



Review

Therapeutic targets for premature ejaculation

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ABSTRACT

Premature ejaculation (PE) is the most common male sexual complaint, and may exert a profound negative impact on the man's life and partnership. Using currently available treatment alternatives (e.g., selective serotonin uptake inhibitor, agents acting locally on the penis), PE can be treated in most, but not all patients. However, since long term success rates have been disappointing, and the only approved treatment so far is the short-acting selective serotonin re-uptake inhibitor dapoxetine, there is currently an intensive search for new treatment modalities. Selection of the most promising therapeutic targets from a host of current and potential candidates depends heavily on their roles in the pathophysiology of PE. Possible central nervous targets that will be discussed are serotonin transporters, and CNS receptors for 5-HT_{1A} and 5-HT_{1B}, dopamine, oxytocin, opioids, neurokinin-1, and glutamate. Putative peripheral targets include α_1 -adrenoceptors, phosphodiesterase enzymes, Rho kinases, purinergic (P2X) receptors, and penile sensory nerves. It is clear that exploiting the full therapeutic potential of these targets will require additional basic and clinical research.

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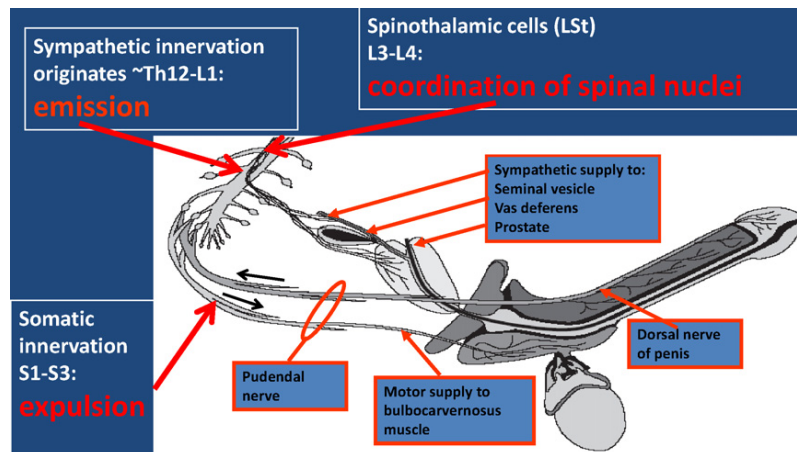


Fig. 1. Nerve structures involved in ejaculation. Ejaculation is the result of a coordinated contractile activity involving different ejaculatory organs organized by the spinal ejaculatory centre (SEG), located at the T12–L1–2 spinal cord level. A key component of this generator is a population of spinothalamic (LSt) neurons. Afferent information is received by the SEG, which co-ordinates sympathetic, parasympathetic and motor outflow to induce the different phases of ejaculation.

1. Introduction

In the treatment of male sexual disorders, focus has been mainly on erectile dysfunction (ED) and ejaculatory disorders, primarily premature ejaculation (PE). Large-scale studies have shown that PE is one of the most prevalent male sexual complaints, affecting as many as 20–30% of men of all age groups and exerting a profound negative impact on the man's life and partnership. Men with PE (short intravaginal ejaculatory latency time, IELT) generally report a lower sense of control over ejaculation, as well as lower satisfaction with sexual intercourse and increased interpersonal distress as compared with men without PE [1–6].

According to Waldinger and Schweitzer [7], four different sub-categories of PE can be distinguished: lifelong PE, acquired PE, natural variable PE, and premature-like ejaculatory dysfunction. The International Society for Sexual Medicine (ISSM) PE Guidelines Committee defined *lifelong PE* as “a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about 1 min of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy” [5]. No consensus regarding a definition of the more variable acquired PE was reached.

Extensive research on the neurobiology of both ED and PE has expanded our understanding of male sexuality, allowing a shift of the treatment paradigms of both disorders from a psychoanalytic to a neurobiological approach [6]. From a research perspective PE was previously somewhat neglected compared to ED, however, there has been a remarkable recent increase in interest and research activities concerning PE.

Although PE is treatable by currently available approaches in many patients, long term success rates have been disappointing. The only approved treatment is the short-acting selective serotonin re-uptake inhibitor, dapoxetine, and there is currently an intensive search for new treatment alternatives. The present review is focused on possible therapeutic targets for future treatments of PE.

2. Animal models of PE

Most of our current understanding of the neurobiology and neuroanatomy of ejaculatory functions has been derived from studies using rats or rabbits with normal sexual behavior. It is obvious that none of these models adequately represents human ejaculatory disorders, and it may be questioned if studies in normal

animals can reflect what is considered a dysfunction in humans. However, if ejaculation is regarded as a biological continuum from early ejaculation toward failure of ejaculation, as has been suggested in humans [8], studies of ejaculation in normal animals may reveal information of translational interest [9,10].

3. Physiology of ejaculation

Ejaculation is basically a spinal reflex initiated by genital and/or brain stimulation through peripheral sensory receptors and afferent pathways, and the centers of the brain involved with ejaculation (Fig. 1). It is the result of a coordinated contractile activity involving different ejaculatory organs and the spinal ejaculatory centre (SEG), located at the T12–L1–2 spinal cord level [11–16]. A key component of this generator is a population of spinothalamic (LSt) neurons, and manipulations of these cells either block or trigger ejaculation. Afferent information, including inputs conveying biochemical or mechanical information from the accessory sex organs [17], is received by the SEG, which co-ordinates sympathetic, parasympathetic and somatic outflow to induce the different phases of ejaculation. The SEG is under inhibitory and excitatory influence of supraspinal sites [13], and its control involves a complex interaction of central serotonergic and dopaminergic neurons with the secondary involvement of e.g., cholinergic, adrenergic, oxytocinergic and GABAergic neurons [11–16].

Ejaculation consists of two main phases, the emission phase and the expulsion phase (Fig. 2). The efferent limb of the ejaculation reflex, responsible for emission, consists of sympathetic efferent fibers (T10–L2) that cause sequential contractions of the epididymis, vas deferens, seminal vesicles and prostate, with closure of the bladder neck [18]. In the emission phase, the contraction of accessory ejaculatory organs induces accumulation of semen in the posterior urethra. Expansion of the posterior urethra creates a feeling of emission and sensory information that is transmitted to the spinal cord. The sensory (afferent) information is transmitted via the dorsal nerve of the penis (S4) to the lumbosacral spinal cord, and is joined by sympathetic afferents from the hypogastric plexus [17]. Traveling up the spinal cord (and joined by visual, auditory and olfactory cerebral afferents), the impulses are integrated by cerebral structures specifically activated during ejaculation to form a tightly interconnected network comprising hypothalamic, diencephalic and pontine areas.

The expulsion phase is initiated somatically from the sacral spinal cord (S2–S4: mechanical centre) via the pudendal nerve,

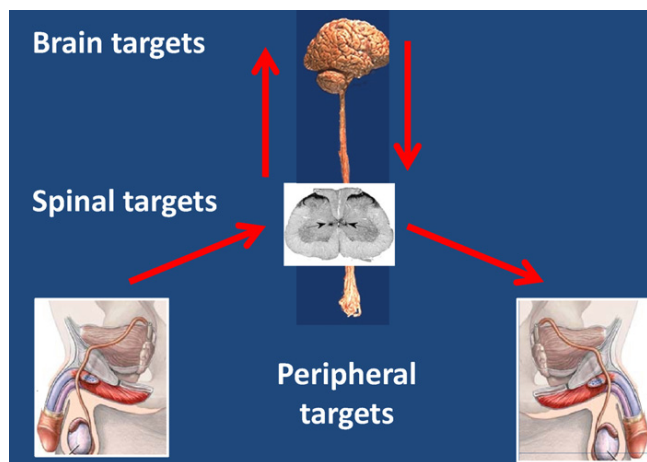


Fig. 2. Targets for drugs meant for treatment of premature ejaculation can be found peripherally or within the central nervous system (brain and spinal cord).

causing rhythmic contractions of the bulbospongiosus and bulbocavernosus muscles and other associated perineal muscles, which force the ejaculate through the distal urethra [15]. The ejaculated semen has a number of components including secretions from the seminal vesicles, prostate and bulbourethral (Cowper's) glands and spermatozoa.

The neurotransmitters involved in this process act together to form a balance between excitatory and inhibitory transmission, which is critical for the normal ejaculatory function, while the imbalance caused by disturbing any of these systems can promote either PE or retarded ejaculation. The endocrine system is also intricately involved in the brain and in the peripheral organs. Hormones regulate sexual behavior primarily by slow, genomically mediated effects. These effects are realized, in part, by enhancing the processing of relevant sensory stimuli, altering the synthesis, release, and/or receptors for neurotransmitters in integrative areas, and increasing the responsiveness of appropriate motor outputs [19–21]. Thus, although many of the individual pieces of the ejaculatory process have been identified, the manner in which these neuroendocrine systems interconnect to mediate a coordinated process has not been well delineated.

4. Pathophysiology of PE

Historically, attempts to explain the etiology of PE have included a diverse range of biologic and psychological factors (see [6]). This approach – dichotomizing between biological vs. psychological, or the psychogenic vs. organogenic – is based upon the premise that incorrectly assumes that psychological processes are somehow independent (and mutually exclusive) of biological events. These factors are not completely independent, as both influences often overlap at the level of the central nervous system. Jannini and Lenzi [22] stated that, irrespective of the ultimate cause, all sexual dysfunctions are per se stressful and a source of psychological disturbances. Thus, all cases of PE are or become psychogenic and capable of provoking a psycho-relational imbalance. While it is clear that all behavioral dysfunctions may negatively influence organic processes (psycho-somatic evidence), it is also plain that a disease or a body symptom may affect behavior (somato-psyche evidence). Jannini and Lenzi [22] concluded that PE should be considered as a psycho-neuro-uro-endocrine disorder affecting the couple.

To explain the pathogenesis of primary PE the ejaculation distribution theory was advanced postulating that the IELT in men is represented by a biological continuum with men with lifelong PE

belonging to the extreme left side of the IELT curve. This biologic variation of the IELT in men may be due to dysregulation of serotonergic receptor subtypes and/or genetic factors. Both animal and human studies have demonstrated the existence of an ejaculation time distribution [2,23]. According to this theory, the ejaculatory threshold for men with low 5-HT levels and/or 5-HT_{2C} receptor hyposensitivity may be genetically “set” at a lower point, resulting in a more rapid ejaculation. In contrast, men with a very high set point may experience delayed or absent ejaculation despite prolonged sexual stimulation and despite achieving a full erection.

5. Treatment of PE – what targets can be defined?

Since ejaculation is basically a spinal reflex with a complex central regulation, targets can be located on different levels (Fig. 3). Since afferent activity is necessary for the initiation of the reflex, it is obvious that peripheral afferent nerves can be a target. The afferent activity is processed by the SEG, and transmitters and transmitter mechanism involved in the control of SEG would thus be possible to target. The supraspinal control of the SEG has been shown to involve e.g., serotonin and dopamine mechanisms, and this seems to be the site of action of drugs currently used for treatment of PE. Interfering with the efferent pathways mediating the contraction of muscles involved in emission should also be expected to delay the expulsion of semen. Even if the mechanisms mentioned can be influenced experimentally, this does not necessarily mean that a useful effect can be achieved clinically. Many of these potential targets are also involved in penile erection and several other actions which may create problems with adverse effects.

A pragmatic classification of possible targets can be in central (brain and spinal cord) and peripheral (Fig. 3).

6. Central targets

The main central targets identified include serotonergic neurotransmission, dopaminergic and oxytocinergic mechanisms, opioid receptors, and mechanisms involved in the control of the SEG.

6.1. Serotonergic neurotransmission

5-HT appears to be a key mediator and is considered the main inhibitory neurotransmitter in the central control of ejaculation [2,14,24,25]. While all of the 5-HT receptor subtypes are found postsynaptically, only 5-HT_{1A} and 5-HT_{1B/D} receptors are located presynaptically, where they mediate negative feedback of 5-HT on its synaptic release [26]. Theoretically, strategies to enhance serotonergic neurotransmission include either blocking 5-HT re-uptake, stimulation of 5-HT release, enhancement of 5-HT synthesis, use of 5-HT agonists to stimulate inhibitory receptors (e.g. 5-HT_{2C}), or use of antagonists of stimulatory receptors (e.g. 5-HT_{1A}).

6.1.1. Serotonin transporters

Serotonergic transporter molecules (5-HTT) are present on the somata and dendrites of 5-HT neurons where they facilitate the re-uptake of 5-HT after cell firing-induced 5-HT release. Inhibition of these transporters cause enhanced 5-HT levels in the synaptic cleft leading to enhanced serotonergic neurotransmission. Selective serotonin uptake inhibitors (SSRIs) delay ejaculation in men with PE, and their clinical effectiveness has been well established [27,28]. SSRIs prolong IELT, but only after chronic administration because acute SSRI administration is probably associated with mild increase in 5-HT release at the synaptic terminal. All SSRIs do not delay ejaculation to the same extent, and the ejaculation-delaying effects seem associated with differential adaptive changes of 5-

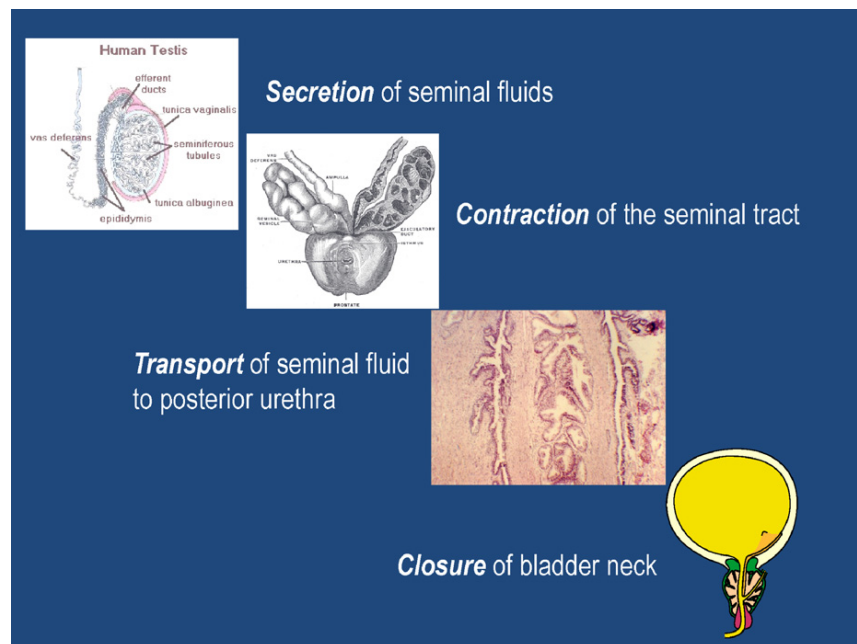


Fig. 3. Anatomical structures involved in the neuromuscular coordinated activity leading to the expulsion of semen out through the meatus.

HT receptors. Although significantly effective when compared to placebo, on demand dapoxetine, which so far is the only approved PE treatment in several countries, is less effective in prolonging IELT than other SSRIs given chronically [29,30].

6.1.2. 5-HT_{1A} receptors

One of the basic features of serotonergic neurotransmission is that any short-term increase in 5-HT release into the synapse is immediately followed by activation of presynaptic 5-HT_{1A} autoreceptors on the cell bodies of serotonergic neurons. Activation of these 5-HT_{1A} autoreceptors decreases (negative feedback mechanism) firing of the serotonin neuron and consequently lowers release of serotonin from the presynaptic neuron into the synaptic cleft. This negative feed-back mechanism can be reduced by a selective 5-HT_{1A} antagonist, e.g., WAY100635. Acute administration of SSRIs also leads to stimulation of the 5-HT_{1A} receptors. However, during chronic administration of SSRIs, 5-HT_{1A} autoreceptors are thought to desensitize over time [31]. It would be of interest if these autoreceptors could be blocked (i.e., immediately desensitized), allowing more pronounced increases in 5-HT levels. Although there is presently insufficient scientific evidence to suggest 5-HT_{1A} receptors as a novel drug target for PE treatment, the 5-HT_{1A} antagonists could disfavor the connection between somatic afferents and the autonomic centers of emission and anxiety. Consequently, these drugs may delay ejaculation (both in normal potent men and in men with PE) and decrease anxiety [32,33].

6.1.3. 5-HT_{1B} receptors

5-HT_{1B} receptors are located on pre- and postsynaptic axon terminals in several brain areas, including the raphe nuclei, lateral hypothalamic area, bed nucleus of the stria terminalis, and nucleus accumbens, and in the spinal cord [34]. These receptors may play a role as autoreceptors controlling 5-HT release in the synaptic cleft [33], as heteroreceptors by inhibiting the release of various neurotransmitters that facilitate ejaculation, such as acetylcholine, GABA, dopamine, glutamate or perhaps galanin [34], or may mediate the inhibition of ejaculation induced by serotonin possibly through a postsynaptic action [24]. Although theoretically interesting, the 5-

HT_{1B} receptors have not yet been shown to be a reasonable target for drugs aimed for PE treatment.

6.2. Dopamine receptors

There is good evidence that dopamine (DA) plays a key role in the male sexual response, including ejaculation [21,35]. The action of DA is mediated by two subfamilies of receptors, D1-like consisting of D1 and D5 receptors, and D2-like, including D2, D3 and D4 receptors [36]. DA receptors are distributed on the soma and across the dendritic tree of dopaminergic neurons. Kitrey et al. [37] microinjected a preferential D3 receptor antagonist (7-OH-DPAT) into the MPOA of rats and found that the drug induced an ejaculation-related response. The authors emphasized that since no anatomical or functional connections have been found between the MPOA and the spinal ejaculation centers, these structures may be indirectly linked through other nuclei like the PVN and the nucleus paragigantocellularis, which have been shown to possess direct connections with spinal autonomic and somatic nuclei [15]. This effect of 7-OH-DPAT was confirmed by intracerebroventricular administration of the drug [38], and it was suggested that targeting brain D3 receptors may provide a therapeutic approach for treating ejaculatory disorders in humans. Further supporting this, a selective dopamine D3 receptor antagonist (SB-277011), delayed ejaculation by specifically and dose-dependently inhibit the expulsion phase without impairing either emission or erection [39]. If these findings are valid also in humans, targeting dopamine D3 receptors would be an interesting therapeutic approach.

6.3. Oxytocin receptors

The involvement of oxytocin at supraspinal and spinal sites in erectile function is well documented [40]. An important role for oxytocin in the control of ejaculation has also been demonstrated. Infused into the cerebral ventricle of male rats free to copulate with a receptive female, oxytocin facilitated ejaculatory behavior by shortening ejaculation latency and post-ejaculatory refractory period [41]. Administered via the intracerebroventricular (i.c.v.)

route, oxytocin was also found to significantly increase latencies of mount and intromission [42]. Furthermore, in the mating test a selective oxytocin-receptor antagonist delivered via i.c.v. route to sexually vigorous male rats was reported to inhibit sexual behavior, including ejaculation, and to reverse the pro-sexual effects of the non-selective dopamine-receptor agonist, apomorphine [43]. Systemic, similarly to central, administration of oxytocin was reported to shorten ejaculation latency and post-ejaculatory interval in sexually active male rats [41,42]. Clément et al. [44], using a selective oxytocin receptor antagonist, demonstrated that brain oxytocin receptors mediated male sexual responses elicited by i.c.v. 7-OH-DPAT in anaesthetized rats. Blockade of L6 spinal oxytocin receptors only impaired the occurrence of ejaculation. Peripheral oxytocin receptors were found to be only marginally involved in 7-OH-DPAT-induced sexual responses.

If oxytocin receptors in the brain and at spinal site should be reasonable targets for PE drugs, several obstacles have to be overcome. One is delivery of the antagonist to the CNS, another issues related to selectivity for ejaculation mechanisms. Considering the central role of oxytocin in erectile responses [40], a favourable effect on ejaculation (delay) may not be possible to obtain without reducing the erectile response. Thus, whether oxytocin receptor antagonists could be a potential addition to the therapeutic armamentarium is awaiting further investigations to address the arguments against the use of such drugs in PE treatment.

6.4. The μ opioid receptor

Carro-Juárez and Rodríguez-Manzo [45] showed that the i.v. injection of morphine in rats inhibited, whereas that of naloxone induced, the expression of the genital ejaculatory motor pattern. Naloxone pretreatment dose-dependently blocked the inhibitory effects of a high dose of morphine upon the rhythmic motor pattern of ejaculation. It was concluded that the findings supported the notion that endogenous opioids modulate the activity of the SEG by exerting an inhibitory influence.

Tramadol is a well-known analgesic drug [46]. By itself, it is a weak μ -receptor agonist, but it is metabolized to several different compounds, some of them almost as effective as morphine at the μ -receptor. The drug metabolites inhibit 5-HT and noradrenaline reuptake. This profile is of particular interest, since both μ -receptor agonism and amine reuptake inhibition may be useful principles for treatment of PE. However, the mechanism of action of tramadol in PE is not known, and particularly the role of μ -receptor stimulation is unclear.

Results from two placebo-controlled studies (one single blind, one double blind) suggest that tramadol might be effective for the on-demand treatment of PE [47,48]. Tramadol 50 mg significantly increased IELT and measures of sexual satisfaction and ejaculatory control compared with placebo ($P < 0.05$ for all). However, a large, international, prospective, randomized, placebo-controlled, double-blind trial of tramadol for the treatment of PE (NCT00983151) was recently stopped prematurely, although no reason has been provided; another similar study (NCT00983736) was stopped because of recruitment difficulties.

The preliminary findings with tramadol suggest that the principle of μ -receptor agonism combined with amine uptake inhibition may be of interest. However, as with all opioids, there might be concerns about the risk of abuse/dependence. This aspect of the use of the drug has been insufficiently clarified.

6.5. Other targets

It is clear that LSt cells play an essential role in control of ejaculation, but currently the neurotransmitters involved in activation of these cells have not been established. The presence of

neurokinin-1 receptors on LSt cells suggests that substance P may regulate ejaculation [49]. Blockade of these receptors at the L3 spinal level significantly decreased ejaculations induced by the dopamine D3 receptor agonist 7-OH-DPAT in anesthetized male rats [50]. However, the ability of substance P, injected intrathecally or intraspinally, to elicit ejaculation has yet to be determined.

Staudt et al. [11] tested the hypothesis that glutamate, via activation of N-methyl-D-aspartic acid (NMDA) receptors in LSt cells, is a key regulator of ejaculation. They found expression of the phosphorylated NMDA receptor subunit 1 (NR1) in LSt cells and that the NR1 receptors were activated in these cells following ejaculation in mating animals, or induced by stimulation of the dorsal penile nerve in anesthetized, spinalized animals. They also found that NR1 activation of LSt cells was an essential trigger for rhythmic bursting of the bulbocavernosus muscle, as dorsal penile nerve stimulation-induced reflexes were absent following administration of an NMDA receptor antagonist in the L3–L4 spinal area, and were triggered by NMDA. NMDA effects were dependent on intact LSt cells and were absent in LSt-lesioned males. These results demonstrated that glutamate, via activation of NMDA receptors in LSt cells, initiates a key afferent signal for ejaculation and the authors suggested that NMDA receptors may provide a target for development of future treatments for sexual dysfunction related to ejaculation.

7. Peripheral targets

Interference with the transport of semen by reducing the sequential contractions of the epididymis, vas deferens, seminal vesicles, prostate, and bladder neck would, at least theoretically, delay ejaculation. However, it also carries the risk of producing retrograde and/or an ejaculation, which may reduce the attractiveness of this approach to treat PE.

7.1. α_1 -Adrenoceptors (ARs)

The sympathetic nervous system plays a main role in the control of the smooth muscles of the accessory sex organs involved in sperm transport, and noradrenaline, acting on α_1 ARs is the principal mediator of contraction. However, the tissue distribution of α_1 AR receptor subtypes varies among the organs participating in seminal emission. In the human vas deferens, α_1 ARs predominate with the α_{1L} subtype mainly found in the longitudinal, and the α_{1A} subtype in circular muscle layers [51], whereas the α_{1A} subtype predominates in the human prostate and urethra [52]. The human bladder outlet (which is responsible for bladder neck closure during ejaculation) showed a predominance of the α_{1D} subtype [52]. It is assumed that inhibition of α_{1A} -AR induces smooth muscle cell relaxation of the vas deferens, seminal vesicles, and prostate, leading to the possibility of delayed ejaculation. However, such an effect may also cause ejaculatory dysfunction, which is well documented for, e.g., tamsulosin, which has a preference for α_{1A} - and α_{1D} -AR, and in particular with the potent and highly selective α_{1A} -AR antagonist, silodosin. The most frequent adverse event with silodosin in the treatment of lower urinary tract symptoms (LUTS) was a reduced or absent ejaculation during orgasm (14%), a reversible effect as a consequence of the potent and selective α_{1A} -AR antagonism of the drug [53]. Whether silodosin can be useful for treatment of PE has apparently not been investigated.

There are few clinical studies comparing the effects of either selective (alfuzosin and terazosin) [54,55] or non-selective (phenoxybenzamine) [56,57] α_1 -AR antagonists with those of placebo in the treatment of PE. The response rate ranged from ~50% to 66.7%, and selective α_1 -AR antagonists were found to be reasonably safe. In the case of phenoxybenzamine, the primary limitation was the incidence and severity of adverse reactions.

The sites of action of the currently used α_1 -AR antagonists in PE have not yet been established. The α_1 -AR receptors of these organs, the ganglia and nerve terminals, and also the CNS, can all influence ejaculation, and the clinical effects of α_1 -AR antagonists in this condition. However, it is unlikely that the effects on ejaculatory function associated with a drug like tamsulosin are due to CNS effects, because tamsulosin has a low potential to cross the blood–brain barrier [58].

The attractiveness of α_1 -AR receptor blockade, subtype selective or not, may be questioned and possible advantages should be weighed against the risk of producing e.g., retrograde and/or anejaculation. However, to prove or disprove the clinical usefulness of this principle in PE treatment, adequately sized, controlled clinical studies are needed.

7.2. Phosphodiesterase (PDE) enzymes

Because of their central roles in smooth muscle cell (SMC) tone regulation and success of sildenafil citrate for the treatment of ED, PDEs have become an attractive target for drug development. The rationale for targeting PDEs for PE based on the presence of PDE-5 mRNA in human vas deferens and prostate [59,60], and the fact that PDE inhibitors can reverse the adrenergic tension of human vas deferens on a seminal vesicle [61,62]. In addition, mice with targeted deletion of eNOS, or rats treated with NO synthase inhibitors, display marked reductions in non-adrenergic, non-cholinergic neurotransmission [63,64]. However, the mechanism(s) by which PDE-5 inhibitors may exert a beneficial effect in men with PE is presently unknown and open for speculation. Aversa et al. [65], reviewing the evidence for a role for PDE-5 inhibitors in the treatment of PE, suggested that available data indicate that there is clinical, anatomical, physiological, pharmacological, and genetic evidence to explain the efficacy of PDE-5 inhibitors. They examined 9 studies on the efficacy of PDE-5-inhibitors in the treatment of PE, alone or in combination with SSRIs, and found that all studies reported some significant changes in the IELT and sexual satisfaction scores, although not all were clinically meaningful. They called for well-designed multicenter studies to further elucidate the efficacy and safety, as well as the mechanisms of action of PDE-5 inhibitors in the treatment of PE.

7.3. Rho kinases

The Rho kinase pathway has been proposed to be one of the sensitizing mechanisms responsible for induction of smooth muscle contraction in accessory sex organs, such as vas deferens and prostate, by increasing Ca^{2+} sensitivity without necessarily changing Ca^{2+} levels. Rho kinase protein is expressed in the mouse vas deferens and in human and rat prostatic smooth muscle cells [66,67]. Amobi et al. [68] showed not only that Ca^{2+} -sensitization mediated by Rho kinase is involved in agonist- or depolarization-induced contraction of rat epididymal vas deferens, but also that Rho kinase inhibitors (Y-27632 and HA 1077) attenuate its contractility. However, Rho kinase is widely distributed not only in the genito-urinary tract, but also in e.g., the systemic vasculature, which creates selectivity problems. Since the discovery that Rho kinase inhibition can produce penile erection in 2001 [69], there seem to have been little or no developments of Rho kinase inhibitors useful for treatment of ED. Considering this, and in the absence of clinical experiences of Rho-kinase inhibitors in PE, it remains a speculation that such drugs would have a future in the treatment of this disorder.

7.4. Purinergic (P2) receptors

The rationale for targeting purinergic receptors for PE is based on the finding of P2X₁ and P2X₂ receptor expression in human vas deferens smooth muscle [70], and that human vas deferens smooth muscle can be contracted by purinergic agonists, even if the adrenergic system is the functionally dominant. However, purinergic co-transmission has also been shown to be functionally significant, most probably acting through the P2X₁ receptor. Thus, electrical field stimulation-induced human vas deferens smooth muscle contractions were significantly reduced to 40% of the initial contraction in the presence of a non-selective purinergic antagonist [70].

There is thus evidence suggesting that ATP signaling via P2X₁ receptors participates in the efferent control of vas deferens and prostate smooth muscle excitability. However, whether this function may be heightened in overactive ejaculatory reflex associated with PE is not known. The finding that mice lacking P2X_{2/3} receptors necessary for e.g., bladder afferent function [71] have increased bladder capacity (delayed voiding!), makes it of interest to test antagonists of P2X_{2/3} in animal models of ejaculation. The purinergic pathways may be novel targets for the pharmacological treatment of PE, and testing P2X_{2/3}-receptor antagonists modulating efferent/afferent activities would be of interest.

7.5. Penile sensory nerves

There is some evidence from the literature that patients with PE have a heightened sensitivity of the glans penis and greater cortical representation of the sensory stimuli from the genital area [72–74]. It would be anticipated that dampening of the sensory input from the glans penis could normalize afferent input and thus increase IELT. Consequently, the use of topical desensitizing agents may be an option. On the other hand, there are findings that refute the role of penile hypersensitivity as a risk factor in PE: (a) Perretti et al. [75] failed to demonstrate a faster conduction along the pudendal sensory pathway or a greater cortical representation of the sensory stimuli from the genital area in PE patients, (b) it has been shown that there was no significant statistical difference in the average vibratory thresholds in patients with PE vs. normal men at the glans penis, dorsum of the penile shaft, and frenulum of the penis either in the flaccid or erect state [76], and (c) Salonia et al. [77] noted that primary lifelong PE patients might suffer from a peripheral hyposensitivity rather than hypersensitivity, both at the index finger and the penile shaft level, compared with healthy controls. Therefore, these results objectively exclude the possibility that a penile hypersensitivity profile may be a contributing aspect of lifelong PE.

Topical agents currently available for PE treatment include sevenserance secret cream (SS-cream), lidocaine cream, prilocaine cream and lidocaine spray (see [78]). A disturbing side effect with these agents may be penile numbness. Although this approach can delay ejaculation, its clinical usefulness has limitations.

8. Summary and future aspects

Currently, serotonergic neurotransmission is considered as the most attractive target for PE, and SSRIs are the most widely prescribed drugs (off label, with the exception of dapoxetine). Since PE is not a life-threatening condition, safety should be a primary consideration when deciding on a course of treatment. Side effects with chronic SSRIs used to treat PE in otherwise healthy young men with PE would not be generally acceptable. For these reasons, targeting 5-HT through the use of SSRIs with short half-life may be an alternative. Another option would be selective targeting of presynaptic 5-HT_{1A} autoreceptor or 5-HT_{1B} receptors. However, there is

currently insufficient scientific evidence to suggest these receptors as novel drug targets for PE. Enhancing the effects of SSRIs with a short half-life could be an alternative approach.

D2-like receptors (D3) or OT receptors seem theoretically as appealing therapeutic targets for PE drugs. However, the role of these receptors in the control of ejaculatory functions needs further study, on selectivity issues, and the development of potent and selective agonist and antagonists is necessary.

Opioid receptors may be interesting targets, but agents acting by stimulation of, e.g., μ -receptors will always include risks of addiction. The safety of tramadol the treatment of PE should be clarified.

Targeting the mechanisms controlling the activity in the SEG is an attractive approach. However, interference with the actions of NMDA receptors will need further studies to clarify issues with selectivity and possible adverse effects.

Targeting peripheral tissues may or may not be an attractive approach and convincing clinical results with available α_1 -AR blockers, and PDE inhibitors are still lacking. Useful Rho kinase inhibitors may be difficult to obtain due to selectivity problems. Before inclusion of the purinergic receptors among potential novel targets for PE, additional research is needed in order to elucidate the role of these receptors in the control of vas deferens and prostate smooth muscle excitability, and in afferent nerve functions. Although targeting of penile sensory nerves may be an attractive way to avoid the systemic side-effects of oral pharmacotherapy, there are practical limitations with this approach.

Contributors

Both authors have contributed to the compilation of references and to the writing of the ms.

Competing interests

None.

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