requires a highly coordinated process mediated by the nervous system, vascular smooth muscle tone regulation, and balancing pro-erectile and anti-erectile molecular mediators [3–4]. The penis is composed of three cylinders of erectile tissue: the corpus spongiosum that surrounds the urethra and is continuous with the glans penis and paired corpora cavernosa. The corpora cavernosa are found dorsally, encased by the dense tunica albuginea, and act as a vascular reservoir composed of trabeculae sinuses supplied by helicine arterioles from the deep penile cavernosal artery originating from the internal pudendal artery. The corpora cavernosal sinuses are drained by emissary venules into the circumflex or deep dorsal veins. These three cylinders are surround by Bucks fascia and Dartos fascia superficially [4–6] (Figure 36.1).

Generally, erections occur when neurotransmitters are released from cavernous nerve terminals leading to relaxation of tonically contracted cavernosal smooth muscle. This relaxation leads to dilation of the arterioles increasing blood flow into the trabeculae sinuses. Increased blood flow engorges the corpora cavernosa stretching the tunica albuginea to its capacity and compressing the venular plexus and restricting venous outflow, described as the veno-occlusive process. The summation of these events leads to increased pressure in the corpora cavernosa and tumescence of the penis. Detumescence is achieved when smooth muscles contract against the closed venous system leading to transient pressure increases. This triggers the venous channels to reopen with a return of basal arterial inflow and finally smooth muscle returning to its normal flaccid contracted state [6–7].

36.2.1 Neurophysiology

Physiologic erection relies on the integration of central, peripheral, and autonomic (sympathetic and parasympathetic) nervous systems. The sympathetic preganglia originate around the 10th to 11th thoracic to the 2nd to 3rd lumbar spinal cord segments. The sympathetic chain ganglia most commonly projecting to the penis are located in the sacral and caudal lumbar ganglia, though a few fibers will travel through the superior mesenteric and inferior hypogastric plexus and ultimately into the pelvic plexus [7–8]. The parasympathetic pathway originates from the second to fourth sacral spinal cord where the preganglionic fibers pass to the pelvic plexus and join sympathetic innervation from the superior hypogastric plexus to form the pelvic plexus. This plexus carries branches to the cavernosal nerves that innervate the penis. The somatic inputs, which comprise sensory and motor nerve signals, are driven via the pudendal nerve that innervates the bulbospongiosus and ischiocavernosus striated muscle, as well as the penile skin and urethra [7].

The parasympathetic pathway via the pelvic plexus activates physiologic erections. This is done by release of acetylcholine from cholinergic presynaptic nerve endings that promotes NO release from the endothelial cells as well as inhibits presynaptic adrenergic neurons. As will be discussed later, the activation of NO is a major driver of erectile function [4,9]. Penile detumescence is regulated by sympathetic release

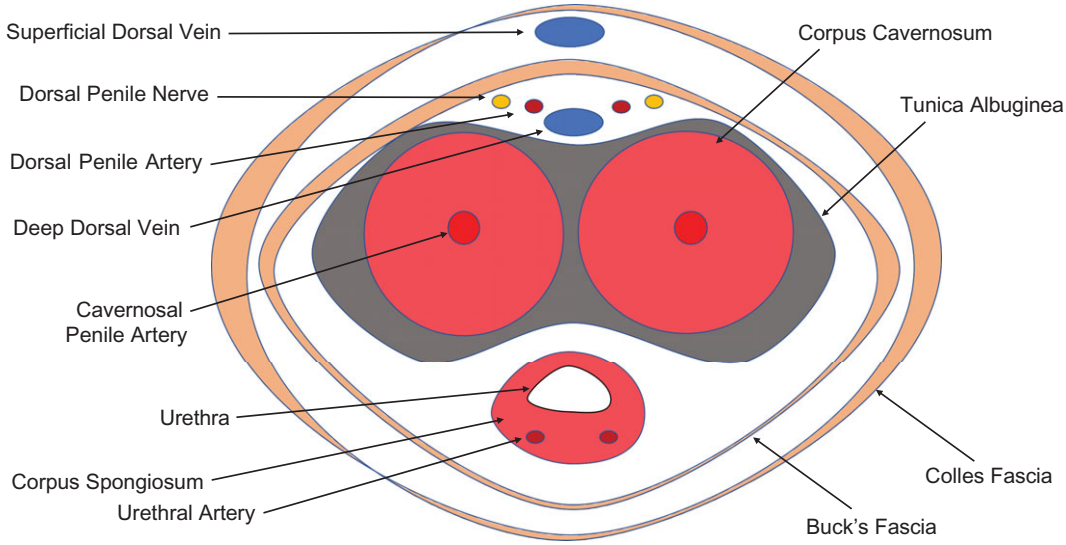

Figure 36.1 Coronal section of penile anatomy

of norepinephrine (NE) from adrenergic neurons stimulating alpha receptors in the penile vasculature and within the corpus cavernosum, ultimately leading to contraction of the arterioles and smooth muscle [8]. Additionally, endothelin, a vasoconstrictor also released by local endothelial cells, leads to long-lasting contractions throughout penile smooth muscle. Some studies suggest that endothelin maintains constriction in the basally flaccid penis, whereas norepinephrine plays an active role in acute detumescence [10].

There are three types of physiologic erections including psychogenic, reflexogenic, and nocturnal (sleep related). Psychogenic is driven by sexual stimulation from auditory, olfactory, visual, and mental erotic factors that activate supraspinal impulses. Animal studies have identified the medial preoptic area (MPOA), the paraventricular nucleus of the hypothalamus, and the hippocampus as some of the key integration centers for these sexual impulses [11]. These signals then travel down the spinal cord through the parasympathetic pathway to elicit penile erections. With regards to the supraspinal component of erections, imaging studies using positron emission tomography and MRI have been done to map brain activation patterns in males triggered by sexual stimuli [12–13]. This research is promising and may one day shed light on higher-level pathologies including sexual deviation, psychogenic ED, and orgasmic dysfunction.

In contrast to psychogenic, reflexogenic erections occur secondary to tactile stimulation of the external genitalia. Afferent sensory impulses travel through the pudendal nerve and either ascend the spinal column to become sensory perception or stimulate the reflexogenic pathways via interactions of the afferent signal with the inferior hypogastric plexus. Efferent signals from the inferior hypogastric plexus in turn stimulate cavernous nerves to elicit erections. This reflexive pathway explains how some patients with upper spinal cord injuries can lose psychogenic erections but have preserved reflexogenic erections. Erections of spinal cord injury men are often not strong enough for intercourse without pharmacologic stimulation [7]. Conversely, animal studies where the spinal cord is removed below the 4th or 5th lumbar can eliminate reflexogenic responses, but if presented with audiovisual stimuli psychogenic erections can occur [14].

Lastly, nocturnal penile tumescence (NPT) occurs during rapid eye movement (REM) sleep. The underlying pathway or evolutionary purpose of NPT is not completely clear; however, some studies suggest the central factors include activation of cholinergic neurons in the lateral pontine tegmentum, inhibition of adrenergic neurons in the locus ceruleus, and downplay of serotonergic neurons in the midbrain raphe [7]. Likewise, given the rise of testosterone during the early morning, some postulate there is an endocrine component in the mechanism as well [15].

36.2.2 Molecular Effectors

The regulation of penile erections depends on molecular transmitters that act at the level of the corporal smooth muscle. Smooth muscle relaxation and contraction is ultimately determined by the level of intracellular calcium. Sympathetic activation via NE causes ion channels to open releasing calcium from intracellular stores as well allowing influx of calcium from extracellular space. The increase in free calcium binds to the compound calmodulin forming a complex that phosphorylates myosin light chain kinase (MLCK). This activation triggers cross-bridging of the myosin filaments leading to muscle contraction [4,7] (Figure 36.2). Another pathway for smooth muscle contraction is altering the receptor sensitivity to calcium via RhoA, a small monomeric G protein. RhoA inhibits one of the regulatory subunits of myosin phosphatase, preventing deactivation of the myofilament and therefore promoting a contracted state [16]. Though both pathways lead to

Table 36.1 Classifications of erectile dysfunction

Organic
I. Vasculogenic
II. Neurogenic
III. Anatomic
IV. Endocrinologic
Psychogenic
I. Generalized
II. Situational

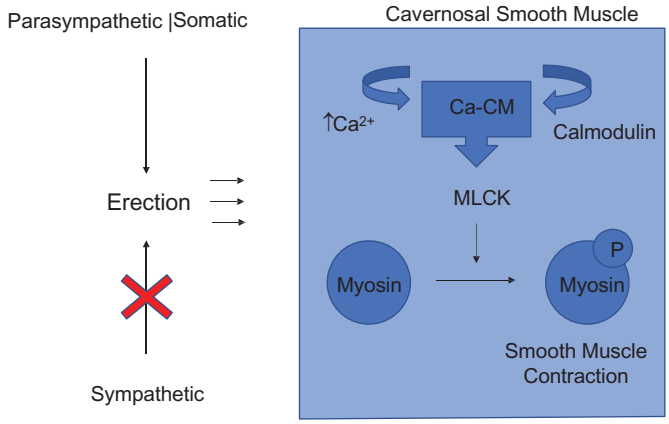

Figure 36.2 Physiology of penile erection and detumescence

smooth muscle contraction, it is believed that increases in cytosolic calcium cause the phasic contraction of penile smooth muscle, whereas the RhoA pathway regulating calcium sensitivity is key in maintaining the tonic contraction of a flaccid penis [17].

NO plays a similarly important role in erectile function. Parasympathetic activation of acetylcholine leads to the release of NO from the nonadrenergic noncholinergic (NANC) nerve fibers as well as from endothelial cells. NO release from the NANC fibers initiate smooth muscle relaxation for erections, whereas the NO from endothelial cells works to maintain the erection [18]. Furthermore, NO activates the secondary messenger cAMP and cyclic guanosine monophosphate (cGMP) that result in the opening of cytoplasmic potassium channels. The net effect is hyperpolarization of the cell, sequestration of intracellular calcium, and blockage of calcium influx [6–7]. As intracellular calcium decreases, fewer calmodulin complexes form and less cross-linking of myosin occurs. This results in smooth muscle relaxation. The process by which cGMP is deactivated is via phosphodiesterase type 5 (PDE5) hydrolysis. An entire class of erectogenic medications called PDE5 inhibitors block PDE5 function thereby promoting cGMP and drive cavernosal smooth muscle relaxation and erections [4].

36.3 Pathophysiology of Erectile Dysfunction

Erectile dysfunction has been classified though two prevailing paradigms: based on etiology, for example trauma, diabetes, drug induced, etc. versus blood flow/mechanism of action, for example failure to initiate (neurogenic/psychogenic), failure to fill (arterial), and failure to store (venous), etc. In the next part of this chapter, we aim to characterize the different pathologies leading to ED. This section has been organized based on the widely accepted classification espoused by the International Society of Impotence Research [19] (Table 36.1).

36.3.1 Vasculogenic

Erectile dysfunction secondary to underlying vascular disease is one of the most prevalent etiologies for organic dysfunction. Arterial insufficiency results in decreased perfusion of the hypogastric-cavernous-helicine arterial system leading to diminished intracavernosal pressures, longer filling times, and decreased penile rigidity. Furthermore, vasculogenic ED may feature veno-occlusive dysfunction (failure to occlude subtunical and emissary veins) either from traumatic injuries, venous shunts, or as degenerative/fibrotic from chronic poor arterial perfusion [7]. Arteriogenic ED is most often caused by atherogenic plaque of the internal pudendal, common penile, and cavernosal arteries [20]. Other focal arterial defects from vascular injury can be seen in men with history of trauma, surgery, and radiation to the pelvis. Arteriogenic ED may also be responsible for cycling-related ED; however, controversy remains whether cycling-related ED is due to neurogenic factors or ischemia [21–24].

Since vasculogenic ED is commonly due to chronic atherosclerotic disease, it often precedes significant cardiovascular and cerebrovascular disease [25]. Therefore, diagnosis of vasculogenic ED in otherwise asymptomatic men may warrant early cardiac and coronary artery disease workup [20].

The oxygen-poor environment of arteriogenic ED alters levels of several transmitters including prostaglandin E1 and transforming growth factor-B1 (TGF-B1) thereby increasing profibrotic and inflammatory cytokines [27,28]. The net effect is further collagen deposition, impaired endothelial vasodilation, and increased vascular resistance. A similar effect can occur with neurogenic ED. Endothelial damage, either through poor perfusion or lack of neurostimulation, leads to loss of smooth muscle and local fibrosis. Along with upregulated inflammatory markers, the endothelium becomes scarred, thereby restricting erectile function [7,27–28]. These changes can cause and worsen veno-occlusive dysfunction [7,28]. Arteriogenic ED often starts as a failure to fill (arterial), but with sustained fibrotic degeneration of cavernosal tissue, secondary veno-occlusive changes can develop.

36.3.2 Neurogenic

Neurologic deficits anywhere along the neuroaxis from brain to cavernosal nerves can lead to ED. An estimated 10–19% of

ED is neurologic in origin [29]. Ultimately, the end result from any neurologic deficit is diminished release of transmitters such as NO to penile smooth muscle. Similar to vascular ED, long-term neurologic ED results in apoptosis of smooth muscle cells and endothelial cells with collagenization of local tissue worsening penile inelasticity [30].

Starting at the level of the brain, the MPOA and hippocampus are the integration centers that translate sexual desire to penile erection. Therefore, neurologic damage, from such conditions as cerebrovascular disease, tumors, dementia, Alzheimer's, temporal lobe epilepsy, and trauma, can directly impact erectile function. Likewise, one study found that 53% of Alzheimer's patients in a study had ED, not related to depression, age of onset, or cognitive impairment, but correlated with the onset of Alzheimer's symptoms [31]. Likewise, many neurologic diseases that cause imbalance in brain neurotransmitters like serotonin and dopamine can cause ED. Classically, this is seen in Parkinson's disease where damage to the substania nigra kills cells producing dopamine and therefore disrupts a major neurotransmitter that potentiates the activation of erections [32]. At the same time serotonin when upregulated also causes ED by altering the central nervous system activation of erectile function. This effect can be seen in the increased rates of sexual dysfunction in patients taking selective serotonin reuptake inhibitors (SSRIs) [33]. Therefore, the balance of serotonin (inhibitory) and dopamine (facilitatory) is critical in normal sexual function [32–33].

Spinal cord injuries can result in variable degrees of ED depending on the level and extent of the injury. As previously discussed, reflexogenic erectile function can occur in patients with upper cord lesions due to an intact inferior hypogastric plexus. As many as 95% of spinal cord lesions above the tenth thoracic vertebral (T10) level have intact reflexogenic erection; however, lower spinal cord injuries preserve reflexogenic erectile function at lower rates. Twenty-five percent of men with spinal cord injury at the sacral spinal levels S2–S4 possess reflexogenic erectile function [29,34]. Disease that can impact the spinal cord includes trauma, disc herniation, tumors, multiple sclerosis, transverse myelitis, syringomeylia, and spina bifida [32–34].

At the level of the peripheral nerves, cavernous nerve injury can result in neurogenic ED in men with pelvic trauma or iatrogenic injury from pelvic surgery. Due to the limited pelvic space and close proximity to pelvic organs high rates of ED have been reported for radical prostatectomy (40–85% at varying centers of excellence [35]) and abdominal perineal resections (61.5% in one study [36]). Even with improved surgical technique, like cavernous nerve sparing radical prostatectomy, only two-thirds of patients undergoing pelvic oncologic surgery will preserve potency, depending on baseline function and extent of oncologic disease [37]. Likewise, patients can sometimes take up to 24 months to recover erectile function [37–38]. This has led to intense research in different medications and protocols for post pelvic surgery nerve rehabilitation [39]. Patients with pelvic trauma may also suffer from both vasculogenic and neurogenic ED given the close proximity of nerves with major blood vessels. This can explain the high level of sexual dysfunction in almost two-thirds of men after pelvic fractures [40].

Additionally, patients with diabetes represent a well-established risk group for ED. Diabetes ED is multifactorial and stems from endothelial dysfunction and neurogenic ED, with autonomic neuropathy and progressive demyelination of peripheral nerves [26].

36.3.3 Endocrine

Testosterone plays a critical role in men's health and male sexual behavior, enhancing sexual interest and increasing frequency of sex and nocturnal erections [41–42]. Additionally, testosterone has important roles in maintaining bone health, body composition, and cardiovascular health [42]. Therefore, testosterone is critical in erectile function. A 2017 meta-analysis inclusive of 14 studies and 2,298 patients showed that testosterone therapy used in hypogonadal men results in dose-dependent improvement in erectile function [43]. Using the validated International Index of Erectile Function Test (IIEF) the authors found that testosterone replacement therapy significantly improved erectile function when compared to placebo (mean difference = 2.31, $p<0.001$). The authors also found greater changes in IIEF score (mean difference 2.95 versus 1.4, $p = 0.02$) in severe hypogonadal men (total testosterone <8 nmol/L) compared to men with milder deficiency (total testosterone <12 nmol/L). Another group also performed a systematic review looking at hypogonadal men (total testosterone <10.4 nmol/L) who failed PDE5 monotherapy treated with PDE5 and testosterone replacement. Though the individual studies were heterogeneous, the authors found that the combination of the two medications may benefit patients who failed monotherapy alone [44]. These studies highlight the central theme that testosterone plays an important role for male sexual health and erectile function. However, this exact relationship is complex and far from linear since increasing testosterone in eugonadal men does not result in improved function [45]. Therefore, additional studies are needed, especially those that look at the correlation of testosterone with other known erectile regulators. For example, some are researching the role testosterone deficiency plays in downregulation of NO synthase via endothelial dysfunction [46]. By improving our understanding of the integration of these components we can seek to find new solutions for erectile dysfunction.

Dysfunction of endocrine hormones at other levels of the hypothalamic-pituitary gonadal axis can also impact erectile function. In patients with hyperprolactinemia, from medications (e.g., dopamine-receptor antagonists or depleting agents) to prolactin-secreting tumors, excess prolactin inhibits hypothalamic gonadotroponin-releasing hormone, which ultimately leads to low testosterone production and ED [41–42].

36.3.4 Psychogenic

Psychogenic ED was once believed to account for most forms of ED [4]. However, current belief is that organic ED is more

common than previously thought and likely coexists in a large portion of psychogenic ED patients. In fact, studies in otherwise healthy men under 40 years of age found 15–72% had identifiable organic causes [47]. As discussed earlier, the brain processes sexual stimuli with input from stimulatory and inhibitory afferent signals. Anxiety and social stress can produce excessive sympathetic outflow. The increased circulatory catecholamine along with increased supra-sacral inhibition by sympathetic tracts can hamper erections. Some studies support this with higher levels of serum norepinephrine (sympathetic pathway) in patients with psychogenic ED compared to controls. A study looking at the level of catecholamines in penile blood during pharmacologic penile stimulation with papaverine showed levels of norepinephrine were higher in psychogenic ED than in those with vasculogenic ED ($p<0.01$), and it was higher in negative responders than in positive responders ($p<0.001$) [48].

A key feature of psychogenic ED is the situational and mental aspect. Components such as comfort with sexual partner, arousability, and higher inhibition due to conflict or threat all can lead to sexual anxiety and psychogenic ED. Therefore, psychogenic ED can be seen with other sexual dysfunctions such as premature ejaculation and also occur during periods of mental stress including death of loved ones and depression [49].

36.3.5 Drug-Induced

Drug-induced ED may contribute to ED in almost a quarter of affected men [50]. Though at times it can be difficult to differentiate between ED due to medication or an underlying disease, there are medications with well-established ED side effects. For instance, antihypertensives such as beta blockers can dampen the neurogenic impulses as well as inhibit the relaxation of the penile arteries. Diuretics can decrease the blood flow necessary to form a robust erection. Antidepressants such as SSRIs lead to excess serotonin, a known erectile inhibitor. Anti-androgen and several antifungal medications work by directly inhibiting testosterone, which as noted in the endocrine section are critical in erectile function [33,50]. Additionally, medications like digoxin, opiates, and H2 blockers have all been linked to ED. Recreational substances such as alcohol and marijuana have also been linked to ED [33]. Chronic alcoholism, for instance, can lead to decreased libido, alcoholic polyneuropathy, and liver dysfunction impacting testosterone levels. Therefore, a workup of ED should include a thorough reconciliation of a man's medication history.

36.4 Conclusion

In this chapter, we summarized the molecular biology and anatomy required to produce erectile function. Erectile function depends on the interactions between multiple body systems and can be influenced by molecular effectors that balance pro and anti-erectile function. The well-orchestrated steps result in smooth muscle dilation and improved vascular flow against venous drainage. Along this same route there are a number of ways erectile function can be disrupted. Erectile dysfunction can have tremendous impact on the male psyche and quality of life. Therefore, it is a critical area of research not only for symptomatic treatment, but durable long-lasting cures.

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