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TOPIC PAPER

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Spinal cord control of ejaculation

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Abstract Ejaculation is a reflex mediated by a spinal control center, referred to as a spinal ejaculation generator. During intercourse, the spinal ejaculation generator integrates the sensory inputs that are necessary to trigger ejaculation. At the time of ejaculation, it coordinates the sympathetic, parasympathetic, and somatic outflow to induce the two phases of ejaculation, i.e. emission and expulsion. It also provides the brain with signals related to the occurrence of ejaculation. Experimental and clinical data evidenced that these functions were devoted to neurons located in the lumbosacral cord. We recently characterized a population of spinothalamic neurons in the lumbar spinal cord of male rats (LSt cells) that constitutes an integral part of the spinal ejaculation generator. LSt cells send projections to the autonomic nuclei and motoneurons involved in the emission and expulsion phase, and they receive sensory projections from the pelvis. LSt cells are activated with ejaculation, but not following other components of sexual behavior, and lesions of LSt cells completely ablate ejaculatory function. These data support a pivotal role for the LSt cells in the control of ejaculation.

Keywords Pudendal motoneurons · Dorsal penile nerve · Galanin · Serotonin · Spinothalamic · Spinal ejaculation generator

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Introduction

Ejaculation, defined as the expulsion of sperm from the urethral meatus, is divided in two successive phases: emission and expulsion [1]. The emission phase consists of closure of the bladder neck (to prevent retrograde flow of sperm into the bladder), and contraction of the seminal vesicles, prostate and vas deferens (to allow transfer of their respective contents into the prostatic urethra) [2–4]. The expulsion phase corresponds to the forceful expulsion of sperm to the urethral meatus, caused by the rhythmic contractions of the bulbospongiosus muscle surrounding the prostatic urethra [5–7]. Thus, efficient ejaculation requires the coordinated responses of visceral organs (seminal vesicle, prostate and vas deferens), striated muscle (the bulbospongiosus muscle), and smooth muscle (the bladder neck). The notion of a spinal center coordinating these reflexes originated from both clinical data in humans and experimental data in animals in the first half of the 1900s [8, 9]. Since, this control center has been referred to as a spinal pattern generator [10], spinal pacemaker [11, 12] or spinal ejaculation generator [1].

The function of the spinal ejaculation center is likely not restricted to the command of the peripheral organs involved in ejaculation. The spinal generator also integrates the sexually related inputs during intercourse that are required to trigger ejaculation. In addition, it is involved in the transmission of signals related to the occurrence of ejaculation to supraspinal structures, possibly contributing to the pleasurable feelings referred to as orgasm. The purpose of this paper is to review the physiological and anatomical data supporting the existence of a spinal ejaculation center. Particular emphasis is placed on a recently identified cell population in the lumbosacral spinal cord that plays a major role in ejaculation and constitutes an essential component of the spinal ejaculation generator [13].

Evidence for a spinal ejaculation generator

In humans, the existence of a spinal ejaculation generator is best illustrated by the ability of vibratory stimulation of the glans penis to induce ejaculation in patients with complete spinal cord transection above the 10th thoracic segmental level [14, 15]. In anesthetized rats acutely spinalized at the thoracic level, the expulsion phase of ejaculation can be elicited by mechanical stimulation of the glans or the urethra, or by electrical stimulation of sensory afferents from the penis [10, 16]. The ability of a peripheral stimulation to induce a complete (humans) or partial (rats) ejaculation despite the loss of reciprocal connections with supraspinal structures implies that the spinal cord contains the complete neural machinery necessary for ejaculation. However, these data do not exclude a potential participation of supraspinal structures as an integral part of the neural circuitry involved in the autonomic control of ejaculation in spinally intact humans and animals [17].

Input to the spinal ejaculation generator

The spinal ejaculation generator converts the sensory signals generated from the pelvis during sexual activity into autonomic and motor outputs [1]. In other words, the spinal ejaculation generator makes the connection between the sensory afferents from the pelvis, and in particular the penis, and the autonomic and somatic neurons controlling ejaculation (Fig. 1). The sensory afferents from the penis are constituted by fibers traveling (distal to proximal) in the dorsal nerve of the penis (DNP), the sensory branch of the pudendal nerve, and the lumbosacral trunk [18]. The idea that inputs necessary for ejaculation are conveyed by the DNP comes from both experimental and clinical data. Electrical stimulation of the DNP can elicit an expulsion reflex in anesthetized, spinalized rats [16]. The expulsion reflexes induced in similar conditions by mechanical stimulation of the glans and/or urethra are also due to recruitment of afferent fibers running in the DNP [10, 19]. Accordingly, local anesthesia of the DNP abolished ejaculation induced by vibratory stimulation of the glans in patients with spinal cord injury [20].

Injection of transganglionic tracer in the distal DNP showed the presence of fiber terminals throughout the lumbosacral enlargement, from the segmental level S2–L1 [21]. These terminals were present in lamina I and II, but most abundant in the lamina III and IV, from the level L6–L4 [21]. Some of these terminals may correspond to the entry of the sensory input to the spinal ejaculation generator.

The activity of the spinal ejaculation generator is also modulated by descending projections from the hypothalamus, preoptic area, and brainstem. These descending projections may be overall excitatory or inhibitory. Electrical stimulation of the hypothalamus induces expulsion reflex in anesthetized rats [22]. Conversely, the expulsion reflex induced by stimulation of pelvic sensory afferents can be triggered only after transection of the spinal cord, presumably allowing the removal of a tonic descending inhibitory input [10, 16].

Lesion experiments pointed to the nucleus paragigantocellularis, pars lateralis (PGRNl), as a major source of descending inhibitory input on ejaculatory reflex. Lesions of the PGRNl decreased the number of intromission necessary to reach ejaculation in behavioral experiments [23, 24]. It also facilitated the appearance of the expulsion reflex upon mechanical stimulation of the glans and urethra in anesthetized rats [25]. Serotonin has been proposed to be the neurotransmitter involved in the descending tonic inhibitory input from the brainstem. Serotonergic neurons projecting to the spinal cord are

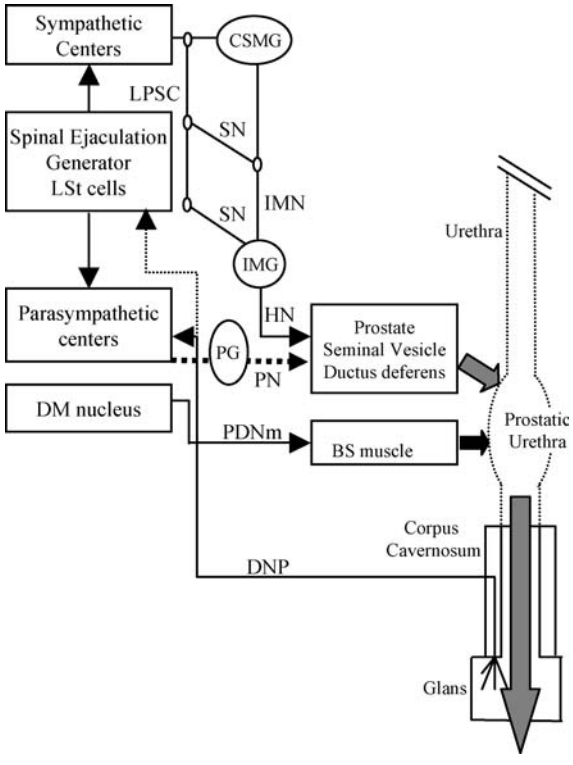

Fig. 1 Representation of the connections of the spinal ejaculation generator. The spinal ejaculation generator receives sensory input from the penis through the dorsal nerve of the penis (*DNP*). In turn, the spinal ejaculation generator projects to the parasympathetic and sympathetic preganglionic neurons, and pudendal motoneurons. The parasympathetic centers, at the lumbosacral level of the spinal cord, project to the sexual accessory glands via the pelvic nerve (*PN*), through the pelvic ganglia (*PG*). The sympathetic centers, at the thoracolumbar level of the spinal cord, project to the pelvic organs via the lateral paravertebral sympathetic chain (*LPSC*), and the intermesenteric (*IMN*) and hypogastric nerves (*HN*). The *IMN* connects the celiac superior mesenteric ganglia (*CSMG*) with the intermesenteric ganglia (*IMG*). Connections from the *LPSC* to the *IMN* and *HN* occur through the splanchnic nerves (*SN*). The motoneurons of the bulbospongiosus muscle (*BS*) are located in the dorsomedian nucleus (*DM*) at the lumbosacral level of the spinal cord and project through the motor branch of the pudendal nerve (*PDNm*)

present in the medial part of the PGRNl and delivery of serotonin at the spinal level inhibited the occurrence of expulsion reflex upon stimulation of the glans and urethra [26]. Conversely, this reflex response was facilitated by lesions of brain serotonergic neurons projecting to the spinal cord [27]. Therefore, the spinal generator might be under the inhibitory influence of PGRNl via serotonin projections. Whether this inhibitory input is exerted on the spinal generator itself or on the primary afferents or target areas of the spinal generator is unknown.

The potential involvement of serotonin as a modulator of ejaculatory reflex is also supported by behavioral data demonstrating that ejaculation was delayed by pharmacological treatment increasing serotonin level [28]. In both rats and humans, chronic treatment with serotonin specific reuptake inhibitors (SSRI) results in a delay of ejaculation. It is assumed that SSRIs increase ejaculation latency by increasing the availability of extracellular serotonin within the spinal cord. Although SSRIs might affect ejaculation by acting on the spinal ejaculation generator, the exact site and mechanisms of action of SSRIs are unclear. Notably, treatment with some SSRIs do not result in a delay of ejaculation, despite the ability of these SSRIs to increase the activity of serotonergic neurons [29]. Alternative explanations for the effect of chronic SSRI treatment include desensitization and differential up and/or down regulation of distinct serotonergic receptor subtypes, together with the direct action of SSRIs at some of these receptors subtypes. Other aminergic receptors may also be affected.

Output of the spinal ejaculation generator

The outputs of the spinal ejaculation generator are constituted by the autonomic neurons controlling the emission phase, and the somatic motoneurons controlling the expulsion phase (Fig. 1). Experimental data have demonstrated that the emission phase is mostly under the control of sympathetic autonomic nuclei, although a participation of the parasympathetic system has been demonstrated for the vas deferens [30]. Tract tracing studies have shown that sympathetic preganglionic neurons innervating the pelvis are located in the intermediolateral cell column (IML) and the dorsal commissural nucleus (DCN) of the lower thoracic and upper lumbar segments (T13–L2) [31, 32]. The axons originating from these sympathetic preganglionic neurons project via the intermesenteric and the hypogastric nerve to innervate the pelvic viscera [33]. In anesthetized rats, electrical stimulation of the hypogastric or intermesenteric nerve induced seminal vesicle, bladder neck and vas deferens contractions [34–37]. Localization of the spinal neurons upstream to the autonomic neurons controlling the prostate and bladder neck have been performed using retrograde transneuronal virus injection in these organs [38–40]. Virus labeled interneurons were notably found in the dorsal gray commissure and lamina X at the L3–S1 spinal levels. These cells may correspond to neurons pertaining to the spinal ejaculation generator.

The expulsion phase is caused primarily by the rhythmic contractions of the bulbospongiosus muscle, although contractions of the ischiocavernosus and anal and urethral sphincters occur concomitantly. The motoneurons of these pelvic muscles are referred to as the pudendal motoneurons. In humans, the pudendal motoneurons are located in a single nucleus called Onuf's nucleus [41]. In the rat, this nucleus consists of a medial and lateral group of motoneurons, the motoneurons of the bulbospongiosus muscle being located in the medial part [18, 42, 43]. Injection of retrograde transneuronal virus into the bulbospongiosus muscle has been performed to identify the interneurons that control the pudendal motoneurons [44, 45]. Following infection with the virus of motoneurons in the medial and to a lesser extent in the lateral nucleus, interneurons were found to be labelled bilaterally in lamina X at the L6 and L5 levels. Interestingly, increasing the post-inoculation

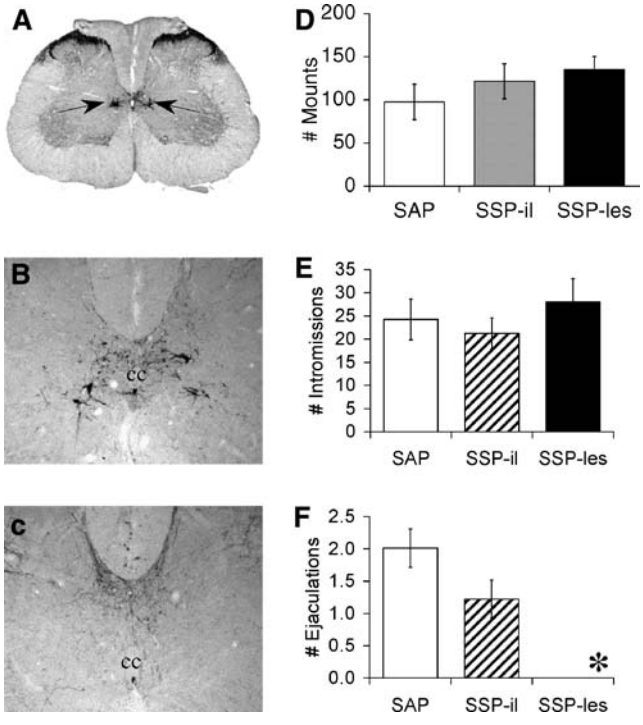

Fig. 2 Effects of LSt cell lesions on rat sexual behavior. **A** A coronal spinal cord section (level L4) immunoprocessed for galanin shows the restricted location of LSt cells around the central canal (*cc*, *arrows*). **B** In control rats with intact LSt cells, galanin-positive cells are present in the region around the central canal from the L2 to L4 levels. **C** These cells are absent in rats with complete LSt cell lesions due to injection of saporin conjugated to a substance P analog (SSP-SAP). Ejaculation (**F**) was completely abolished in rats with complete LSt cell lesions (*SSP-les*), although the number of mounts (**D**) and intromissions (**E**) displayed by these rats did not differ from control rat with intact LSt cells. Control rats correspond to rats either injected with unconjugated saporin (*SAP*), or to rats with missed injection leading to incomplete lesion of LSt cells, (*SSP-il*)

time survival led to an increase in the number of infected neurons in lamina X form the L5–L1 level. Again, these interneurons are candidates for forming an integral part of the spinal ejaculation generator.

The lumbar spinothalamic cell population as a component of the spinal ejaculation generator

Studies using the expression of the protein product of the immediate early gene c-fos as a marker of neural activation have demonstrated that some neurons were specifically activated after mating in the central gray of the lumbar spinal cord [46]. Unfortunately, these experiments were not able to unambiguously characterize neural components of the spinal ejaculation generator, because no specific phenotype and hence specific function could be associated with any of these viral, tracer or Fos-positive cells. A major breakthrough came from the identification of a population of neurons in the central gray of lumbar levels L3–4 that play a pivotal role in the control of ejaculation [13]. This population of neurons consists of cells located in lamina X and the medial portion of lamina VII of lumbar segments 3 and 4 (L3–4, Fig. 2A). They contain galanin, cholecystokinin, and enkephalin [47–49] and have projections to a nucleus within the posterior intralaminar thalamus: the parvocellular subparafascicular thalamic nucleus (SPFp) [48, 49]. Based on their location and thalamic projections, these particular cells are referred to as lumbar spinothalamic (LSt) cells.

The involvement of LSt cells in sexual behavior was first studied using c-fos as a marker of neural activation. We demonstrated that LSt cells expressed Fos with ejaculation, but not following social interaction, mounts, or intromissions [50]. These data suggested a specific involvement of LSt cells in ejaculation, but not with other components of sexual behavior.

To further test the functional role of the LSt cells, we investigated the effects of lesions of the LSt population on sexual behavior [13]. Since the LSt cells are sparsely distributed within the central gray of L3–4, traditional lesion techniques would have resulted in lesions of many other neurons in addition to LSt cells. LSt cells express the NK1 receptor almost exclusively in the central gray. We therefore infused, at the location of LSt cells, the toxin saporin (SAP) conjugated to SSP, a substance P analog with high affinity for NK-1R (SSP-SAP) to lesion specifically LSt cells [51]. Control animals were injected with unconjugated equimolar concentrations of SAP. Sexual behavior was observed during 6 weekly tests starting at 10 days following surgery. Completeness of LSt lesions was determined based on cell counts for galanin-IR and

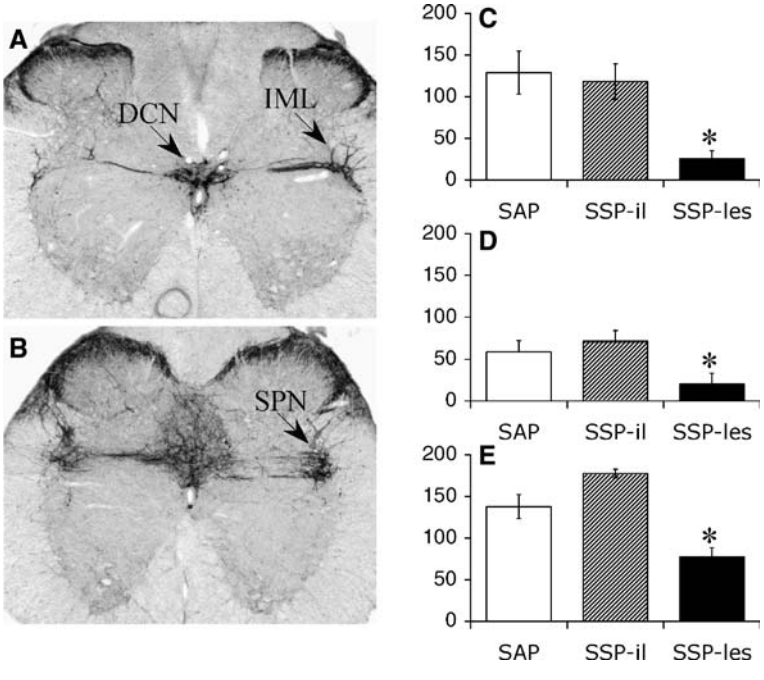

Fig. 3 LSt cells projection to autonomic sympathetic and parasympathetic centers. Coronal sections of rat spinal cord immunoprocessed for galanin (**A** and **B**). **A** At the thoracolumbar level, galanin fibers are present in the dorsal commissural nucleus (*DCN*) and the intermediolateral cell column (*IML*), corresponding to the location of the sympathetic neurons controlling the sexual accessory glands. **B** Galanin fibers are also abundant at the lumbosacral level in the sacral parasympathetic nucleus (*SPN*), which contains the parasympathetic preganglionic neurons projecting to pelvic viscera. Note that galanin is also present in the dorsal horn at all spinal levels. **D–F** Optical density (in pixels ×1,000) corresponding to galanin immunoreactivity was measured in LSt lesion and control rats in the *DCN*, *IML* and *SPN* [13]. Selective lesion of LSt cells using local injection of saporin conjugated to a substance P analog (*SSP-les* rats) dramatically reduced galanin immunoreactivity in the *DCN* (**C**), *IML* (**D**) and *SPN* (**E**) compared to control rats with intact LSt cells (either injected with unconjugated saporin (*SAP*), or with missed injection leading to incomplete lesion of LSt cells (*SSP-il*)

NK-1R-IR neurons. Results revealed that a portion of the SSP-SAP treated males had complete lesions of LSt cells, as defined by less than one-third of the number of LSt cells observed in untreated rats (SSP-les, see Fig. 2C for an illustration). No lesions were present in SAP-treated males (SAP; Fig. 2B). Despite the severe reduction in LSt neurons in SSP-les rats, there was no overall reduction in numbers of neurons, demonstrated with immunoreactivity for NeuN, a neuron-specific marker, indicating that the lesions were restricted to LSt cells. LSt cell lesions did not affect the display of mounts and intromissions (Fig. 2D, E) but completely disrupted the display of ejaculatory behavior (Fig. 2F). Examination of female partners revealed that seminal plugs were uniformly absent throughout the testing sessions. In contrast, SAP-treated males, or SSP-SAP treated males with incomplete lesions (SSP-il), continued to ejaculate regularly after surgery. The preservation of the intromission/mount ratio suggests that the processing of pelvic sensory input related to sexual activity preceding ejaculation was not affected in LSt lesion rats. This demonstrates that the processing of sexually relevant somatic sensory input is not dependent on LSt cells. Therefore, the elimination of ejaculation can not be explained by the disappearance of sexually related sensory input, as is the case in experiments involving transection of the afferent sensory pathway from the penis [52, 53]. Altogether, these results demonstrate that the LSt cells form a critical and specific component of the ejaculation generator.

LSt connections to sensory input and autonomic and somatic outflow

The location of the LSt cells fits with the anatomical data reviewed above, locating the spinal ejaculation generator in the lumbosacral spinal cord. The location of the LSt cells in L3–4 levels also corroborates with the finding that the expulsion reflex induced by mechanical stimulation of the glans and urethra could not be obtained in anesthetized rats when spinal transection was performed below the L2 segmental level, i.e. within the LSt cell cluster [54].

LSt cells also appear to be in an ideal position to coordinate the outflow necessary for ejaculation based on their projections to autonomic and motor nuclei. Specifically, galanin-positive axons are normally located in the areas containing the sympathetic nuclei involved in the control of the emission phase of ejaculation (Fig. 3A). However, in animals lacking LSt cells (using SSP-SAP to lesion LSt cells as described above), galanin fiber labeling in these autonomic nuclei was eliminated, indicating that these galanin-positive axons originate from the LSt neurons in L3–4 [13] (Fig. 3C, D). In addition, the lesion experiments also showed that LSt cells send a dense projection to the sacral parasympathetic nucleus (SPN) in the intermediolateral cell column of the upper sacral segments, where parasympathetic preganglionic neurons are located [55, 56] (Fig. 3B, E). The parasympathetic nucleus contains visceromotoneurons that control a variety of pelvic organs, including the penis [57] and prostate [39]. Experimental data suggest that stimulation of parasympathetic preganglionic neurons increases the rate of secretion of prostatic and seminal fluid from the epithelial cells before the emission phase takes place. For example, parasympathomimetic drug administration increased the rate of prostatic secretion in rats [58], and, in the seminal vesicles, parasympathetic innervation is associated with the glandular epithelium [59]. Therefore, we hypothesize that one function of the LSt projections to the SPN is to increase the secretion of fluids from the sexual accessory glands. It should be noted here that the SPN is traditionally considered a major autonomic proerectile center [60]. However, the persistence of visible penile erection during the ex-copula reflex test in LSt lesion rats does not support a major proerectile role for LSt cells.

The projections of LSt cells to sympathetic and parasympathetic nuclei were further confirmed by preliminary data from our laboratory using injections of the Bartha strain of the pseudorabies virus (PRV) into the penis. These virus injections resulted in a labeling of LSt cells [61] that was preceded by PRV labeling in DCN and SPN. PRV labeling was not observed in any other interneurons in the central portion of the spinal cord, indicating that the DCN and SPN are the primary efferent targets of LSt cells. Finally, Newton and coworkers have demonstrated that LSt cells have projections to pudendal motoneurons [62]. LSt cells are thus in the position to influence the somatic components of ejaculation.

In conclusion, these projections to the autonomic parasympathetic and sympathetic nuclei and pudendal motoneurons place the LSt cells in an ideal position to command (1) an increased rate of secretion of seminal fluids from the accessory glands before the emission phase, (2) the emission phase per se, and (3) the expulsion phase.

Spinothalamic-forebrain pathways

The neural pathways for relay of ejaculation-related sensory information to the brain are currently unclear. However, the LSt cells previously discussed for their role in triggering ejaculation might form a nodal point in this pathway. Hemisections [48, 50], retrograde tracing from medial SPFp [49] and anterograde tracing from the lumbar spinal cord [63] have established the existence of projections from the LSt cells to the medial portion of the parvocellular subparafascicular nucleus of the thalamus (SPFp). In LSt cells as well as in medial SPFp, Fos is induced only following ejaculation and not following other components of sexual behavior [49, 64, 65]. The LSt-medial SPFp pathway contains the neuropeptides galanin, cholecystokinin, and enkephalin [47–49]. We tested the hypothesis that cells in the medial SPFp are

involved in the processing and relay of ejaculation-related signals through their galanin projections. Preliminary data from our laboratory showed that galanin infusions into medial SPFp, but not neighboring thalamic areas, dramatically inhibit male sexual behavior [66]. This finding suggests that endogenous galanin is released in medial SPFp upon ejaculation, where it acts to suppress sexual behavior during the post ejaculatory interval or sexual satiety. A recent study by Holstege and coworkers [67] used positron emission tomography to study increases in regional cerebral blood flow during ejaculation in men. Increased blood flow was observed following ejaculation compared to sexual stimulation in the mesodiencephalic junction, which includes the location of the SPFp. These findings further support the importance of the LSt-SPFp pathway for the processing of ejaculation related signals.

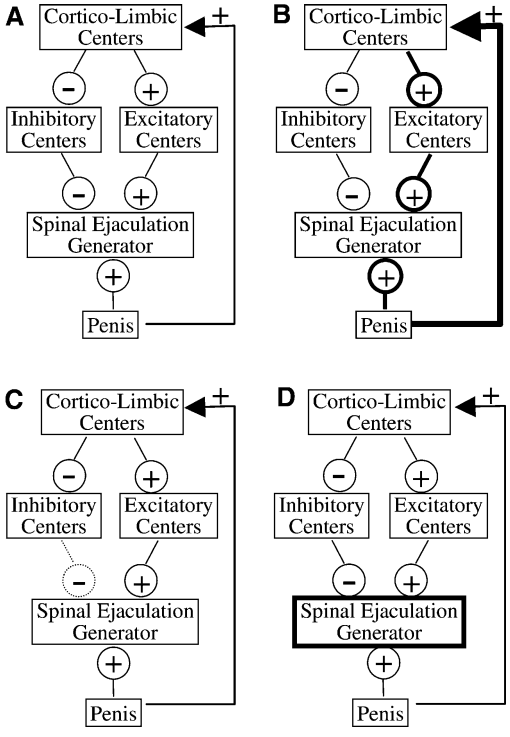

Fig. 4 Hypothesis for the neuropathophysiological basis of rapid ejaculation. **A** During sexual arousal, integrative centers activate and inhibit the structures sending excitatory and inhibitory input to the spinal ejaculation generator respectively. The spinal ejaculation generator also receives direct excitatory input from the penis. Supraspinal processing of somatic sensory input from the penis gives a strong positive feed back to the higher integrative center. Ejaculation latency depends on the balance between the convergent central and peripheral excitatory input and the remaining inhibitory input received by the spinal ejaculation generator. **B** A first hypothesis is that rapid ejaculation is caused by an increase of the excitatory input on the spinal ejaculation generator, for either peripheral and central origin, or both. **C** Alternatively, rapid ejaculation might be due to an impairment of the descending inhibitory tone. **D** A third hypothesis is that a "constitutive" hypersensitivity of the spinal generator itself might be at the origin of rapid ejaculation

Functional hypothesis

Our current view of the neurobiology of ejaculation is summarized in Fig. 4. In short, ejaculation is a spinal reflex controlled by the spinal ejaculation generator, itself modulated by sensory input from the pelvis and descending input from inhibitory and excitatory centers in the brainstem and the hypothalamus. These supraspinal centers at the origin of the descending input are in turn controlled by higher centers, which are notably responsible for switching on the state of sexual excitement, and likely correspond in part to the anatomical substratum of libido. These higher centers correspond to the psychological control of ejaculation, and are referred to as cortico-limbic centers. More downstream pathways correspond to the autonomic control of ejaculation, i.e. not under voluntary control. During sexual intercourse, the cortico-limbic centers inhibit and activate the inhibitory and excitatory centers respectively, shifting the supraspinal tone to the spinal ejaculation generator from overall inhibitory to excitatory (Fig. 4A). Note that this mechanism is positively reinforced by the supraspinal processing of sexually related sensory input from the penis. The spinal ejaculation center also receives direct excitatory sensory input from the penis (Fig. 4A). We hypothesize that the amount of peripheral stimulation required to trigger ejaculation depends on both the descending input from supraspinal centers and the intrinsic capacitance of the spinal ejaculation center.

Where does the neuropathophysiological basis of ejaculatory dysfunction fit in this current view? The most common form of male sexual dysfunction related to ejaculation is premature ejaculation [68, 69], and we will present three hypothesis for the underlying neurobiology of this particular dysfunction based on the present model.

First, rapid ejaculation could be due to an excessive response in the penile afferent fibers, a condition described as penile hypersensitivity [70] (Fig. 4B). Accordingly, topical application of lidocaine-prilocaine cream delays ejaculation [71]. Topical anesthesia might reduce the intensity of ejaculatory relevant sensory input going *directly* to the spinal ejaculation generator, thus delaying ejaculation. Alternatively, the reduced perception of the sensory input from the penis after lidocaine-prilocaine application ("numbness" due to partial anesthesia) might reduce activation of the higher centers. This in turn may lead to a reduction of the descending facilitatory input to the spinal ejaculation center. In line with the latter proposal, patients with premature ejaculation were shown to have a greater cortical representation of sensory stimuli of the glans penis than normal controls [72].

A second hypothesis is that there exists an imbalance between the descending inhibitory and excitatory inputs, resulting in a lack of efficient inhibition of the spinal ejaculation generator (Fig. 4C). This reduced inhibition would facilitate the activation of the spinal ejaculation

generator in response to a minimal amount of peripheral stimulation. This hypothesis is in agreement with the current view that SSRI delay ejaculation by enhancing the activity of the descending inhibitory serotonergic projections from the brainstem to the spinal ejaculation generator [68]. As mentioned earlier, the mechanisms underlying the ability of SSRIs to delay ejaculation and the site of action of serotonin on the spinal ejaculation generator are currently unclear. The reduction of libido in some patients chronically treated with SSRIs suggests that an inhibition of some descending excitatory input to the spinal generator might also occur [73].

The third hypothesis states that rapid ejaculation might be due to a hypersensitivity of the spinal ejaculation center (Fig. 4D). In other words, the spinal generator would require a minimal amount of stimulation to trigger ejaculation because of an intrinsic condition, which could be biologically inherited or acquired through life. This hypothesis is not yet supported by any clinical or experimental data.

Conclusion

A more advanced understanding of the spinal control of ejaculation is necessary for the development of additional treatments for premature ejaculation and ejaculatory function in paraplegic men. Major gaps in our knowledge remain, including: the sensory signals and pathways that trigger ejaculation, the supraspinal circuitry that influences the spinal ejaculation generator, the ascending anatomical pathways that relay sensory signals related to ejaculation to the brain, and finally, the neural circuitry in the brain involved in the rewarding aspects of ejaculation.

The discovery of the LSt cells gives the first identification of an integral component of the spinal ejaculation generator. Because specific lesioning of the LSt cells abolishes ejaculation without apparently affecting somatic sensory input from the pelvic area, LSt cells appear as an ideal target for the treatment of rapid ejaculation and other ejaculatory dysfunction. According to our model, any condition of premature ejaculation would benefit from a pharmacological treatment increasing the threshold of stimulation (of either peripheral or central origin) necessary for activation of LSt cells. Design of such a pharmacological treatment implies the identification of the neurotransmitters involved in the modulation of LSt cell activity, together with the identification of the intracellular mechanisms leading to their activation at the time of ejaculation.

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