

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.

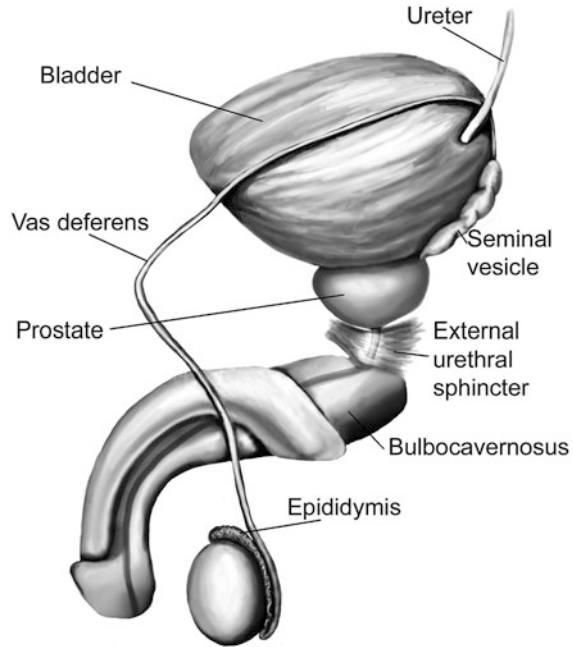
Gross Anatomy of Ejaculation

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 alkalizes 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 (Propulsatile 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

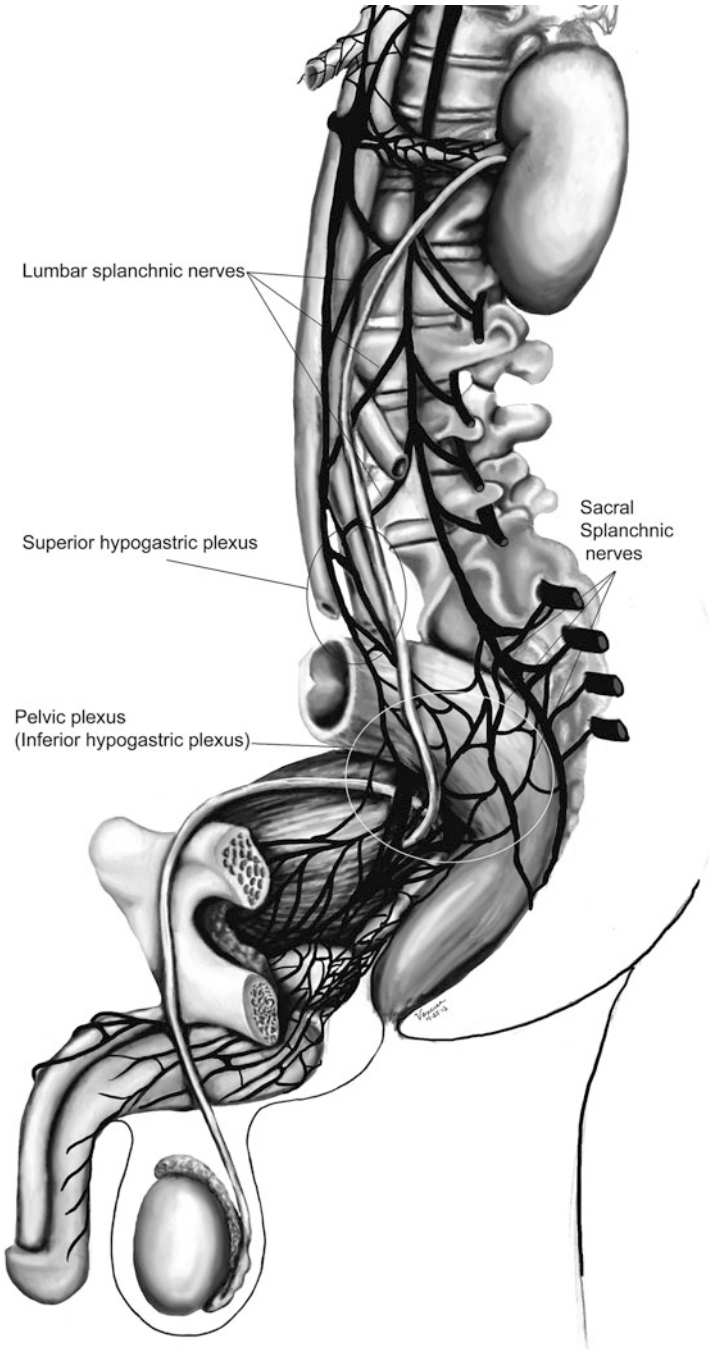


Fig. 2.2 Peripheral nerves and tracts involved in emission and ejaculation

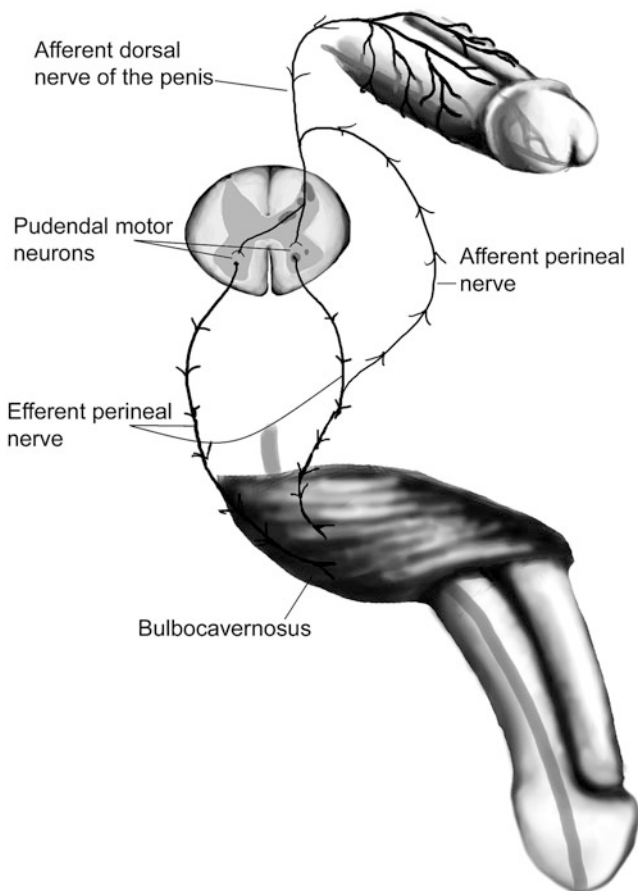


Fig. 2.3 Reflex circuit necessary to elicit ejaculation and bulbospongiosus contraction

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.

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