



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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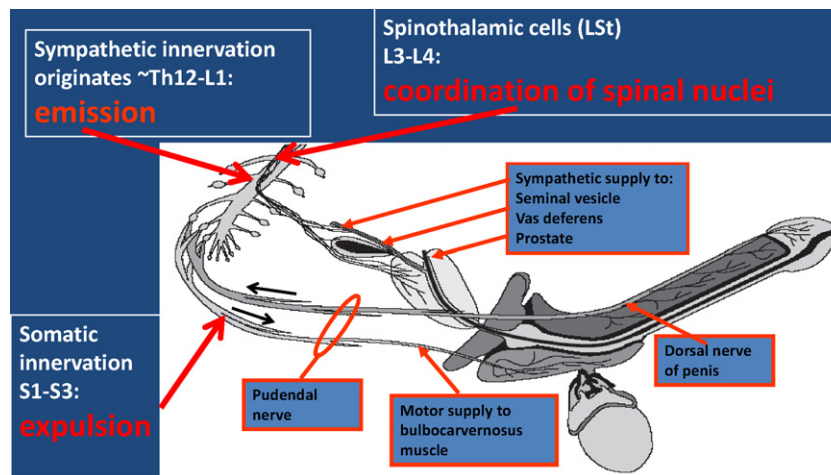


Fig. 1. Nerve structures involved in ejaculation. Ejaculation is the result of a coordinated contractile activity involving different ejaculatory organs organized by the spinal ejaculatory centre (SEG), located at the T12–L1–2 spinal cord level. A key component of this generator is a population of spinothalamic (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,

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