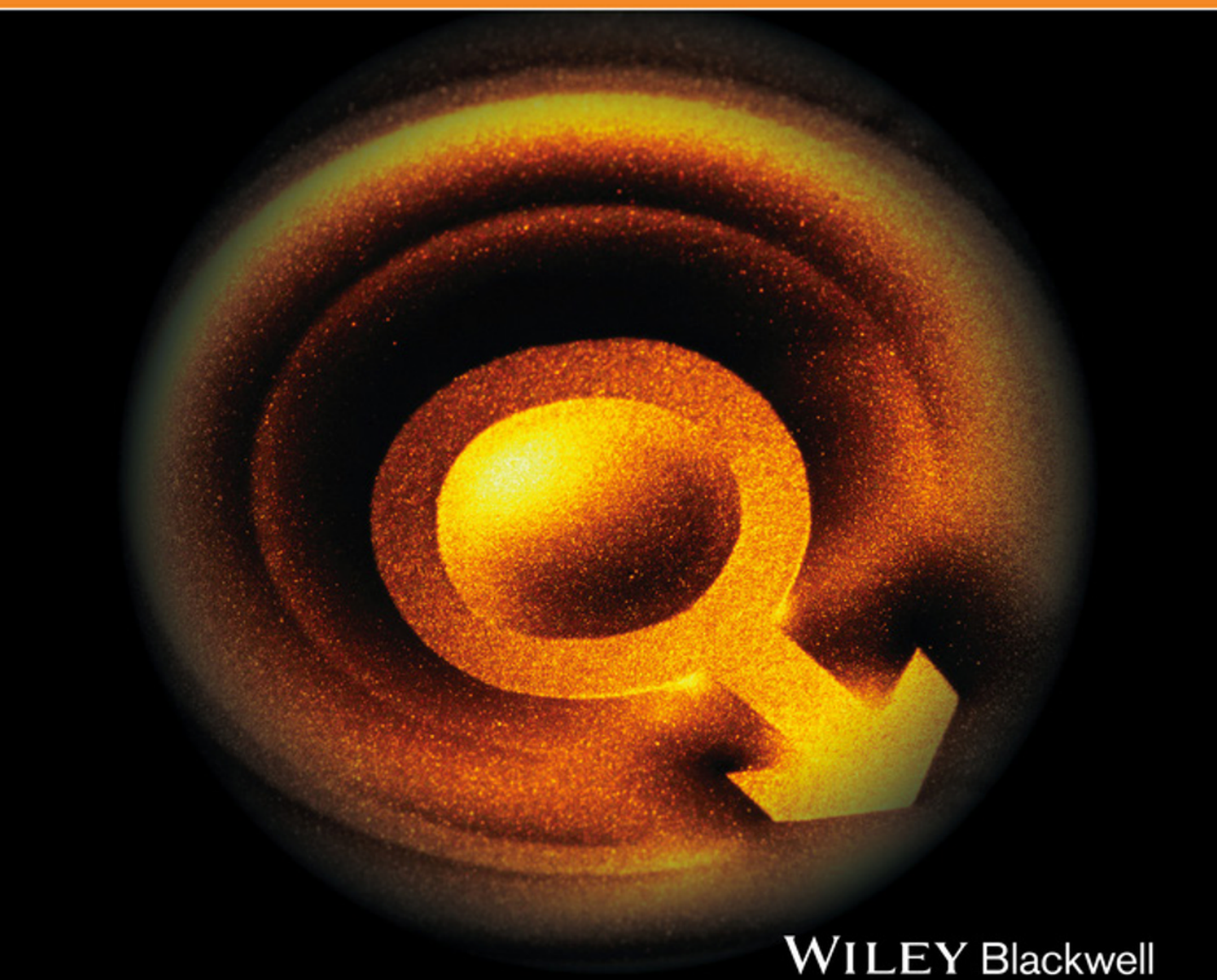
Male Sexual Dysfunction

A Clinical Guide

Edited by
Suks Minhas and John Mulhall



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Foreword

This is a very important book. Its importance lies in the fact that male sexual health is these days central to very many men's quality-of-life. Male sexual dysfunction, resulting from aging or some disease process, such as diabetes, can therefore have serious, and often underestimated, repercussions. Men, particularly as they age, are extremely dependent on a lasting relationship with their partner for their well-being. In general, single or divorced men have a lower quality-of-life and higher risk of mortality than those who sustain their relationships in the longer term. Marital breakdown, which may be the consequence of male sexual dysfunction, can also have an impact on the next generation. The financial and emotional strains resulting from a fractured relationship may take a significant toll on the children, as well as on the two conflicted adults themselves.

As populations around the world age and increase, the incidence of male sexual dysfunction is set to rise and rise. Fortunately, as so well described in this book, its management has been transformed over the last 20 years by the advent of safe and effective pharmacotherapy, and, in selected cases, specialized andrological surgery. Viagra is still the world's most instantly recognizable pharmaceutical brand, and is now much more affordable in its generic form: sildenafil. However, counterfeit products, often containing hazardous ingredients, are unfortunately increasingly available, often over the internet, and have recently been associated with several deaths in the Far East. Intracavernosal injection therapy, pioneered originally by the impressive Professor Giles Brindley, has an increasingly important role to play in the more difficult-to-treat men, who are usually either post-pelvic surgery or longstanding diabetics. The third-line treatment for refractory cases of erectile dysfunction by implantation of inflatable or semi-rigid penile implants, which, provided that it is skillfully performed, can yield excellent results, is also well described in this excellent volume, along with other specialized surgical procedures for Peyronie's disease and other andrological conditions that can impact negatively on sexual function.

After many years in the wilderness "men's health" is at last beginning to take center stage. Sexual health is central to a man's self-esteem and well-being. I have high hopes that this book, edited by two of the world's leading experts in the specialty, which I whole-heartedly commend to you, will be widely read, not only by those with a special interest in male sexual health, but also by generalists and family practitioners, as well as nurse specialists. Only by improving the lamentably deficient knowledge about the safe and effective treatment options now available for the very many men who are affected by male sexual dysfunction, will their lives be improved and their relationships preserved. This is undoubtedly a most laudable ambition.

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CHAPTER 1

Epidemiology of male sexual dysfunction

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The broad term of sexual dysfunction includes erectile dysfunction, ejaculatory dysfunction, hypogonadism and low sexual desire, Peyronie's disease and other penile morphological alterations, and urinary incontinence associated with sexual function. Knowledge of the epidemiology of various sexual dysfunctions is important in designing sexual health programs and allocation of budget and healthcare resources, in patients' and partners' education, and in clinical assessment of individual subjects. There are numerous epidemiologic studies in the contemporary medical literature, comprehensively detailing the prevalence of sexual dysfunctions; however, reported epidemiologic data vary greatly. Several factors account for these inconsistent data. The main one is probably the definition used to define a particular sexual dysfunction. For example, in selected high-quality studies reporting on erectile function outcome in the post radical prostatectomy male population, more than 20 different definitions of favorable erectile function were used. Hence, the reported incidence of adequate erectile function varies, ranging from 25 to 78%.[1] Since the definition of sexual dysfunction is not unified, it is not unreasonable to expect variation in sexual dysfunction epidemiologic data: the higher the threshold for normal sexual function, the greater is the incidence of sexual dysfunction. Moreover, sexual dysfunction is commonly assessed using questionnaires. More objective modalities, such as hemodynamic assessment of the penis by Doppler ultrasound of the erect penis to establish a diagnosis of vasculogenic erectile dysfunction, or stopwatch-measured intravaginal ejaculatory latency time for establishing a diagnosis of premature ejaculation, are not commonly employed to define a sexual dysfunction. Not surprisingly, the type of questionnaire used in a certain study may also have an impact on epidemiologic findings.[2] Another issue in sexual function epidemiologic research is the study population, as the prevalence of sexual dysfunction varies greatly according to age, risk factors, demographic population characteristics, and other population-related factors.[3–8] An important consideration in the epidemiology of sexual dysfunction is the existence of specific risk factors in specific populations. There are many well-studied risk factors for sexual dysfunction.[9] Common risk factors include cardiovascular diseases, obesity, hypertension, hyperlipidemia, smoking, lower urinary tract symptoms, radical pelvic surgery and, of course, diabetes.[10–12] Radical pelvic surgery has a multifaceted impact on sexual function. For example, radical prostatectomy affects erectile function mainly by disruption of neural pathways, causing un-ejaculation resulting from removal of anatomic structures – the prostate and seminal vesicles – and increasing the risk of urinary incontinence during sexual activity owing to urinary sphincter weakness and even increasing the risk of penile morphologic changes, penile length loss, and Peyronie's disease.[13,14] There are also other, less commonly discussed but nonetheless important, factors that may be associated with the epidemiology of sexual dysfunction. It has been suggested that the prevalence of sexual dysfunction may be related to the availability of therapies and interventions for sexual dysfunction.[4] New therapies may increase patients' and partners' awareness and hence increase reporting of sexual dysfunction. In the light of these difficulties in measuring and reporting sexual dysfunction, epidemiologic data should be interpreted cautiously.

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Erectile dysfunction

Erectile dysfunction is the most commonly researched and discussed sexual dysfunction, and the most prevalent sexual dysfunction in older men. The first landmark study that looked at the epidemiology of erectile dysfunction was the Massachusetts Male Aging Study, by Feldman et al. and published in 1994.[15] This was a community-based observational study, and looked at a random sample of non-institutionalized men aged 40–70 years in the Boston area. Erectile function was assessed by a self-administered questionnaire, and the study's main findings were that the combined prevalence of minimal, moderate, and complete impotence was as high as 52%; subject age was the variable most strongly associated with impotence; and the prevalence of complete impotence tripled from 5 to 15% between subject ages 40 and 70 years.[15] Another pivotal erectile dysfunction epidemiologic study was the Cologne Male Survey by Braun et al., published in 2000.[10] This study looked at a European population, not a random sample but a representative sample of 8000 men, using a validated questionnaire. Results of this study were based on approximately 4500 evaluable questionnaires yielding a response rate of 56%. The prevalence of erectile dysfunction in this study was 19.2%, with a steep age-related increase (2.3 to 53.4%) and a high rate of conditions comorbid with erectile dysfunction – hypertension, diabetes, pelvic surgery, and lower urinary tract symptoms – corroborating findings of earlier studies of different populations. The most extensively studied risk factors for erectile dysfunction are cardiovascular risk factors, primarily diabetes, and other risk factors, including the metabolic syndrome and its components (abdominal obesity, dyslipidemia, hypertension, and impaired fasting glucose), smoking, ischemic heart disease, and peripheral vascular disease and other cardiovascular risk factors.[7,16,17] Recognition of these important risk factors, especially modifiable cardiovascular risk factors, may improve patient knowledge and awareness, and provide a window for cardiovascular disease diagnosis and early intervention in men with newly diagnosed erectile dysfunction, leading to not only better sexual health but also better overall health.[18–20] The main pathophysiologic link between erectile dysfunction and cardiovascular morbidity is probably endothelial dysfunction.[21] However, there are risk factors other than cardiovascular ones, both organic and psychological, that are associated with increased risk of erectile dysfunction. Among the significant organic non-vascular risk factors is Peyronie's disease, an underdiagnosed condition in men presenting with newly diagnosed erectile dysfunction.[22] Peyronie's disease may contribute to the development of erectile dysfunction probably by altering the elastic properties of the penile tunica albuginea.[23] Another not uncommon risk factor for erectile dysfunction is testosterone deficiency (hypogonadism). It is well established that adequate testosterone levels are required not only for the penile vascular response during erection, but also to preserve penile structural integrity.[24,25] Erectile dysfunction is more prevalent in men with certain non-organic risk factors, such as emotional, couple related, and socioeconomic factors, creating a complex picture when the epidemiology of erectile dysfunction is discussed in certain specific populations.[8,26] A good example of an emotional risk factor for erectile dysfunction is depression. In a study by Shiri et al. the incidence of erectile dysfunction was 59/1000 person-years in men with depressive mood and 37/1000 person-years in those without depression.[27] Theses authors also found that the association of depression and erectile dysfunction is bidirectional: not only were men with depression at increased risk for erectile dysfunction, but also men with erectile dysfunction were at increased risk for depression.

In summary, the prevalence of erectile dysfunction is high and age-dependent, with more than half of men at age of 50 years or older being affected. There are many risk factors for erectile dysfunction, hence epidemiologic data in specific populations should be viewed with careful consideration of the specific characteristics of the population reviewed.

Premature ejaculation

Premature ejaculation is likely the most common sexual dysfunction in men across all age groups and populations, with a worldwide prevalence of approximately 30%.[28,29] For clinical research purposes the accepted definition of premature ejaculation is an intravaginal ejaculatory latency time (IELT) of 1–2 minutes; a prospectively stopwatch-measured IELT is preferred over self- or partner-reported IELT upon recall. While there is a definition of premature ejaculation for research

purposes, in clinical practice there is no agreed definition. Waldinger et al. surveyed a population of 500 couples who were recruited from five countries, aged 18 years or older, had a stable heterosexual relationship for at least 6 months, with regular sexual intercourse. In their study, the median IELT was 5.4 minutes and the range was 0.55 to 41 minutes.[30] In their study, the median IELT decreased significantly with age, from 6.5 minutes in the 18–30 years group, to 4.3 minutes in the group older than 51 years, while other studies did not show this age-related increase in prevalence of premature ejaculation.[31,32] Regardless of whether the prevalence of premature ejaculation is clearly age-related or not, it is obvious that in younger men who are less likely to have other sexual dysfunctions such as organic erectile dysfunction, premature ejaculation is the most prevalent sexual dysfunction. In the real-world clinical setting, the use of stopwatch IELT to define premature ejaculation is definitely not a practical approach. Other ways to categorize men as having premature ejaculation are based on men self-reporting low or absent control over ejaculation irrespective of the duration of the ejaculation time, on the resulted distress for them or their sexual partner or both, or on patients' report that they "climax too soon." Indeed, in a Canadian web-based study of more than 3800 men, the prevalence of premature ejaculation (PE) ranged from 16% to 24% depending on the definition of PE utilized.[31] The etiology underpinning this high prevalence remains to be clarified, but current evidence reflects a shift from psychogenic theories to more neurobiological bases. While elucidation of the etiology of premature ejaculation is undoubtedly important for development of more effective therapies, it is clear that, whatever the cause of the condition, it is associated with a significant burden on psychological and overall health.[29] Generally, men with premature ejaculation are more likely to self-report other sexual dysfunctions (e.g., anorgasmia, low libido, erectile dysfunction) and psychological disturbances (e.g., depression, anxiety, excessive stress) than men without PE.[33] Similarly, as for other sexual dysfunctions, the epidemiology of PE may vary in special groups. Tang and Khoo showed that PE prevalence varied according to ethnicity.[32] It is worth mentioning that in their study, which included men in a primary care setting not a general population sample, the prevalence of PE was about 40%, significantly higher than in the general population. Shindel et al. looked at the prevalence of PE in another population of great interest, infertile couples, and found that about 50% of men reported that they ejaculated more rapidly than they wished. When men reported PE, their partners agreed with the diagnosis in 47% of cases. Female partners of men who did not report PE, reported PE in 11% of cases. Partner frustration related to PE was reported by 30% of men. Partners agreed that they were frustrated in 43% of these cases. Among the 70% of men who did not report partner frustration from PE, 93% of the partners agreed that they were not frustrated.

In summary, PE is hard to define exactly, yet it is the most prevalent sexual dysfunction and the most significant sexual dysfunction in young men.

Peyronie's disease

Peyronie's disease is commonly undiagnosed.[34] The main clinical symptom is penile curvature; however, men may have significant Peyronie's disease, manifested by penile plaques, erectile dysfunction, penile pain, and penile shortening, even without a curvature. Not uncommonly, the underlying cause of erectile dysfunction in poor responders to phosphodiesterase 5 inhibitors is Peyronie's disease. The diagnosis of Peyronie's disease in these men is established by physical examination and penile Doppler ultrasound in certain cases.[35] Moreover, in men who are not sexually active or in men who are sexually active without achieving erection and performing penetration, the penile curvature may not be seen and Peyronie's disease may exist but remain undiagnosed. Therefore, the reported prevalence of Peyronie's disease depends on the manifestations of this condition, on a high index of suspicion, and on patients, partners, and sexual health care providers' awareness. Epidemiological data on Peyronie's disease are limited. Prevalence rates of 0.4–9% have been published, but the majority of the medical literature supports a prevalence rate of 3–8% or 5–8%.[36,37] In the past, Peyronie's disease was considered a condition that is limited to older men. However, newer data show that Peyronie's disease does occur also in younger men and even in teenagers, but the prevalence in these very young men remains unknown.[38] Men younger than 40 years are more likely to present at an earlier stage of Peyronie's disease, to have diabetes, and to have more than one plaque at the time of presentation.[39] In certain

populations at risk, the prevalence of Peyronie's disease is far greater. Diabetes, genetic predisposition, trauma of the penis, systemic vascular diseases, smoking, and alcohol consumption are all mentioned in the medical literature as risk factors for Peyronie's disease.[40,41] In diabetic men, not only is Peyronie's disease more prevalent, but also it tends to manifest in older age, and present with longer duration and greater severity: There is greater penile curvature and more pronounced penile deformity, and a greater prevalence of coexisting erectile dysfunction, probably resulting both from penile structural alterations due to Peyronie's disease itself and from diabetic vascular disease.[42] Tal et al. looked at the incidence of Peyronie's disease in a very distinct population consisting of men who had had radical prostatectomy as a monotherapy for prostate cancer, and calculated the 3-year post-prostatectomy incidence to be 16% and a mean time to presentation of 14 months after surgery.[14] Rhoden et al. conducted a case-control study to shed more light on Peyronie's disease risk factors, and found that race is a strong risk factor for Peyronie's disease, with an odds ratio of 8.5.[43] Interestingly, in this study, higher low-density lipoprotein (LDL)-cholesterol level (>130 mg/dL) and increased waist circumference (>102 cm) actually had a protective effect in Peyronie's disease, with an odds ratio of 0.5 for both. Moreno and Morgentaler investigated the association of testosterone deficiency and Peyronie's disease. Their study is of special significance since testosterone is a principal anabolic hormone in men and definitely has a major role in maintaining the health of penile tissues. In their pilot study, the severity of penile curvature correlated significantly with free testosterone level but not with total testosterone level, and a possible important association between testosterone deficiency and Peyronie's disease was suggested.[44] Besides the epidemiology of Peyronie's disease itself, sexual healthcare professionals should be aware of the epidemiology of emotional conditions in Peyronie's disease, which are under-represented in the medical literature and often under-diagnosed and treated in daily clinical practice. Consistent data from two leading sexual medicine centers in the United States show that the psychological burden in men with Peyronie's disease is great, possibly greater than in men with other sexual dysfunctions.[45,46] Overall very high rates of emotional burden and relationship problems attributable to Peyronie's disease were found: 81% and 54%, respectively, predictors of which were penile length-loss and inability to have intercourse. Using validated instruments, it was demonstrated that 48% of men with Peyronie's disease had clinically meaningful depression that would warrant medical evaluation. This high level of depression stayed consistent across time since diagnosis, suggesting that most men do not psychologically adjust to their diagnosis of Peyronie's disease; all men with Peyronie's disease should be considered for appropriate mental health screening. This high prevalence of psychological morbidity may be attributable to the fact that there is no fully effective treatment for Peyronie's disease, and men with symptomatic Peyronie's disease will never regain their pre-morbid penile function, appearance, and length.

In summary, the epidemiology of Peyronie's disease is intriguing: Its prevalence is higher and its age distribution is broader than previously thought; there are numerous suggested risk factors and a very high risk of associated psychological morbidity, inherent to changes in penile appearance and function, that should not be overlooked.

Hypogonadism

Hypogonadism (low testosterone) is under-diagnosed and under-treated. The significance of hypogonadism diagnosis and treatment cannot be over-emphasized, as androgen receptors and testosterone activity exist in most body tissues, organs, and systems. Testosterone deficiency effects are not limited to sexual function: besides desire and erection, it may also affect bone health, muscle mass, hematopoiesis, cognitive function, spermatogenesis and seminal fluid production, vascular and cardiac performance, lipid and glucose metabolism, and many other metabolic, primarily anabolic, processes. The key to diagnosis is awareness of the high prevalence of testosterone deficiency, identification of populations at risk, and early symptoms and laboratory evaluation. Worth mentioning is that symptoms of hypogonadism are not specific and can be attributed to other medical conditions, such as hypothyroidism or depression. Therefore, questionnaires are neither sensitive nor specific for hypogonadism screening or diagnosis, and must be combined with measured plasma testosterone levels.[47,48] Clinically, it was suggested that the findings that are best correlated with late onset hypogonadism

are sexual symptoms (poor morning erection, low sexual desire, erectile dysfunction) and total testosterone level of less than 11 nmol/L (<320 ng/dL).[49] Epidemiologic questionnaire-based studies without testosterone measurement failed to correctly define the true prevalence of hypogonadism, yielding an overestimated prevalence of up to 80%.[50] Combining hypogonadism symptoms and plasma testosterone levels, Araujo et al. found that the overall prevalence of symptomatic testosterone deficiency in a random sample of men from the Boston Area Community Health Survey was 5.6%. In this study, symptomatic testosterone deficiency prevalence increased with age, yielding a prevalence of 18.4% in men over 70 years old.[51] Age-related increased prevalence of hypogonadism was also demonstrated in the Baltimore Longitudinal Study of Aging: the prevalence of hypogonadal testosterone levels was about 20% in men over 60 years old, 30% in men over 70 years old, and 50% in those over 80 years of age, using total testosterone criteria; the prevalence was even greater when free testosterone criteria were employed.[52] The prevalence of testosterone deficiency is increased in men with certain risk factors such as diabetes, cancer, lung disease, other systemic diseases, obesity, the metabolic syndrome, and erectile dysfunction, and in men with reduced mass and function of testicular tissue, for example, infertile men, men having varicocele, and men after unilateral orchiectomy.[53–55] Diabetes is a well-studied risk factor for testosterone deficiency: in a study by Corona et al. the prevalence of hypogonadism was 24.5% in diabetic men versus 12.6% in non-diabetic subjects, which was statistically significant after adjustment for age and body mass index (BMI).[56] Similar results were recently published by Al Hayek et al.: the prevalence of hypogonadism was 24.3% in diabetic and 8.3% in non-diabetic patients.[57] Hypogonadism also is common in men with erectile dysfunction, with a reported prevalence of approximately 30–40%.[58,59] Not uncommonly, erectile dysfunction is the presenting symptom. This population of men presenting with erectile dysfunction deserves special attention: it is a unique opportunity to impact men's health. Correct evaluation and management of testosterone deficiency and other cardiovascular risk factors may actually reduce future cardiovascular morbidity and mortality. Therefore, symptomatic treatment of erectile dysfunction in these men without in-depth risk factor identification should be discouraged.

Less discussed risk factors for hypogonadism include poorly functioning testicular tissue and/or reduced testicular mass. Hypogonadism is more common among infertile men, with an estimated prevalence of 20–30%.[60] Men with non-obstructive azoospermia, especially in Klinefelter's syndrome, are at even greater risk. Surgical sperm retrieval procedures may cause further testicular tissue insult and reduce Leydig cell mass and testosterone production. While azoospermia is uncommon in men (0.5–2%), varicocele is fairly common, with an incidence of 15% in the general male population and up to 40% in infertile men. Recent studies have shown that men with varicocele are at increased risk for low testosterone levels; furthermore, varicocele repair may increase testosterone levels and may be considered as a definitive treatment for hypogonadism.[61–63]

In summary, hypogonadism is a treatable cause of sexual dysfunction. While sexual dysfunction may be the presenting symptom, the benefits of testosterone level normalization are much broader. Awareness of the epidemiology of testosterone deficiency, especially in high-risk populations, is the key to diagnosis and treatment.

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CHAPTER 2

Physiology of ejaculation

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Introduction

From the moment a man gets sexually aroused until he ejaculates there is a remarkable and very intriguing closely synchronized cooperation between his brain, his spinal cord, and his genital system. When a man starts to make love with his partner, his brain has to decipher the affective and erotic load of tactile impulses that come from the skin of various parts of his body, including the skin of his genitals. Indeed, in such circumstances the brain has to decipher the information that comes along with the notion of being touched by another person. The nervous system contains special nerve fibers that convey "affective" information when being touched and run from the skin to the central nervous system. This has only recently been discovered. These nerve fibers are called low threshold mechanoreceptive C tactile (CT) afferents.[1] They enable the brain to perceive with which "feelings" another person is touching the skin. However, research of these fibers in relation to erotic touch or sexuality is still in its infancy. These fibers are important not only for human beings but also for animals. By the activation of these affective peripheral nerve fibers an animal perceives the affective state of the other animal that is touching his or her hairy skin.

This chapter will describe the function of the anatomical structures that are required for ejaculation. Physiology is the term to denote this function.

The spinal cord and the brain of male rats

Ejaculation, that is, the rhythmic forceful expulsion of semen, results from a closely synchronized cooperation between different peripheral nerves, the spinal cord, and the brain. There are two successive phases during this synchronized coordination, emission and expulsion. The first phase starts in the spinal cord once the brain is informed that sexual activity is at hand.

Research in male rats has provided us with fundamental knowledge of what is actually happening during ejaculation at a physiological level. The synchronized coordination is mediated by a group of spinothalamic neurons in the lumbar part of the spinal cord. These neurons have been called the spinal generator of ejaculation (SGE).[2,3] They run from the spinal cord ("spino") to the thalamus ("thalamic") in the brain.

The spinal cord and the SGE

The SGE has been investigated in male rats since the 1980s.[2–4] In rodents it has been found that the SGE is located in lamina X and the medial part of lamina VII around the central canal, at the third and fourth lumbar (L3-L4) spinal segments. Afferent fibers in neurons from the genitals, conveying sensory information, terminate in the SGE. In the SGE these neurons contact interneurons that convey information to various other

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neurons. These interneurons contain the neuropeptides galanin, cholecystokinin, enkephalin, and gastrin-releasing peptide, and express neurokinin-1 (NK1), NMDA, and androgen receptors. A number of neurons of the SGE run to a very specialized area in the thalamus in the brain, the so-called parvocellular part of the subparafascicular nucleus of the thalamus. Therefore these neurons in the SGE are called lumbar spino-thalamic (LSt) cells. Other neurons of the SGE make contact with spinal nuclei of the autonomic nervous system and somatic neurons.

The brain and the SGE

The SGE not only receives information from peripheral neurons and conveys their information to other neurons, but also its activity is mediated by the brain. The male rat brain contains a specific network for ejaculation (for review see Refs 5,6). As the localization of these specific neurons is bound to very tiny specific places in the brain, the names of their localization have become rather long and difficult to pronounce. They are located in the medial amygdala (posterodorsal part), the thalamus (parvicellular subparafascicular nucleus), the stria terminalis (posteromedial bed nucleus), the hypothalamus (posterodorsal and medial preoptic nuclei, paraventricular nucleus, and lateral hypothalamus), and the pons (raphe and gigantocellular nuclei). Neurons in these areas project to the medial preoptic area (MPOA), a key center in the control of ejaculation. The MPOA in turn contacts the caudal raphe and gigantocellular nuclei either directly or after relaying in periaqueductal gray[7] and the paraventricular nucleus of the hypothalamus (PVN).[8]

Peripheral nerves and ejaculation

In order to get an ejaculation integration of three sorts of nerve fibers has to be established: sympathetic neurons, parasympathetic neurons, and somatic nerves. These neurons originate in different areas of the spinal cord. Notably, when nerves convey information from the periphery (e.g., from the skin) to the central nervous system the nerve is called an afferent neuron. In contrast, when a nerve runs from the central nervous system to the periphery it is called an efferent neuron. In the case of ejaculation, both afferent and efferent neurons play a role in its neurophysiology.

Afferent neurons

The SGE receives information from the genitals through two afferent nerve pathways: the dorsal nerve of the penis and sympathetic neurons. These sensory afferent neurons terminate in the medial dorsal horn and the dorsal gray column of the spinal cord.[2,9]

The dorsal nerve of the penis

The dorsal nerve of the penis is the end branch of the pudendal nerve. It is a sensory nerve, which means that it only conveys sensory information from the penis to the spinal cord and the brain. It receives sensory information from sensory receptors in the penile skin, prepuce, and glans.[10,11] These sensory receptors are free nerve endings[12] and also encapsulated receptors (so-called Krause-Finger corpuscles) in the glans penis.[12] Stimulation of these Krause-Finger corpuscles facilitates the ejaculatory reflex.

Sympathetic nerves of the genitals

Sympathetic neurons from the genitals accompany the hypogastric nerve and, after passing through the paravertebral lumbosacral sympathetic chain, enter the spinal cord via thoracolumbar dorsal roots.[13]

Efferent neurons

From the SGE three sorts of neurons are sent to the genitals: sympathetic neurons, parasympathetic neurons, and somatic neurons.

Sympathetic neurons

The cell bodies of the sympathetic neurons are located in the thoracolumbar part of the spinal cord. The sympathetic neurons leave the spinal cord through the ventral roots. They first run to the paravertebral sympathetic chain. From this relay station they run directly via the splanchnic nerves to the intermesenteric ganglia (IMG), but may also reach the intermesenteric ganglia indirectly by first relaying in the celiac superior mesenteric ganglia (CSMG) to reach the IMG via intermesenteric nerves (IMN).[14]

Emanating from the IMG (which is called the superior hypogastric plexus in humans) are the hypogastric nerves. These sympathetic nerves join the parasympathetic nerves in the pelvic nerve and together they form the pelvic plexus.[14]

From the pelvic plexus both sympathetic and parasympathetic nerves innervate the anatomical structures that are involved in ejaculation.

Parasympathetic neurons

The cell bodies of the parasympathetic neurons are located in the sacral parasympathetic nucleus (SPN),[15] in the sacral spinal cord of a human. The parasympathetic neuron fibers travel in the pelvic nerve and are later joined by the sympathetic neuron fibers from the hypogastric nerves. Both the parasympathetic and sympathetic nerve fibers run to the pelvic plexus, which is called the inferior hypogastric plexus in humans. From this plexus the parasympathetic neuron fibers reach the pelvic anatomical structures that are involved in ejaculation.

Somatic neurons

In humans the cell bodies of somatic neurons are located in the sacral spinal cord (Onuf's nucleus). These somatic neurons proceed via the motor branch of the pudendal nerve to the pelvic floor striated muscles, including the bulbospongiosus and ischiocavernosus muscles.[16]

Emission and the autonomic nervous system

The emission phase

During the emission phase of ejaculation, the following genital anatomical structures play a major role: testis, epididymis, ductus deferens, vesica seminalis, prostate, bladder neck, and prostatic part of urethra. In addition, during emission, the functionality of particularly the autonomic (e.g., sympathetic and parasympathetic) centers in the thoraco-lumbar-spinal cord are essential.

Testis and epididymis

Spermatozoa are produced in the seminiferous tubules of the testes and translocated into the head of the epididymis. The epididymis, consisting of epithelial cells, connective tissue, and smooth muscle cells, consists of three parts: the head (caput), the body (corpus), and the tail (cauda). The spermatozoa in the seminiferous tubules and early epididymis are non-motile but become motile after maturation (18–24 hours) along the epididymis.[14] Mature spermatozoa are stored in the tail of the epididymis. During sexual arousal they are released in the ductus (or vas) deferens. The volume of spermatozoa is only less than 0.1 % of the total volume of the ejaculate.

Ductus deferens

The ductus deferens passes through the inguinal canal to enter the pelvic cavity. There it joins the excretory duct of the seminal vesicle forming the ejaculatory duct. The ejaculatory duct traverses the prostate and opens into the prostatic portion of the urethra via the verumontanum (a 2–3 mm high intraluminal urethral crest in humans). The last part of the ductus deferens is enlarged to form the ampulla.[14]

During the emission phase of ejaculation, strong peristaltic contractions of the ductus deferens bring spermatozoa into the ejaculatory duct and then into the urethra, where they are mixed with seminal fluids, excreted by the prostate and vesica seminalis.

Seminal vesicles

The seminal vesicles are two tubular glands lying between the posterior wall of the bladder base and the rectum. Each vesicle joins with the ductus deferens as it enters the prostate to form the ejaculatory duct. Epithelial cells of the inner layer of the seminal vesicles secrete 50–80% of the entire ejaculatory volume.[14]

The seminal vesicle secretions are thick, alkaline, and contain substances providing the spermatozoa with a protective and nutritive environment.[14]

During the emission phase of ejaculation, seminal vesicle fluid is expelled into the prostatic urethra via the excretory duct following contractions of smooth muscle cells of the gland.

Prostate

The prostate produces 15–30% of the total volume of sperm. Prostatic secretions are milky, slightly alkaline, and enhance spermatozoan survival. During the emission phase of ejaculation, muscular elements of the gland contract and eject the secretions into the prostatic urethra via the prostatic ducts and the utricle opening into the verumontanum.

Cowper's glands

The bulbourethral, or Cowper's glands are located posterolaterally to the membranous portion of the urethra at the level of the urogenital diaphragm. Bulbourethral

gland excretory ducts extend forward through the urogenital diaphragm and open into the cavernous urethra. Bulbourethral clear thick secretions are poured into the urethra as sexual arousal increases. Their role is dual: neutralizing urine acidic residues and lubricating the urethra before sperm passes through.[14]

The seminal fluid with spermatozoa (semen) is poured into the posterior urethra via phasic contractions of the glands and their ducti while the bladder neck is firmly closed to prevent backflow into the bladder.

Expulsion and the somatic nervous system

During the expulsion phase of ejaculation, the following genital anatomical structures play a major role: urethra, pelvic floor striated muscles, bulbospongiosus muscle, and ischiocavernosus muscle. In addition, during expulsion, the functionality of particularly somatic spinal centers and nerves is important.

Somatic centers innervate the pelvic floor striated muscles, particularly the bulbospongiosus and ischiocavernosus muscles. The contractions of both muscles enable the expulsion of semen from the urethra. The bulbospongiosus muscle encompasses the median part of the penile root (bulb). The ischiocavernosus muscles surround the lateral roots of the penis (cura).

While the external urethral sphincter relaxes, intense rhythmic contractions of both muscles compress the urethra and corpus cavernosum. These contractions lead to the characteristic forceful pulsatile expulsion of sperm. Their intense contractions also contribute to further rigidity of the penis and probably also to the orgasmic feeling.

The central nervous system and ejaculation

In the SGE peripheral information from the genitals is integrated with information from the brain. his information can be summarized as either excitatory or inhibitory information affecting a spinal ejaculatory reflex. Actually, the extent of central serotonin (5-hydroxytryptamine, or 5-HT) neurotransmission and activity of certain 5-HT receptors determine whether the spinal ejaculatory reflex is inhibited or facilitated. This mechanism of action of serotonin is actually the mechanism by which selective serotonin reuptake inhibitors (SSRIs) modulate the duration of the intravaginal ejaculation latency time (IELT) in men and the ejaculatory latency (EL) in rodents.

However, it is in the brain that information from all the senses (visual, auditory, olfactory, gustatory, tactile) together with feelings, emotions, perceptions, and eroticism are integrated in cerebral (somato)sensory areas and also become integrated with motor centers that in turn provide descending information to the SGE.

Most detailed information of the brain areas involved in ejaculation is derived from studies of male rats. These animal studies were performed long before clinicians started to become interested in the neurobiology of ejaculatory disorders, for example, premature ejaculation. Particularly, studies using Fos protein expression as a marker for neuronal activity have contributed to our current knowledge on which brain areas are involved in ejaculation.[17]

The brain structures that play a specific role in ejaculation are medial amygdala (posterodorsal part) (MeApd), the thalamus (parvicellular subparafascicular nucleus) (SPFp), the stria terminalis (posteromedial bed nucleus) (BNSTpm), the hypothalamus (posterodorsal preoptic nucleus (PNpd), paraventricular nucleus, and lateral hypothalamus), and the pons (raphe and gigantocellular nuclei).[14]

Connections between these substructures and the medial preoptic area (MPOA) of the hypothalamus have been found to be essential for ejaculation.[17,18] Experiments have shown that emission and expulsion disappear after lesioning the MPOA,[19] or can be elicited by chemical[20,21] or electrical[22,23] stimulation. The MPOA has no direct connection with the SGE in the spinal cord. However, the MPOA affects the two ejaculatory phases by interconnecting with other areas in the brain that are involved in ejaculation: the paraventricular nucleus of the hypothalamus (PVN),[24] the periaqueductal gray (PAG),[25] and the paragigantocellular nucleus (nPGi) of the medulla oblongata.[26]

The parvocellular neurons of the PVN directly innervate autonomic neurons in the lumbosacral spinal cord[27,28] and the pudendal motoneurons located in the L5-L6 spinal segments in rats.[28] The PVN also has direct neuronal connections with the nPGi in the brainstem.[29]

Orgasm

In normal circumstances an ejaculation is accompanied by an orgasmic sensation. Orgasm is a complex neurophysiological process that consists of an intense cerebral discharge but also whole-body physiological changes.[14] The exact area in the brain where the orgasmic sensations are produced is not yet identified. However, in recent years brain imaging studies have provided new data about the areas that are activated and/or inhibited during orgasm. For example, in a positron emission tomography (PET) study in healthy male volunteers it was found that at the time of ejaculation, the strongest activation was found in the mesodiencephalic transition zone including the ventral tegmental area (VTA), SPFp, and medial and ventral thalamus. These thalamic areas are known to be associated with rewarding processes, visceral sensory responses, and control of pelvic floor motoneurons and sympathetic preganglionic neurons throughout the spinal cord.[14] This study and various other brain imaging studies have provided indications that the VTA is a key area of the neuronal substrate of orgasm.

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CHAPTER 3

Physiology of penile erection

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A better understanding of smooth muscle physiology, the nitric oxide pathway, neurophysiology, and functional penile anatomy has been instrumental in gaining a deeper understanding of erectile physiology. Knowledge of normal physiology aids in understanding the pathophysiology and developing potential therapeutics for erectile dysfunction.

Functional anatomy

Penile erectile tissues, vascular and cavernosal smooth muscle, and support structures are essential to tumescence. The human penis is composed of three cylindrical structures bound together by the tunica albuginea, ligaments, and muscles. There are the paired corpora cavernosa and a single corpus spongiosum, which houses the urethra. The complex yet tightly regulated interplay between these erectile tissues, vessels, and nerves is essential to penile erection and detumescence.

Tunica albuginea

The tunica albuginea (TA) is a bilayered structure composed of an inner circular layer and outer longitudinal layer. Additionally, it has multiple sublayers that surround and support the cavernosal tissues. Although its collagen fibers provide rigidity to support high pressures during erection, it is also flexible due to its elastin content. The inner layer is oriented in a circular fashion. From this layer, intracavernous pillars emanate and provide strength to the erectile tissues in addition to supporting the septum. The outer layer of the bilayered TA is oriented longitudinally and extends the length of the penis from the glans to the crura. These fibers are absent between the 5.00 and 7:00 positions, which is an area of relative weakness. Contrary to the corpora cavernosa, the corpus spongiosum lacks an outer longitudinal layer and intracorporeal supports, which leads to lower pressures during erection.

In addition to providing support for erectile tissues, the TA plays an essential role in tumescence by obstructing venous outflow. Emissary veins course between the inner and outer layers of the TA. With increasing intracorporeal pressures from arterial inflow, these veins are compressed between these layers, which diminishes venous outflow leading to higher pressure engorgement, the so-called veno-occlusive mechanism.

Erectile tissues

The paired corpora cavernosa are spongy cylinders containing erectile tissues encircled by the tough yet flexible TA and also surrounded by the ischiocavernosus muscle. Contraction of these muscles at the crus during erection further blocks venous outflow, leading to increased rigidity and further increases intracavernous pressures. Although the corpora cavernosa are separated by a septum, it is incomplete, and there is common flow distally. Within the corpora cavernosa there is a fibrous support skeleton composed of pillars from the TA and the incomplete septum. Furthermore, there are a series of interconnected sinusoids, which accommodate blood during erections. These are supported by elastic fibers and collagen and separated by smooth muscle trabeculae. Relaxation of these smooth muscles allows increased cavernosal engorgement.

In the flaccid state, blood slowly diffuses from central to peripheral sinusoids. Given this slow flow, blood gas levels are venous throughout the sinusoids.

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However, during erection, with rapid entry of arterial blood, central and peripheral sinusoidal blood gas levels approach that of arterial blood. Additionally, there are many endothelial-derived factors in the sinusoid and cavernosal smooth muscle cells that regulate vasoconstriction and dilation. These are discussed below.

The corpus spongiosum has larger sinusoids than the corpora cavernosa and is a lower pressure system given the lack of an outer longitudinal layer. This is completely absent in the glans penis as well. Additionally, the corpus spongiosum is surrounded by the bulbospongiosus muscle. During micturition, contraction helps to empty the urethra. During erections, contraction compresses the erectile tissue and deep dorsal vein leading to increased pressure and rigidity. Additionally, its rhythmic contraction assists with ejaculation.

Penile vasculature

Arterial supply

The internal pudendal artery, which is the terminal branch of the anterior trunk of the internal iliac artery, is usually the main source of blood to the penis. There is, however, significant variability in penile blood flow with accessory branches from the external iliac, obturator, vesical, and femoral arteries, which may often be the dominant source of blood. The internal pudendal artery terminates as the common penile artery, which branches into the dorsal, bulbourethral, and cavernous arteries. Distally these rejoin at the glans penis. The dorsal artery supplies blood to the glans, skin and subcutaneous tissue of penis. The bulbourethral artery supplies the corpus spongiosum and urethra. The cavernous artery gives off straight and helicine branches, which open directly into the sinusoids without intervening capillaries. During erection, when smooth muscle is relaxed, these are straight and dilated allowing arterial inflow; however, they become contracted and tortuous in the flaccid state, when smooth muscle is contracted, which decreases inflow.

Venous drainage

Penile venous drainage originates from tiny venules in the peripheral sinusoidal tissues, which travel in the trabeculae between the TA and peripheral sinusoids and form the subtunical venous plexus. These give rise to the emissary veins, which travel between the layers of the TA. During erection, compression of these by the TA limits venous outflow, which contributes to penile engorgement.

Neuroanatomy

Peripheral innervation

The penis is supplied by autonomic and somatic nerve fibers. Autonomic innervation to the corpora cavernosa and spongiosum is in the form of sympathetic and parasympathetic fibers via the cavernous nerves. Somatic fibers are both sensory and motor, allowing for cutaneous sensation and contraction of the bulbospongiosus and ischiocavernosus muscles.

Somatic innervation

Somatosensory innervation originates distally in sensory receptors of the skin, glans, and urethra. Additionally, sensory receptors are present in the corpora cavernosa. The glans is very highly innervated with thin myelinated A_d and unmyelinated C fibers. These sensory fibers form the dorsal nerve of the penis, which will coalesce with other fibers to become the pudendal nerve. The pudendal nerve enters the spinal cord at the S2-S4 levels. These fibers convey sensory information via the spinothalamic and spinoreticular tracts to the central nervous system. In addition to somatic functions, the dorsal nerve has autonomic functions, as evidenced by the presence of nerve bundles containing nitric oxide synthase (NOS). Onuf's nucleus, located in the S2-S4 segments, provides motor neurons that supply the pudendal nerve. These innervate the bulbospongiosus and ischiocavernosus muscles.

Autonomic innervation

Autonomic innervation is responsible for tumescence and detumescence. Specifically, sympathetic stimulation leads to detumescence whereas parasympathetic activation leads to erection. Thus, sacral parasympathetic fibers are responsible for tumescence and sympathetic thoracolumbar fibers are responsible for detumescence.

Sympathetic pathways

Penile sympathetic innervation to the pelvic plexus originates from T11 to L2 spinal segments. The presynaptic sympathetic cell bodies supplying these fibers are located in the lateral column between T10-T12 and L1-L2. These travel to the pelvic plexus via the hypogastric nerve. This forms the superior hypogastric plexus, which is formed from sympathetic fibers from the celiac plexus and lumbar splanchnic nerves, and the inferior mesenteric plexus.

Parasympathetic pathways

Parasympathetic fibers arise from presynaptic neuronal cells in the intermediolateral cell columns located between the S2 and S4 sacral spinal cord segments as pelvic splanchnic nerves and join the hypogastric nerves. These will join sympathetic fibers from the superior and inferior hypogastric plexuses and join the pelvic plexus. Recent studies demonstrate that many of these plexuses are a mix of sympathetic and parasympathetic nerves. From the pelvic plexus, autonomic nerve fibers that supply the penis form the cavernous nerves.

Central pathways

Spinal pathways

In the spinal cord, thoracolumbar sympathetic, sacral parasympathetic, and sacral pudendal motoneurons are involved with erections. The thoracolumbar center is generally inhibitory to erections whereas parts of the sacral and pudendal promote erections.

Supraspinal pathways

Centers in the brain play an essential role in initiation, inhibition, and maintenance of erections by integrating and processing multiple sensory inputs. Although multiple areas are involved in sexual function, including many areas of the forebrain, hypothalamus, brainstem, and midbrain, animal studies have demonstrated that penile sensory information is specifically relayed to the pons, brainstem, hypothalamic medial preoptic area (MPOA), paraventricular nucleus (PVN), thalamus, and cortex. MPOA stimulation causes erections via increased parasympathetic outflow. Additionally, the PVN also is pro-erectile when stimulated with apomorphine via dopaminergic receptors. However, in addition to these centers, there are many other areas in the brain responsible for regulation of erectile function.

These central structures are responsible for psychogenic, reflexogenic, and nocturnal erections. Psychogenic erections are penile erections from audiovisual stimulation. Central impulses activate the spinal centers to cause an erection. Reflexogenic erections are induced by genital stimulation. Sensory fibers will relay this information via ascending fibers to the brain, which processes this and activates autonomic centers to produce an erection. Nocturnal erections occur during rapid eye movement sleep. Functional studies show increased activity in the pontine area, amygdalae, and anterior cingulate gyrus. There is decreased activity in the prefrontal and parietal cortex.

Hemodynamics of penile erection and detumescence

Corpora cavernosa

Penile tumescence is ultimately controlled by vascular and corporeal smooth muscle regulation of blood flow. Erections result from relaxation of cavernosal and vascular smooth muscles, which leads to sinusoidal relaxation, arterial dilation, and venous compression. This leads to increased arterial inflow, decreased venous outflow, and ultimately penile engorgement. When the penis is flaccid, vascular and cavernosal smooth muscles are in a tonically contracted state. This limits the amount of arterial blood flow so that the partial pressure of oxygen (pO_2) approaches that of venous blood (35 mmHg). As a result of sexual stimulation, neurotransmitters are released from the cavernous nerve endings, leading to a cascade of events resulting in penile erection. The following events occur:

1. Smooth muscles in the arteriolar and arterial walls relax, leading to vascular dilation and increased blood flow to the penis.
2. With the influx of arterial blood and relaxation of smooth muscles, the cavernosal sinusoids expand and become engorged with trapped blood.
3. Sinusoidal expansion leads to mechanical compression of the subtunical venous plexus between the engorged sinusoids and tough TA. This leads to decreased venous outflow and increases sinusoidal blood trapping and engorgement.
4. As a result of this trapped blood, the TA stretches, leading to occlusion of the emissary veins between the layers of the TA, which further decreases venous outflow.
5. Consequently, penile blood pO_2 increases to 90 mmHg (closer to arterial oxygen levels) and the intracavernous pressure increases to 100 mmHg
6. The amalgamation of these events leads to penile erection, with the penis going from a flaccid state to the full erection phase.
7. Contraction of the ischiocavernosus muscle during erection further increases pressure during the rigid erection phase.

Detumescence occurs when arterial inflow decreases due to smooth muscle contraction. It has been described in three phases in the animal model:

1. Initially, a transient increase in intracorporeal pressure is noted due to smooth muscle contraction against a closed venous system during erection.

2 This leads to a slow decrease in corporeal pressure as venous channels reopen due to decreased mechanical compression.
3 Lastly, there is a rapid fall in pressure as venous outflow is completely restored.

Corpus spongiosum and glans penis

Although there is increased blood flow to the glans penis and corpus spongiosum during erection, due to the lack of a longitudinal TA layer and thinner TA, the pressure is one-third to one-half that in the corpora cavernosa. Engorgement of the glans during the full erection phase is due to partial compression of the deep dorsal and circumflex veins between Buck's fascia and the corpora cavernosa. Additionally, contraction of the ischiocavernosus and bulbospongiosus muscles promotes engorgement and increases pressure in the glans and spongiosum by compression of the spongiosum and penile veins during the rigid erection phase.

Neurophysiology of erections

Smooth muscle contraction and detumescence

Sympathetic activity is conveyed by α-adrenergic receptors. These are found throughout the cavernosal tissues and vasculature. Specifically, postsynaptic α1a and α1d receptors and presynaptic α2 receptors convey sympathetic stimulation to induce contraction of smooth muscles. Furthermore, norepinephrine seems to be the preferred neurotransmitter. The sympathetic nerves induce detumescence and maintain penile flaccidity by increasing sarcoplasmic free calcium (Ca^{2+}) levels, which promotes smooth muscle contraction. Presynaptic α2-adrenergic receptors increase extracellular calcium entry via membrane ion channels, and α1 receptors release sequestered intracellular calcium in addition to promoting entry of extracellular calcium. This leads to muscle contraction and maintenance of contractile tone, as discussed below.

Additionally, endothelin-1, which is synthesized and present in sinusoidal endothelial tissues, acts as a vasoconstrictor. It also potentiates the constrictor response to catecholamines on the sinusoidal endothelial tissue. These direct and indirect mechanisms suggest endothelin-1 is involved in detumescence. These effects are mediated by the ET-A and ET-B endothelin receptors; the former mediates contraction, whereas ET-B mediates relaxation.

Furthermore, constrictor prostanoids including prostaglandin I_2 (PGI_2), $PGF_{2\alpha}$, and thromboxane A_2 are produced by the cavernous tissues and may play a role in smooth muscle contraction, detumescence, and vasoconstriction. These also attenuate the dilatory effects of nitric oxide when released simultaneously, thus rendering it less effective. Additionally, angiotensin II, which is part of the renin-angiotensin system, is present in cavernosal endothelial and smooth muscle cells and mediates contraction via AT-I receptors. Thus, in the flaccid state, corporeal tissues are in a semicontracted state, which is attained through a combination of intrinsic muscle activity, adrenergic neurotransmission, and endothelium-derived factors.

Smooth muscle relaxation and tumescence

Parasympathetic nerve fibers release acetylcholine (ACh), vasoactive intestinal peptide (VIP), and nitric oxide (NO). The predominant neurotransmitter responsible for erections is NO, by causing smooth muscle relaxation. NO is released from non-adrenergic/non-cholinergic fibers within the erectile tissues. It is a gaseous molecule produced in nerve endings and endothelial tissues. NO is synthesized in nitrergic fibers and endothelial cells by nitric oxide synthase (NOS) via the conversion of L-arginine and oxygen to L-citrulline and NO. This reaction requires a pO_2 greater than 55 mmHg. NOS is present in endothelial cells (eNOS), neuronal cells (nNOS), and as an inducible form (iNOS). Although all three types are present in the corpora, eNOS and nNOS are primarily responsible for erections. NO catalyzes the conversion of guanosine-5′-triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) via soluble guanylyl cyclase. cGMP leads to smooth muscle relaxation, as discussed below.

Additionally, cavernous tissue is rich in muscarinic receptors, which respond to ACh. Although this is not the primary neurotransmitter involved in tumescence, it may indirectly contribute to muscle relaxation by stimulating NO release and presynaptic inhibition of norepinephrine release from adrenergic neurons. Furthermore, although endothelium releases factors that promote vasoconstriction, it may also produce vasorelaxation via endothelium-derived hyperpolarization factor, PGI_2, and endothelin-1 via ET-B receptor activation.

Other neurotransmitters

Multiple other neurotransmitters may play a role in erectile function. Specifically, serotonergic receptors may inhibit sexual function, sexual drive, and erections, whereas dopaminergic input, via D1, D2, and D4 receptors, and adrenergic receptors promotes sexual function. For instance, apomorphine, which has D1 and D2 receptor activity, induces erection-absent sexual stimulation. Gamma-aminobutyric acid (GABA), cannabinoids, prolactin, and opioids may have an inhibitory role on sexual function and erectile function. Oxytocin, NO, and melanocortins promote erectile function.

Given the complexity of erectile function and regulation, there is significant cross-reactivity between tumescence and detumescence systems. For instance, noradrenergic receptors are modulated by nitrergic fibers and, conversely, adrenergic fibers regulate NO release via α2 presynaptic action. Additionally, there is communication at the level of the vascular smooth muscle as well.

Smooth muscle physiology

Smooth muscle contraction: penile flaccidity (Figure 3.1)

In the flaccid state, cavernous smooth muscle remains tonically contracted, which is termed the latch state. This allows maintenance of a basal tone with minimal energy expenditure. Studies have demonstrated spontaneous contractile activity in smooth muscle, which may also be activity induced. Smooth muscle contraction is regulated by sarcoplasmic Ca^{2+} levels. Ca^{2+} binds to calmodulin, a calcium-binding messenger protein, which triggers a cascade of events allowing myosin to crosslink to actin and contract the muscle.

Once Ca^{2+} binds to calmodulin, the affinity of the Ca^{2+}-calmodulin complex for myosin light chain kinase (MLCK), a serine/threonine-specific protein kinase, increases. MLCK is activated once bound by the Ca^{2+}-calmodulin complex. This leads to phosphorylation of

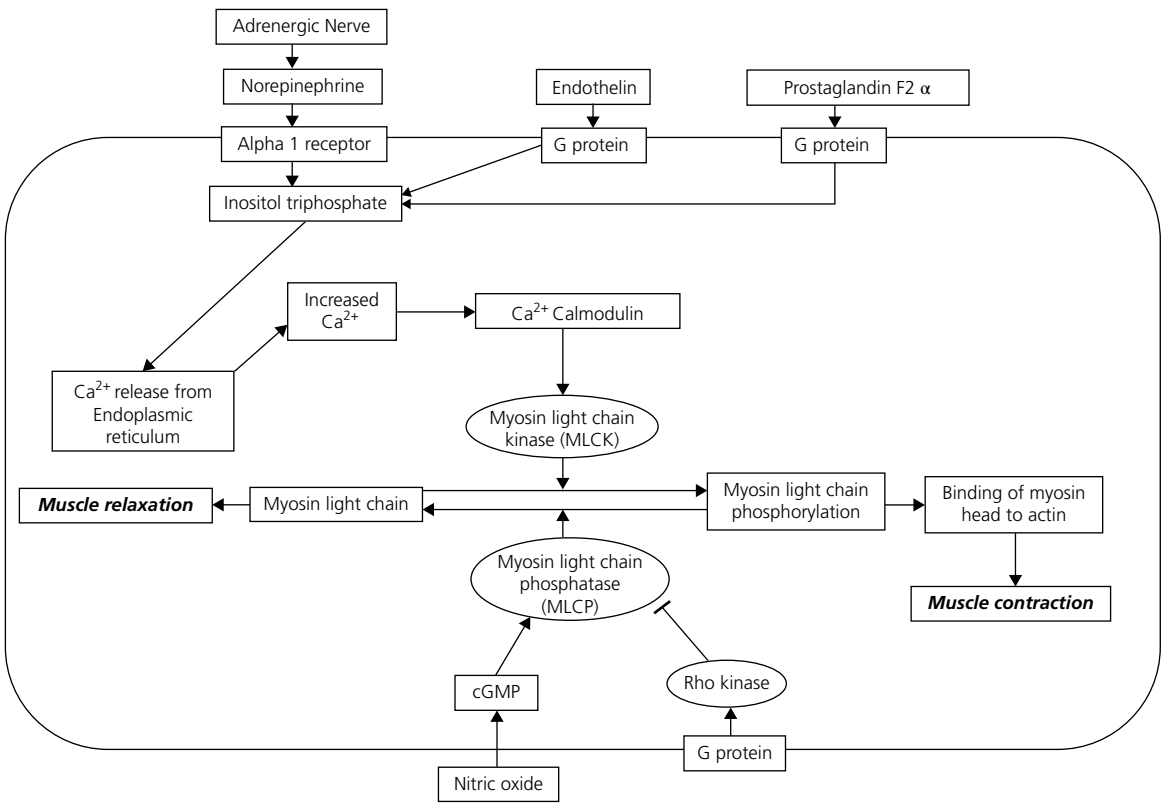

Figure 3.1 Pathways regulating smooth muscle contraction, which leads to detumescence.