

Chapter 2

Physiology of Ejaculation

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Abbreviations

BNST	Bed nucleus of the stria terminalis
CCK	Cholecystokinin
cGMP	Cyclic guanosine monophosphate
DCN	Dorsal central autonomic nucleus
fMRI	Functional magnetic resonance imaging
IML	Intermediolateral cell column
LCTF	Lateral central tegmental field
LSt cells	Lumbar spinothalamic cells
MEA	Medial amygdala
MPOA	Medial preoptic area
NO	Nitric oxide
nPGi	Nucleus paragigantocellularis
NPY	Neuropeptide Y
PDE5-I	Phosphodiesterase-5 inhibitor
PET	Positron emission tomography
PVN	Paraventricular nucleus of the hypothalamus
SPFp	Parvocellular subparafascicular thalamic nucleus
VIP	Vasoactive intestinal peptide
VTA	Ventral tegmental area

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Introduction

Despite being one of the most prevalent sexual dysfunctions [1–3], ejaculatory dysfunction is often misdiagnosed or disregarded. Additionally, no therapies currently exist as definitive “cures” for these disorders. This is likely due to the fact that despite its pervasiveness, surprisingly little is still understood regarding the physiology of ejaculation (for review see [4]). New research continues to provide findings that contribute to our insight and thus potential treatment approaches. This chapter aims to provide an overview of the anatomy as well as contemporary theories of peripheral and central neurophysiology of ejaculation.

Ejaculation is the forcible ejection of seminal fluid from the urethral meatus that commonly accompanies sexual climax and orgasm. *Ejaculation, however, should not be confused with orgasm.* Orgasm is a distinct entity from ejaculation characterized by a physical and emotional sensations experienced at the peak of sexual arousal usually after stimulation of a sexual organ. Orgasm is a purely cerebral and emotional cortical occurrence, though in normal male physiology, orgasm coincides with ejaculation. It should be noted that even in the published literature and among experts, there seems to oftentimes be confusion between these two terms.

To understand the complex process of ejaculation, it is important to understand the myriad of systems required for normal ejaculation. We will first review the gross anatomy of the pelvis as it pertains to the ejaculatory mechanism as well as the dynamic changes that occur with ejaculation. We then review the neuroanatomy of the spinal cord and the brain that are responsible for ejaculatory function. Finally, we will review the neurotransmitters implicated in ejaculatory function and dysfunction.

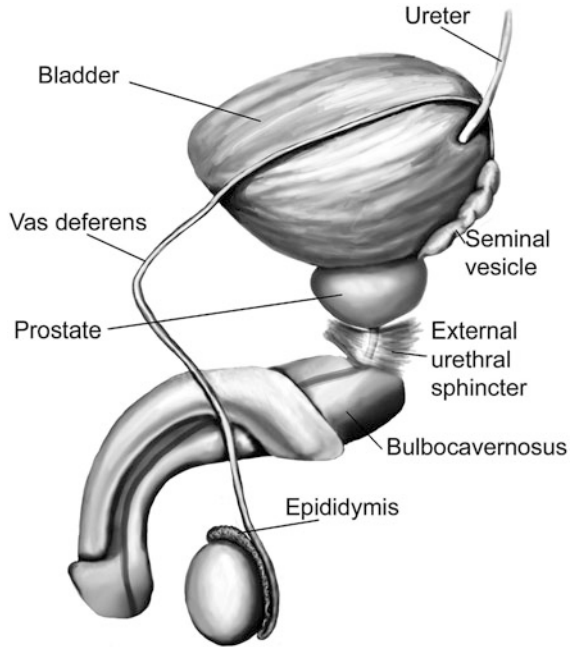
Gross Anatomy of Ejaculation

The process of ejaculation can be divided into two distinct phases: emission and expulsion. We will first review the anatomical structures and their actions, which contribute specifically to each phase.

Emission (Seminal Emission)

Emission is a physiologic process involving the distal epididymis, the vas deferens, the seminal vesicles, the prostate gland, the prostatic urethra, and the bladder neck (Fig. 2.1). The initial step in emission commences with closure of the bladder neck due to sympathetic innervation of the base of the bladder. This action prevents the retrograde flow of ejaculate into the bladder. After bladder neck closure, secretion of fluid from the prostate, laden with acid phosphatase, citric acid, and zinc mixes

Fig. 2.1 Gross anatomy of the structures involved in ejaculation



with spermatozoa-rich fluid from the vas deferens in the prostatic urethra. Subsequent contribution of seminal vesicle fluid replete with fructose alkalinizes the final ejaculatory product. A minor component of the emission phase also includes excretion of fluid from both Cowper's glands and periurethral glands. In total, the composition of ejaculate consists of prostatic fluid (10 % of volume), vasal fluid (10 % of volume), seminal vesicle fluid (75–80 % of volume), and fluid from the Cowper's and periurethral glands (or glands of Littre) [5].

Expulsion (Propulsive Expulsion)

Expulsion consists of discharge of the products of emission from the urethra through the coordinated actions of the bladder neck, urethra, and pelvic striated muscles. The expulsion phase follows the emission phase. Relaxation of the external urinary sphincter (with a closed bladder neck) is followed by clonic contractions of the prostate, bulbospongiosus muscle, ischiocavernosus, levator ani, and transverse perineal muscles [6–8]. Through rhythmic contractions lasting 0.6–1.0 s with latency time of 0.7 s between, and a total mean duration of contraction lasting 4.2 s, semen is expelled from the urethra [8].

Neuroanatomy of Ejaculation

Beyond the anatomical details of the ejaculatory response, an intact spinal cord and peripheral nervous system are essential to coordinate the numerous steps in the reflex. The sympathetic, parasympathetic, and somatic nervous systems all contribute to the ejaculatory response. Generally, the sympathetic nervous system regulates emission, while the somatic nervous system moderates expulsion. The role of parasympathetic innervation in ejaculation has still not been clearly elucidated, though it does certainly play a role in secretion of seminal fluids from epithelial cells and accessory sex glands during sexual arousal.

Emission

The pelvic plexus, also known as the inferior hypogastric plexus, is composed of dense sympathetic and parasympathetic nerve fibers, which innervates the organs involved in emission. This plexus consists of fibers that flank the rectum and can be found posterolateral to the seminal vesicles. Sympathetic innervation originates from the intermediolateral cell column (IML) and the dorsal central autonomic nucleus (DCN) of the thoracolumbar spine at T10–L2 coalesces in the lumbar sympathetic ganglia of the paravertebral sympathetic trunk and then passes posterior to the vena cava into the interaortocaval space on the right or lateral to the aorta on the left. The nerve fibers then combine anterior to the aortic bifurcation and course caudally on the anterior surface of L5 to form the superior hypogastric plexus (adrenergic nerves), which then terminate at postganglionic fibers that innervate the bladder neck, prostate, vas deferens, and seminal vesicles. These fibers are responsible for the emission events such as bladder neck closure and seminal vesicle emission [9]. The superior hypogastric plexus continues on inferiorly and splits into the bilateral inferior hypogastric plexuses. Familiarity with this functional anatomy is important in retroperitoneal surgeries, such as retroperitoneal lymphadenectomies for testis cancer or aortoiliac vascular operations, as disruption of the sympathetic fibers of either the superior or inferior hypogastric plexuses can result in disordered emission and retrograde ejaculation (see Fig. 2.2).

Expulsion

Expulsion is a spinal cord reflex that is mediated by somatic motor components of the perineal branch of the pudendal nerve that originate from nerve roots S2–S4 as well as by concurrent relaxation of external urethral sphincter and urogenital diaphragm. Specifically, the perineal nerve, which consists of afferent and efferent axons, innervates the bulbospongiosus muscle. Motor neurons in the pudendal

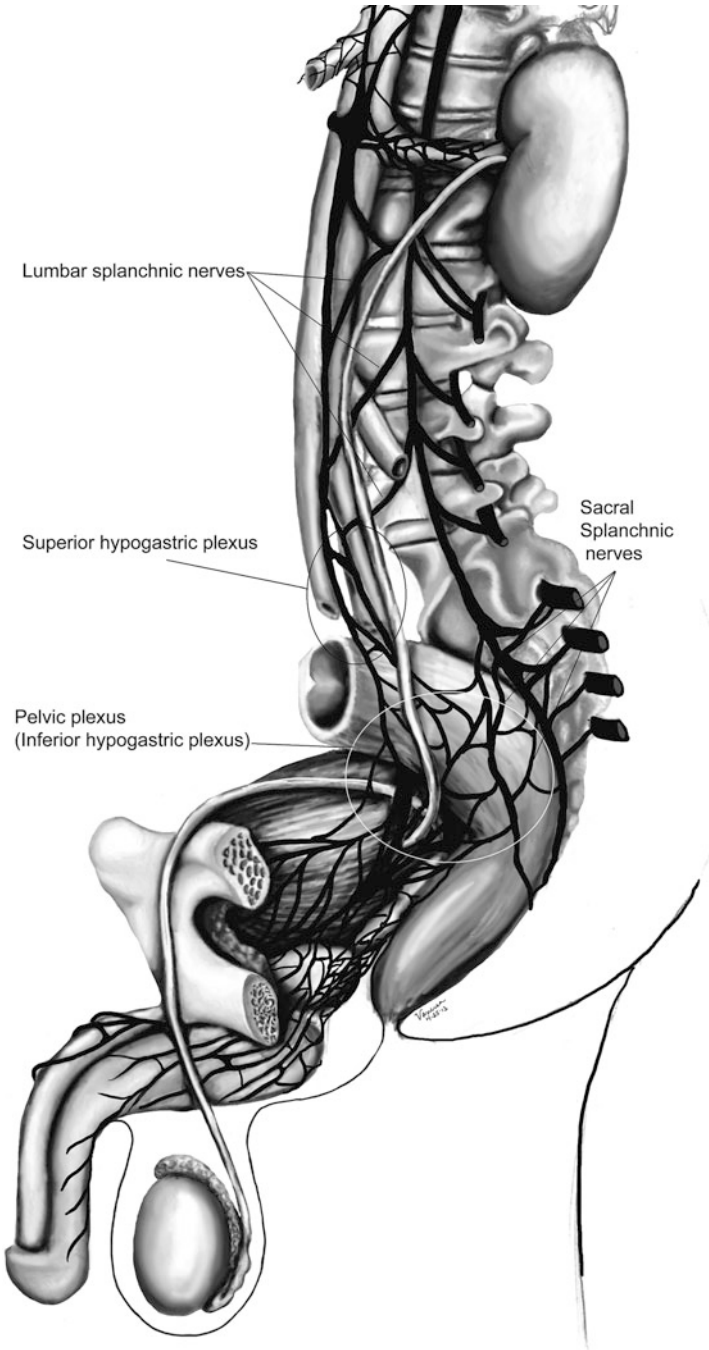


Fig. 2.2 Peripheral nerves and tracts involved in emission and ejaculation

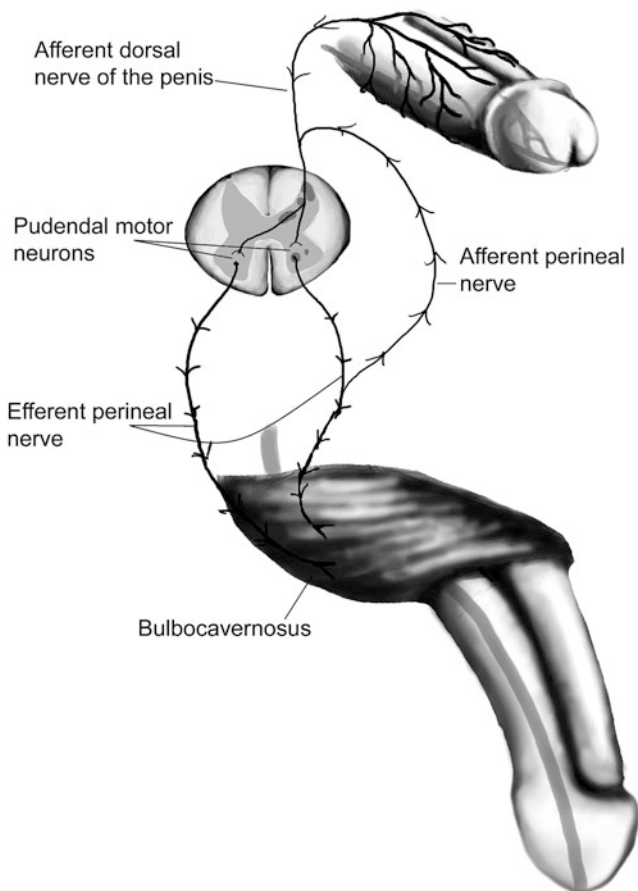


Fig. 2.3 Reflex circuit necessary to elicit ejaculation and bulbospongiosus contraction

nucleus that reside in sacral segments of the conus medullaris, specifically the nucleus of Onuf, supply these sensory axons of the perineal nerve as well as receive synaptic input from two sets of diverging axons of the dorsal nerve of the penis. One set of axons courses along the dorsolateral aspect of the penis and innervates the penile shaft and glans, while the other set of axons branches ventrolaterally and innervates the anterior urethra. These neural pathways are arranged in reflex circuits that are necessary to elicit ejaculation and bulbospongiosus contraction [10]. In essence, the sensory axons of the afferent perineal nerve and the dorsal and ventrolateral branches of the dorsal nerve of penis synapse on pudendal motor neurons in the conus medullaris. The efferent portion of the circuit exits the spinal cord via the perineal nerve to terminate on muscle fibers of the bulbospongiosus muscle for somatic reflex control of these muscles leading to ejaculation [11] (Fig. 2.3).

While both the bladder neck and proximal portion of the urethra are richly comprised of smooth muscle fibers with both sympathetic and parasympathetic innervation, the external urethral sphincter and pelvic floor striated muscles are controlled exclusively by the somatic nervous system. Although the somatic nervous system is typically under voluntary control, it is unclear whether the expulsion phase of ejaculation can be voluntarily controlled. Additionally, the evidence is undecided on which afferent signals are essential for the action of the spinal reflex controlling expulsion. While some data suggested that the viscerosensory deposition of semen in the bulbous urethra itself may trigger clonic contraction of the pelvic striated muscles fundamental to expulsion [12], other results suggest emission is not a required sensory stimulus as demonstrated by the occurrence of dry ejaculation as well as the presence of rhythmic pelvic striated muscle contractions despite a history of prostatectomy, vesiculectomy, or urethrectomy [8, 13]. Studies in rats have also shown maintenance of ejaculatory motor patterns despite urethral anesthetization or seminal emission reduction through medical [14] or surgical means [15]. Meanwhile, studies in humans have shown bulbospongiosus muscle contractions in response to electrical stimulation of the penile dorsal nerve, mechanical distension of the bulbar urethra, and magnetic stimulation of the sacral root [16–18].

Studies have also been performed evaluating the role of the unique somatosensory input from tactile penile stimulation. While the penis contains a high density of sensory nerve fibers, it has a lower tactile sensitivity than the skin of other body parts [19] but increases greatly during erection [20–22]. This plasticity may be explained by the presence of encapsulated nerve endings known as lamellated corpuscles that are distinctive to the glans penis [23–25]. While free nerve endings that sense deep pressure and pain comprise the main variety of nerve fibers in the glans, lamellated corpuscles (also known as Pacinian corpuscles) that sense vibration and pressure have also been found in a 10:1 ratio to free nerve fibers. This is in contrast to the Meissner's and Merkel cell corpuscles, the mechanoreceptor counterparts in the glabrous skin of the fingerpads, which direct tactile sensitivity and are rarely found, if at all, in the glans.

Additionally, the human penile afferent innervations are mainly composed of thinly, myelinated A δ and unmyelinated C fibers that mediate fast and slow afferent conduction, respectively, and form the majority of the free nerve endings. This nerve variety may contribute to the adaptive response of the penis to low force vs. noxious high threshold stimulation. These high threshold sensory fibers may exert an inhibitory effect on reflex penile muscle contractions [26–29]. While the presence of these nerve receptors has been identified, their specific role in the complex interplay of sensory mechanisms responsible for initiating ejaculation remains ambiguous.

Central Neurophysiology of Ejaculation

Spinal Network

The presence of a spinal ejaculatory generator that coordinates peripheral afferents and somatic and sympathetic efferents has been proposed for at least the past decade and may provide a cohesive explanation of the physiology behind ejaculation. Control of ejaculation at the spinal cord level is indicated by the ability to induce ejaculation in patients with complete spinal cord transection above the tenth thoracic level (T10) through penile vibratory stimulation. This demonstrates the endurance of emission reflexes even after spinal cord trauma as well as coordinated control of pelvic floor and bulbospongiosus muscles despite the disconnection of neural pathways from supraspinal control [30–32].

Research in rats have identified a group of spinal neurons, known as lumbar spinothalamic (LSt) cells, which are integral to the generation of ejaculation. Anatomically, these interneurons are located in lumbar spinal cord (L3–4) and are clustered in laminae 10 and 7 located near the central canal of the spinal cord. They also have thalamic projections, hence their name. Functionally, LSt cells have also been found to be under both inhibitory and excitatory control by supraspinal areas, highlighting the facilitatory and inhibitory influence of supratentorial centers and the presence of an LSt-forebrain pathway.

Brain Network

It is important to note that much of the studies on ejaculation have been performed on animals, mostly rats. While these are mammalian models and offer a close representation of the human neural network, these studies have not been performed on primates or dogs that have prostates with more comparable anatomy. However, the results still provide a foundation for the elucidation of human supraspinal activity during ejaculation.

Neuronal mapping studies in rats have used Fos protein, a marker of neuronal activation, to determine expression patterns in brain structures during general sexual activity as well as ejaculation [33, 34]. Various subdivisions of the medial preoptic area (MPOA), the bed nucleus of the stria terminalis (BNST), the medial amygdala (MEA), and the posterior thalamus have been found to be activated during general sexual activity [35, 36]. Ejaculation-specific Fos activity has been localized to regions in the MEA, the BNST, and the medial portion of the parvocellular subparafascicular thalamic nucleus (SPFp) located in the posterior thalamus [36–38]. However, studies utilizing lesion techniques suggest that these brain structures may not be ejaculation-specific but rather associated with transmission of copulatory information or even inhibition of signals in the post-ejaculatory refractory period [39].

In humans, PET and fMRI studies showed strong activation in the ventral tegmental area (VTA) (a known reward center), the subparafascicular nucleus, ventromedial posterior thalamic nucleus, intralaminar nuclei, and lateral central tegmental field specifically during ejaculation. Activation of the lateral putamen, various aspects of the prefrontal, temporal, parietal, and insular cortex; as well as the cerebellum have been seen during ejaculation and orgasm. The parietal cortex, in particular, receives information from the pudendal sensory nerve fibers, bolstering the suggestion of its involvement in ejaculation [40, 41]. Interestingly, no activation was found in the hypothalamus or preoptic area as has been reported in rat studies. Only the lateral central tegmental field (LCTF) and the SPFP were found to be activated in both humans and rats. Deactivation of the medial aspect of the amygdala was also noted during all aspects of sexual activity including ejaculation [42]. This amygdala finding correlates with our current knowledge of the amygdala's role in processing fear and the near-inability of humans to achieve ejaculation while sensing danger or fear, despite penile vibratory stimulation. In essence, animal and human imaging studies confirm a definite role of midbrain structures in regulating ejaculation in facilitatory and inhibitory manners, though the exact mechanisms are still unclear.

Retrograde tract-tracing studies suggest a connection between the medial aspect of the SPFP supraspinally and the spinal LSt cells. These neurons express the neuropeptides galanin and cholecystokinin (CCK) [43, 44]. These galanin-specific nerve fibers have also been found to correlate with ejaculation-associated neurons with strong Fos activity, providing further support for a spinothalamic pathway of ejaculation [38]. Galanin may be responsible for the inhibition of sexual activity after ejaculation as determined by brain infusion studies [45]. Additional evidence for a LSt-medial SPFP-forebrain pathway is bolstered by findings that (a) LSt cells have projections to pudendal motoneurons [26, 46], (b) Lst cells have been found to be post-ejaculation specific and are not present in female rats [47], (c) administration of a 5-HT1A receptor agonist known to specifically target ejaculation yielded positive LSt cell and associated supraspinal FOS [47–50], and (d) selective Lst inhibition and lesion testing solely produces decreases in ejaculation without changes in general sexual activity [51]. These findings support the central role of Lst neurons in the coordination of supratentorial and spinal control of ejaculation.

Other supraspinal centers have been implicated in inhibitory and excitatory control over the spinal ejaculatory center. Studies in rats have shown that the paraventricular nucleus (PVN) of the hypothalamus may yield excitatory influences over seminal emission, though it may not necessarily be compulsory in the erectile or ejaculatory process [52, 53]. The MPOA also appears to play an excitatory role in ejaculatory reflexes through dopaminergic actions on D2 receptors and resultant contraction of pelvic striated muscles along with erection [54–56]. The nucleus paragigantocellularis (nPGi) in the rat medulla, on the other hand, appears to affect an inhibitory control over ejaculatory reflexes through its serotonergic projections to the spinal ejaculation generator in the lumbosacral spinal cord [57, 58]. Therefore, other brain centers may influence the spinal ejaculatory center, either through

a spinal pathway or by an even as yet undiscovered mechanism. It is important to note that these brain areas implicated in rat models have not, and may never be, confirmed in humans due to ethical research standards. However, they provide insight into possible human neural pathways taking into account for species differentiation.

Neurotransmitters

Neurochemical Regulation

Besides knowledge of cholinergic and noradrenergic pathways and other neurotransmitters (VIP, NO, NPY) known to be present at these nerve terminals [59–61], the exact function of these chemicals have been difficult to determine due to species variability, inconsistent study results, and receptor subtype polymorphism. The most studied in animal models (dopamine and serotonin) have highlighted the vital role of these neurotransmitters in the control of ejaculation. Furthermore, the association of SSRI antidepressants with delayed ejaculation and the excitatory sexual side effects of dopamine agonists in Parkinsonian patients have highlighted this clinically.

Dopamine

Dopamine appears to play an excitatory role in ejaculation. This was first suggested when stimulation of sexual behavior was incidentally observed in male Parkinson's patients receiving L-DOPA and then confirmed in rats [62–64]. Interestingly, not only did Parkinson's patients given L-DOPA find resolution of their motor symptoms, they also experienced hypersexuality in the form of increased libido, masturbation, sexual hallucinations, and spontaneous nocturnal erections. The specificity of the dopamine receptor involved was established with experiments using a 5-HT_{1a} agonist known to stimulate ejaculation; however, with the administration of a D₂ receptor antagonist, it lost this ability [65, 66].

Studies in rats show increased sexual activity and ejaculation with increased MPOA dopamine levels, though its temporal relationship remains unclear [67]. Correspondingly, injection of the dopamine agonist apomorphine into the MPOA increased ejaculation frequency [68, 69], while injection of the dopamine antagonist flupenthixol decreased ejaculatory occurrence [70]. Of the five dopamine G-protein-coupled receptor subtypes, D₁ and D₅ couple positively with adenylate cyclase (AC) activity while D_{2–4} couple negatively. The AC negatively coupled receptors appear to mediate the dopaminergic effects on ejaculation, demonstrated by experiments showing D₁ antagonists and D₂/D₃ agonists stimulate seminal emission and ejaculation [54, 71–75]. While the excitatory role of dopamine in

sexual behavior has long been established, these studies implicate the generally stimulatory effect of dopamine on the ejaculatory process.

These biochemical findings further correlate with clinical findings of ejaculatory delay in patients treated with dopaminergic antagonists for schizophrenia or anxiety [71, 72]. Dopamine antagonists such as haloperidol, thioridazine, and sulpiride have been found to delay ejaculation. A double-blind crossover study in patients with premature ejaculation found significant improvement in ejaculation latency after administration of dopamine antagonists metoclopramide hydrochloride or sulpiride. Similar results were found with dose-dependent amounts of risperidone, a dopamine and serotonin receptor antagonist, and levosulpiride, a dopamine antagonist [73].

Serotonin

In contrast, serotonin generally exerts an inhibitory effect in the neuromodulation of ejaculation, though this varies depending on receptor subtype. Of the 15 known 5-HT receptors, 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2c} have consistently been shown to be involved in the regulation of ejaculation. Due to their heterogeneity, 5-HT receptors have been grouped into seven major families (5-HT₁₋₇) based on function and location. All are G-protein-coupled receptors except for the 5-HT₃ receptor. Similarly, all receptors are located postsynaptically, except for 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors which are presynaptic and involved in negative feedback. Immunocytochemical studies have confirmed the ubiquitous presence of these 5-HT receptors throughout the central and peripheral nervous system, from the brainstem, hypothalamus (MPOA), and BDNT to the dorsal horns of the spinal cord and even structures involved in ejaculation such as the seminal vesicles, vas deferens, urethra, and prostate [74–76].

Somatodendritic 5-HT_{1A} receptor activation appears to abbreviate ejaculation latency times [77] while presynaptic 5-HT_{1B} and postsynaptic 5-HT_{2c} stimulation may increase ejaculatory latency times [78, 79]. However, 5-HT_{1A} at other neural sites, such as the brain, spinal cord, and autonomic ganglia, may exert either excitatory or inhibitory effects on ejaculation [80].

Nitric Oxide

The role of nitric oxide in *erection* (specifically the activation of guanylate cyclase resulting to an increase in cyclic GMP and subsequent smooth muscle relaxation of the corporal cavernosal blood vessels) is well established. However, the role of nitric oxide in the *ejaculatory* process has come to light in the recent debate over the use of phosphodiesterase-5 inhibitors (PDE5-I) for premature ejaculation. While PDE5-Is, which inhibit cGMP degradation and thus increase perfusion to the penis, are established in the treatment of erectile dysfunction, the suggestive effects of

PDE5-Is on ejaculatory dysfunction merits a look into the role of nitric oxide in ejaculation [81, 82].

The mechanism of action of nitric oxide in ejaculation is best approached centrally vs. peripherally. Studies on both humans and animals have found that nitric oxide (an inhibitory mediator) can act centrally by decreasing sympathetic drive as well as peripherally by inhibiting sympathetic vasoconstriction and inducing smooth muscle dilation of the vas deferens and seminal vesicles [83]. Specifically, central manipulation through intrathecal injection of sildenafil in rats has shown a resultant increase in NO and cGMP levels in the MPOA [84]. Increased NO activity in the MPOA in turn decreases sympathetic tone in the periphery which can inhibit ejaculation [85]. Alternatively, microinjection of *N*-nitro-*L*-arginine methyl-ester (NAME), an inhibitor of nitric oxide synthase, increased the number of seminal emissions and decreased the latency to first seminal emission in rats [86].

Peripherally, nitroergic innervation and nitric oxide synthase/cGMP and cAMP signaling pathways have been identified in human skeletal muscle as well as the smooth muscle of the vas deferens, seminal vesicles, prostate, and urethra [87–91]. As such, drugs such as PDE5-Is or NO donors that increase intracellular cGMP or cAMP diminish human seminal vesicle contraction and inhibit seminal emission in rats [86]. Conversely, NO inhibitors, such as *L*-nitro-arginine-methyl-ester, decrease the contractile response of human seminal vesicles [92] and guinea pig vas deferens [93], as well as reduce the latency to emission in rats [94]. Further, knockout mice with a homozygous deletion in the gene encoding endothelial NOS have decreased latency to emission with less stimulation than their wild-type counterparts [95].

While the action of nitric oxide in some central and peripheral pathways has been identified, the clinical application of NO modulators has yet to be elucidated. An understanding of these pathways as well as the physiology of ejaculation will build a foundation for future approaches to the treatment of ejaculatory disorders.

Summary

- Ejaculation consists of two phases: emission (deposition of seminal fluids and sperm in the posterior urethra) and ejaculation (propulsion of this ejaculate out of the urethra).
- Ejaculation culminates through the interaction of supraspinal, spinal, and peripheral neural pathways.
- A spinal ejaculation generator containing LSt cell has been discovered that appears to be a pivotal mediator in the ejaculatory process.
- Many neurotransmitters have been identified in the ejaculatory neuraxis; however, laboratory and clinical evidence support a general excitatory and inhibitory role of dopamine and serotonin, respectively, and an inhibitory role of nitric oxide.

- Little is still known regarding the physiology of ejaculation. Better understanding will assist with future clinical therapies for ejaculatory dysfunction, the most commonly reported sexual complaint.

References

1. Hendry WF. Disorders of ejaculation. *Ann R Coll Surg Engl.* 1999;81(5):352–8.
2. Althof SE. Prevalence, characteristics and implications of premature ejaculation/rapid ejaculation. *J Urol.* 2006;175(3 Pt 1):842–8.
3. Lewis RW, Fugl-Meyer KS, Bosch R, Fugl-Meyer AR, Laumann EO, Lissa E, Martin-Morales A. Definitions, classifications and epidemiology of sexual dysfunction in sexual medicine sexual dysfunctions in men and women. In: Lue TF, Basson R, Rosen R, Giuliano F, Khoury S, Montorsi F, editors. *Sexual medicine sexual dysfunctions in men and women.* Oxford: Health Publication Ltd; 2004. p. 37–72.
4. Mulhall J. Premature ejaculation. In: Wein AJ, Kavoussi L, Novick AC, Partin AW, Peters CA, editors. *Campbell-Walsh urology.* 10th ed. Philadelphia, PA: Elsevier Saunders; 2011. p. 770–9.
5. Master VA, Turek PJ. Ejaculatory physiology and dysfunction. *Urol Clin North Am.* 2001;28(2):363–75. x.
6. Yang CC, Bradley WE. Somatic innervation of the human bulbocavernosus muscle. *Clin Neurophysiol.* 1999;110(3):412–8.
7. Gerstenberg TC, Levin RJ, Wagner G. Erection and ejaculation in man. Assessment of the electromyographic activity of the bulbocavernosus and ischiocavernosus muscles. *Br J Urol.* 1990;65(4):395–402.
8. Vaucher L, Bolyakov A, Paduch DA. Evolving techniques to evaluate ejaculatory function. *Curr Opin Urol.* 2009;19(6):606–14.
9. Lipshultz LI, Howards SS, Niederberger CS. *Infertility in the male.* 4th ed. Cambridge, UK: Cambridge University Press; 2009.
10. Yang CC, Bradley WE. Innervation of the human anterior urethra by the dorsal nerve of the penis. *Muscle Nerve.* 1998;21(4):514–8.
11. Wieder JA, Brackett NL, Lynne CM, Green JT, Aballa TC. Anesthetic block of the dorsal penile nerve inhibits vibratory-induced ejaculation in men with spinal cord injuries. *Urology.* 2000;55(6):915–7.
12. McKenna KE, Chung SK, McVary KT. A model for the study of sexual function in anesthetized male and female rats. *Am J Physiol.* 1991;261(5 Pt 2):R1276–85.
13. Bergman B, Nilsson S, Petersen I. The effect on erection and orgasm of cystectomy, prostatectomy and vesiculectomy for cancer of the bladder: a clinical and electromyographic study. *Br J Urol.* 1979;51(2):114–20.
14. Holmes GM, Sachs BD. The ejaculatory reflex in copulating rats: normal bulbospongiosus activity without apparent urethral stimulation. *Neurosci Lett.* 1991;125(2):195–7.
15. Larsson K, Swedin G. The sexual behavior of male rats after bilateral section of the hypogastric nerve and removal of the accessory genital glands. *Physiol Behav.* 1971;6(3):251–3.
16. Nordling J, Andersen JT, Walter S, Meyhoff HH, Hald T, Gammelgaard PA. Evoked response of the bulbocavernosus reflex. *Eur Urol.* 1979;5(1):36–8.
17. Opsomer RJ, Caramia MD, Zarola F, Pesce F, Rossini PM. Neurophysiological evaluation of central-peripheral sensory and motor pudendal fibres. *Electroencephalogr Clin Neurophysiol.* 1989;74(4):260–70.
18. Shafik A, El-Sibai O. Mechanism of ejection during ejaculation: identification of a urethro-cavernosus reflex. *Arch Androl.* 2000;44(1):77–83.
19. Symonds C. *Studies in neurology.* London: Oxford University Press; 1970.

20. Johnson RD. Efferent modulation of penile mechanoreceptor activity. *Prog Brain Res.* 1988;74:319–24.
21. McKenna K. Ejaculation. In: Knobil E, Neill JD, editors. *Encyclopedia of reproduction.* New York: Academic; 1999. p. 1002–8.
22. Hull E, Meisel R, Sachs B. Male sexual behavior. In: Pfaff D, Arnold A, Etgen A, Fahrbach S, Rubin R, editors. *Hormones, brain and behavior.* New York: Academic; 2002. p. 3–137.
23. Johnson RD, Halata Z. Topography and ultrastructure of sensory nerve endings in the glans penis of the rat. *J Comp Neurol.* 1991;312(2):299–310.
24. Johnson R, Dugan V. Responses of spine associated penile mechanoreceptors to tangential mechanical stimulation. *Soc Neurosci Abstr.* 1988;14:726.
25. Gray BW, Beckett SD, Henry DF. Microscopic characteristics of genital end bulbs in the penis of bulls. *Am J Vet Res.* 1985;46(11):2393–8.
26. De Groat WC, Steers WD. Autonomic regulation of the urinary bladder and sexual organs. In: Loewy AD, Spyer K, editors. *Central regulation of autonomic function.* Oxford: Oxford University Press; 1990. p. 310–33.
27. Halata Z, Munger BL. The neuroanatomical basis for the protopathic sensibility of the human glans penis. *Brain Res.* 1986;371(2):205–30.
28. Calaresu FR, Mitchell R. Cutaneous mechanoreceptors in the glans penis of the rat. *Brain Res.* 1969;15(1):295–7.
29. Kitchell RL, Gilanpour H, Johnson RD. Electrophysiologic studies of penile mechanoreceptors in the rats. *Exp Neurol.* 1982;75(1):229–44.
30. Sonksen J, Biering-Sorensen F, Kristensen JK. Ejaculation induced by penile vibratory stimulation in men with spinal cord injuries. The importance of the vibratory amplitude. *Paraplegia.* 1994;32(10):651–60.
31. Brackett NL, Ferrell SM, Aballa TC, Amador MJ, Padron OF, Sonksen J, et al. An analysis of 653 trials of penile vibratory stimulation in men with spinal cord injury. *J Urol.* 1998;159(6):1931–4.
32. Biering-Sorensen F, Laessoe L, Sonksen J, Bagi P, Nielsen JB, Kristensen JK. The effect of penile vibratory stimulation on male fertility potential, spasticity and neurogenic detrusor overactivity in spinal cord lesioned individuals. *Acta Neurochir Suppl.* 2005;93:159–63.
33. Newman SW. The medial extended amygdala in male reproductive behavior. A node in the mammalian social behavior network. *Ann N Y Acad Sci.* 1999;877:242–57.
34. Pfaus JG, Heeb MM. Implications of immediate-early gene induction in the brain following sexual stimulation of female and male rodents. *Brain Res Bull.* 1997;44(4):397–407.
35. Coolen LM, Peters HJ, Veening JG. Fos immunoreactivity in the rat brain following consummatory elements of sexual behavior: a sex comparison. *Brain Res.* 1996;738(1):67–82.
36. Coolen LM, Peters HJ, Veening JG. Distribution of Fos immunoreactivity following mating versus anogenital investigation in the male rat brain. *Neuroscience.* 1997;77(4):1151–61.
37. Veening JG, Coolen LM. Neural activation following sexual behavior in the male and female rat brain. *Behav Brain Res.* 1998;92(2):181–93.
38. Coolen LM, Veening JG, Petersen DW, Shipley MT. Parvocellular subparafascicular thalamic nucleus in the rat: anatomical and functional compartmentalization. *J Comp Neurol.* 2003;463(2):117–31.
39. Coolen LM. Neural control of ejaculation. *J Comp Neurol.* 2005;493(1):39–45.
40. Perretti A, Catalano A, Mirone V, Imbimbo C, Balbi P, Palmieri A, et al. Neurophysiologic evaluation of central-peripheral sensory and motor pudendal pathways in primary premature ejaculation. *Urology.* 2003;61(3):623–8.
41. Arnow BA, Desmond JE, Banner LL, Glover GH, Solomon A, Polan ML, et al. Brain activation and sexual arousal in healthy, heterosexual males. *Brain.* 2002;125(Pt 5):1014–23.
42. Holstege G, Georgiadis JR, Paans AMJ, Meiners LC, VanderGraaf FHCE, Reinders AATS. Neural correlates of human male ejaculation. *J Neurosci.* 2003;23:9185–93.
43. Nicholas AP, Zhang X, Hokfelt T. An immunohistochemical investigation of the opioid cell column in lamina X of the male rat lumbosacral spinal cord. *Neurosci Lett.* 1999;270(1):9–12.

44. Ju G, Melander T, Ceccatelli S, Hokfelt T, Frey P. Immunohistochemical evidence for a spinothalamic pathway co-containing cholecystokinin- and galanin-like immunoreactivities in the rat. *Neuroscience*. 1987;20(2):439–56.
45. Truitt WA, Dominguez JM, Adelman J, Coolen LM. Galanin infusions into the medial parvocellular parafascicular thalamic nucleus inhibit male sexual behavior. *Horm Behav*. 2003;44:81.
46. Allard J, Truitt WA, McKenna KE, Coolen LM. Spinal cord control of ejaculation. *World J Urol*. 2005;23(2):119–26.
47. Truitt WA, Shipley MT, Veening JG, Coolen LM. Activation of a subset of lumbar spinothalamic neurons after copulatory behavior in male but not female rats. *J Neurosci*. 2003;23(1):325–31.
48. Ahlenius S, Larsson K, Svensson L, Hjorth S, Carlsson A, Lindberg P, et al. Effects of a new type of 5-HT receptor agonist on male rat sexual behavior. *Pharmacol Biochem Behav*. 1981;15(5):785–92.
49. Lee RL, Smith ER, Mas M, Davidson JM. Effects of intrathecal administration of 8-OH-DPAT on genital reflexes and mating behavior in male rats. *Physiol Behav*. 1990;47(4):665–9.
50. Coolen LM, Olivier B, Peters HJ, Veening JG. Demonstration of ejaculation-induced neural activity in the male rat brain using 5-HT_{1A} agonist 8-OH-DPAT. *Physiol Behav*. 1997;62(4):881–91.
51. Truitt WA, Coolen LM. Identification of a potential ejaculation generator in the spinal cord. *Science*. 2002;297(5586):1566–9.
52. Wagner CK, Clemens LG. Projections of the paraventricular nucleus of the hypothalamus to the sexually dimorphic lumbosacral region of the spinal cord. *Brain Res*. 1991;539(2):254–62.
53. Wagner CK, Clemens LG. Neurophysin-containing pathway from the paraventricular nucleus of the hypothalamus to a sexually dimorphic motor nucleus in lumbar spinal cord. *J Comp Neurol*. 1993;336(1):106–16.
54. Hull EM, Warner RK, Bazzett TJ, Eaton RC, Thompson JT, Scaletta LL. D₂/D₁ ratio in the medial preoptic area affects copulation of male rats. *J Pharmacol Exp Ther*. 1989;251(2):422–7.
55. Hull EM, Eaton RC, Markowski VP, Moses J, Lumley LA, Loucks JA. Opposite influence of medial preoptic D₁ and D₂ receptors on genital reflexes: implications for copulation. *Life Sci*. 1992;51(22):1705–13.
56. Sato Y, Christ GJ. Differential ICP responses elicited by electrical stimulation of medial preoptic area. *Am J Physiol Heart Circ Physiol*. 2000;278(3):964–70.
57. Marson L, List MS, McKenna KE. Lesions of the nucleus paragigantocellularis alter ex copula penile reflexes. *Brain Res*. 1992;592(1–2):187–92.
58. Marson L, McKenna KE. A role for 5-hydroxytryptamine in descending inhibition of spinal sexual reflexes. *Exp Brain Res*. 1992;88(2):313–20.
59. Grundemar L, Hakanson R. Effects of various neuropeptide Y/peptide YY fragments on electrically-evoked contractions of the rat vas deferens. *Br J Pharmacol*. 1990;100(1):190–2.
60. Zoubek J, Somogyi GT, De Groat WC. A comparison of inhibitory effects of neuropeptide Y on rat urinary bladder, urethra, and vas deferens. *Am J Physiol*. 1993;265(3 Pt 2):R537–43.
61. Domoto T, Tsumori T. Co-localization of nitric oxide synthase and vasoactive intestinal peptide immunoreactivity in neurons of the major pelvic ganglion projecting to the rat rectum and penis. *Cell Tissue Res*. 1994;278(2):273–8.
62. Gessa GL, Tagliamonte A. Role of brain monoamines in male sexual behavior. *Life Sci*. 1974;14(3):425–36.
63. Tagliamonte A, DeMontis G, Olianias M, Vargiu L, Corsini GU, Gessa GL. Selective increase of brain dopamine synthesis by sulpiride. *J Neurochem*. 1975;24(4):707–10.
64. Giuliano F, Allard J. Dopamine and male sexual function. *Eur Urol*. 2001;40(6):601–8.
65. Clement P, Bernabe J, Kia HK, Alexandre L, Giuliano F. D₂-like receptors mediate the expulsion phase of ejaculation elicited by 8-hydroxy-2-(di-N-propylamino)tetralin in rats. *J Pharmacol Exp Ther*. 2006;316(2):830–4.

66. Matuszewich L, Lorrain DS, Trujillo R, Dominguez J, Putnam SK, Hull EM. Partial antagonism of 8-OH-DPAT'S effects on male rat sexual behavior with a D2, but not a 5-HT1A, antagonist. *Brain Res.* 1999;820(1–2):55–62.
67. Hull EM, Du J, Lorrain DS, Matuszewich L. Extracellular dopamine in the medial preoptic area: implications for sexual motivation and hormonal control of copulation. *J Neurosci.* 1995;15(11):7465–71.
68. Hull EM, Bitran D, Pehek EA, Warner RK, Band LC, Holmes GM. Dopaminergic control of male sex behavior in rats: effects of an intracerebrally-infused agonist. *Brain Res.* 1986;370(1):73–81.
69. Scaletta LL, Hull EM. Systemic or intracranial apomorphine increases copulation in long-term castrated male rats. *Pharmacol Biochem Behav.* 1990;37(3):471–5.
70. Pehek EA, Warner RK, Bazzett TJ, Bitran D, Band LC, Eaton RC, et al. Microinjection of cis-flupenthixol, a dopamine antagonist, into the medial preoptic area impairs sexual behavior of male rats. *Brain Res.* 1988;443(1–2):70–6.
71. Compton MT, Miller AH. Sexual side effects associated with conventional and atypical antipsychotics. *Psychopharmacol Bull.* 2001;35(3):89–108.
72. Peeters M, Giuliano F. Central neurophysiology and dopaminergic control of ejaculation. *Neurosci Biobehav Rev.* 2008;32(3):438–53.
73. Sato Y, Horita H, Kurohata T, Adachi H, Tsukamoto T. Effect of the nitric oxide level in the medial preoptic area on male copulatory behavior in rats. *Am J Physiol.* 1998;274(1 Pt 2):R243–7.
74. Azmitia E, Gannon P. The ultrastructural localization of serotonin immunoreactivity in myelinated and unmyelinated axons within the medial forebrain bundle of rat and monkey. *J Neurosci.* 1983;3(10):2083–90.
75. Descarries L, Beaudet A, Watkins KC. Serotonin nerve terminals in adult rat neocortex. *Brain Res.* 1975;100(3):563–88.
76. Kim SW, Paick JS. Peripheral effects of serotonin on the contractile responses of rat seminal vesicles and vasa deferentia. *J Androl.* 2004;25(6):893–9.
77. Rowland DL, Houtsmuller EJ. 8-OH-DPAT interacts with sexual experience and testosterone to affect ejaculatory response in rats. *Pharmacol Biochem Behav.* 1998;60(1):143–9.
78. Hillegaart V, Ahlenius S. Facilitation and inhibition of male rat ejaculatory behaviour by the respective 5-HT1A and 5-HT1B receptor agonists 8-OH-DPAT and anpirtoline, as evidenced by use of the corresponding new and selective receptor antagonists NAD-299 and NAS-181. *Br J Pharmacol.* 1998;125(8):1733–43.
79. Foreman MM, Hall JL, Love RL. The role of the 5-HT2 receptor in the regulation of sexual performance of male rats. *Life Sci.* 1989;45(14):1263–70.
80. Giuliano F, Clement P. Physiology of ejaculation: emphasis on serotonergic control. *Eur Urol.* 2005;48(3):408–17.
81. Wang WF, Minhas S, Ralph DJ. Phosphodiesterase 5 inhibitors in the treatment of premature ejaculation. *Int J Androl.* 2006;29(5):503–9.
82. Chen J, Keren-Paz G, Bar-Yosef Y, Matzkin H. The role of phosphodiesterase type 5 inhibitors in the management of premature ejaculation: a critical analysis of basic science and clinical data. *Eur Urol.* 2007;52(5):1331–9.
83. Asimakopoulos AD, Miano R, Finazzi Agro E, Vespasiani G, Spera E. Does current scientific and clinical evidence support the use of phosphodiesterase type 5 inhibitors for the treatment of premature ejaculation? A systematic review and meta-analysis. *J Sex Med.* 2012;9(9):2404–16.
84. Sato Y, Zhao W, Christ GJ. Central modulation of the NO/cGMP pathway affects the MPOA-induced intracavernous pressure response. *Am J Physiol Regul Integr Comp Physiol.* 2001;281(1):R269–78.
85. Pfaus JG. Neurobiology of sexual behavior. *Curr Opin Neurobiol.* 1999;9(6):751–8.
86. Hull EM, Lumley LA, Matuszewich L, Dominguez J, Moses J, Lorrain DS. The roles of nitric oxide in sexual function of male rats. *Neuropharmacology.* 1994;33(11):1499–504.

87. Dixon JS, Jen PY. Development of nerves containing nitric oxide synthase in the human male urogenital organs. *Br J Urol.* 1995;76(6):719–25.
88. Hedlund P, Ekstrom P, Larsson B, Alm P, Andersson KE. Heme oxygenase and NO-synthase in the human prostate—relation to adrenergic, cholinergic and peptide-containing nerves. *J Auton Nerv Syst.* 1997;63(3):115–26.
89. Jen PY, Dixon JS, Gosling JA. Co-localization of nitric oxide synthase, neuropeptides and tyrosine hydroxylase in nerves supplying the human post-natal vas deferens and seminal vesicle. *Br J Urol.* 1997;80(2):291–9.
90. Kaminski HJ, Andrade FH. Nitric oxide: biologic effects on muscle and role in muscle diseases. *Neuromuscul Disord.* 2001;11(6–7):517–24.
91. Uckert S, Bazrafshan S, Scheller F, Mayer ME, Jonas U, Stief CG. Functional responses of isolated human seminal vesicle tissue to selective phosphodiesterase inhibitors. *Urology.* 2007;70(1):185–9.
92. Bultmann R, Klebroff W, Starke K. Nucleotide-evoked relaxation of rat vas deferens: possible mechanisms. *Eur J Pharmacol.* 2002;436(1–2):135–43.
93. Kato K, Furuya K, Tsutsui I, Ozaki T, Yamagishi S. Cyclic AMP-mediated inhibition of noradrenaline-induced contraction and Ca^{2+} influx in guinea-pig vas deferens. *Exp Physiol.* 2000;85(4):387–98.
94. Bialy M, Beck J, Abramczyk P, Trzebski A, Przybylski J. Sexual behavior in male rats after nitric oxide synthesis inhibition. *Physiol Behav.* 1996;60(1):139–43.
95. Kriegsfeld LJ, Demas GE, Huang PL, Burnett AL, Nelson RJ. Ejaculatory abnormalities in mice lacking the gene for endothelial nitric oxide synthase (eNOS $^{-/-}$). *Physiol Behav.* 1999;67(4):561–6.