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Phosphodiesterase 5 Inhibitors in Rapid Ejaculation

Potential Use and Possible Mechanisms of Action

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Abstract

Rapid (premature) ejaculation (RE) is a very common sexual disorder. This condition may be primary or secondary to underlying disease. Control of RE has been primarily focused on behavioural therapy, topical anaesthetics, tricyclic antidepressants and selective serotonin reuptake inhibitors; however, an approved treatment does not exist.

Recently, a number of clinical trials have studied the potential effectiveness of the phosphodiesterase (PDE)-5 inhibitor sildenafil in the treatment of RE. Results of most of these studies have been encouraging. Available data indicate that there is clinical, anatomical, physiological, pharmacological and genetic evidence to explain the efficacy of PDE5 inhibitors in RE. The rationale for the use of PDE5 inhibitors in the treatment of RE could be due to possible peripheral and central mechanisms. Possible peripheral ejaculation retarding capabilities may include modulation of the contractile response of the vas deferens (VD), seminal vesicles (SV), prostate and urethra, induction of a state of peripheral analgesia, and prolongation of the total duration of erection. Possible central mechanisms may involve lessening of the central sympathetic output. Furthermore, there is evidence from knockout mice to explain the efficacy of PDE5 inhibitors in RE. Mice lacking the gene for endothelial nitric oxide synthase develop a condition similar to RE. On the other hand, mice lacking the gene for heme oxygenase-2 develop a condition similar to delayed ejaculation.

This review also discusses the findings against the use of these agents in RE. In conclusion, a review of the literature suggests the potential usefulness of PDE5 inhibitors as a promising line of therapy in RE but further studies are needed.

Rapid (premature) ejaculation (RE) has been described as the commonest form of male sexual dysfunction and implies that a man is unable to exert voluntary control over the ejaculatory reflex, with the result that once he is sexually aroused orgasm is achieved rapidly. The condition is most common among young adults and men who lack sexual experience and frequency. This disorder could have profound effects on the psychosexual relationship of a couple and in its severe form can lead to secondary erectile dysfunction (ED). Management of RE should be preceded by an accurate diagnosis reached after a complete medical and sexual history and physical examination. It is important to quantify as

much as possible the time from the onset of erection and of intromission to the occurrence of ejaculation. It is also important to determine the expectations of the patient and his partner regarding the duration of the sexual act. A careful psychological evaluation is also indicated to determine if a concomitant psychosexual issue exists. Historically, therapies for RE have centred on psychological techniques, particularly behavioural therapy. Although the pharmacological treatment scheme for this disorder involves topical anaesthetics, antipsychotics, α-adrenoceptor antagonists, tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), an approved treatment does not exist. Besides their success in the treatment of ED, phosphodiesterase (PDE)-5 inhibitors have been evaluated in a few clinical trials to investigate whether they actually delay ejaculation in humans. This review highlights the rationale for use of PDE5 inhibitors in the treatment of RE, presents data from a limited number of the available clinical studies, looks at the current knowledge explaining the possible mechanisms of action of PDE5 in this disorder and discusses evidence from knockout mice, as well as the contradictory evidence against the use of these agents in RE.

1. Anatomy and Physiology of Ejaculation

Ejaculation is actually two separate processes; emission and ejaculation proper. Emission is the deposition of seminal fluid and sperms from the distal epididymis, vas deferens (VD), seminal vesicles (SV) and prostate into the prostatic urethra. Seminal fluid deposition occurs in an orderly fashion. First, the prostatic smooth muscle contracts, expressing the prostatic secretions into the posterior urethra, then the ampulla and VD release the sperm-rich fraction and finally the SV deliver fluid.[1] Subsequent to this deposition, ejaculation is the forcible expulsion of seminal contents from the urethral meatus.[2] The structures mainly involved in emission and ejaculation include VD, SV, ejaculatory ducts, bladder neck, prostate and the muscles of the perineal floor (i.e. the ischiocavernosus and bulbocavernosus).[3] The walls of the VD, SV, ejaculatory ducts and prostate contain smooth muscle cells and their lumina are lined by columnar epithelium.[2,3] Contractions of the perineal striated muscles participate in the ejaculation proper and generate the sensation of orgasm.[4] Ejaculation is under the control of the sympathetic (T10-L2) and somatic nervous systems (S2-4); the sympathetic nervous system primarily controls emission, whereas the somatic governs ejaculation proper.[2]

Although motor innervation of the human VD, SV, bladder neck and prostate is formed predominantly by noradrenergic nerves, less dense cholinergic innervation has also been shown within the musculature of these organs.[5,6] Autonomic nerves occur not only in the muscle coats, but also form a dense plexus immediately beneath the epithelial lining.[7,8] Such nerves possibly perform secretomotor[9] and/or motor[9,10] functions and are known to be rich in acetylcholine esterase.[9] Table I summarises the recent anatomical and physiological findings, suggesting a role for the nitric oxide/cyclic guanosine monophosphate (NO/cGMP) phosphodiesterase signalling pathway in the modulation of emission and ejaculation.

1.1 Definition of Rapid Ejaculation (RE)

RE is the most common form of male sexual dysfunction affecting an estimated 35% of men.[47] There remains no universally agreed definition of RE. Masters and Johnson defined RE as the inability to inhibit ejaculation long enough for the partner to reach orgasm 50% of the time.[48] On the other extreme, Kaplan defines it as the absence of voluntary control over the ejaculatory reflex, regardless of time, number of thrusts or orgasmic occurrence of the partner.[49] In 1973, Obler defined this disorder in terms of ejaculation in less than 2 minutes, presumably timed from the start of vaginal penetration.[50] However, Obler's definition completely ignores the female sexual response. Waldinger et al. defined RE as ejaculation that occurs in <1 minute

Table I. Recent anatomical and physiological findings suggesting a role for the NO/cGMP pathway in modulation of emission and ejaculation

Findings	References
Peripheral	
Detection of NOS and HO-2 within nerves of human VD, SV, prostate and urethra[a]	8,10-18
Co-localisation of NOS and tyrosine hydroxylase in nerves of human SV and VD may indicate modulatory effect on noradrenergic mechanisms[a]	9,13,19
Demonstration of PDE activity in human SV, prostate and skeletal muscles[b]	20-23
Demonstration of NANC-mediated relaxation in human SV, prostate and urethra, and guinea pig VD	24-29
cGMP and/or cAMP act as relaxants in human SV, and rat and guinea pig VD	24,27,30-32
Central	
Demonstration of PDE isoenzyme activity in CNS[b]	33-37
Detection of NOS activity in areas of CNS responsible for behaviour and sex drive[c]	38-43
NO activity in MPOA inhibits ejaculation by decreasing sympathetic tone	41,44-46

a NO and HO-2 could have a role in regulation of smooth muscle contractility of the VD, SV, prostate and urethra in collaboration with other neurochemical transmitters.

b This may indicate that these organs may be a site of action of PDE5 inhibitors.

c This indicates a role of NO in central regulation of sex drive.

cAMP = cyclic adenosine monophosphate; **cGMP** = cyclic guanosine monophosphate; **HO-2** = heme oxygenase-2; **MPOA** = medial preoptic area of hypothalamus; **NANC** = nonadrenergic noncholinergic; **NO** = nitric oxide; **NOS** = nitric oxide synthase; **PDE** = phosphodiesterase; **SV** = seminal vesicle; **VD** = vas deferens.

from the start of vaginal penetration.[51] The Diagnostic and Statistical Manual of Mental disorders fourth version (DSM-IV) further expands the definition to "persistent or recurrent ejaculation with minimal sexual stimulation and before the person wishes it…" which is associated with "…marked distress or interpersonal difficulty…".[52] Rowland et al.[53] suggested a common model for defining RE groups to guide future research. They suggested a flowchart which began with the DSM-IV criteria of diagnosis in addition to the following steps:

- self-identification by patient himself;
- sexual history to confirm RE;
- absence of the exclusion criteria;
- preliminary decision from history; and
- final research decision, elaborating the RE classification with additional information relevant to aetiology and treatment implications.

Lastly, the international committee of the first consultation on ED[54] suggested the following criteria for definition of RE: (i) the general criteria for sexual dysfunction according to International Classification of Disease 10th revision must be met (F52); (ii) inability to delay ejaculation sufficiently to enjoy lovemaking as manifest as either (a) occurrence of ejaculation before or very soon after the beginning of intercourse (if time limit is required, before or within 15 seconds of the beginning of intercourse) or (b) ejaculation occurs in absence of sufficient erection to make intercourse possible; and (iii) the problem is not the result of prolonged abstinence from sexual activity.

Despite disagreement in the definition, there is no difficulty in recognising and diagnosing RE by patient history and most studies seem to agree that an ejaculatory latency time of <1–2 minutes is bothersome enough to most men and their partners for them to consider treatment.

RE can be divided into primary and secondary RE. Patients with primary RE are those experiencing the problem chronically since the beginning of their sexual lives, whereas patients with secondary RE are those experiencing RE after years of healthy sexual function.[55] The causes of RE are unknown in most patients; psychological or biological factors or both may contribute to the pathogenesis. Table II summarises causes of RE and their possible mechanisms in the genesis of the disorder.

2. Efficacy of Phosphodiesterase (PDE)-5 Inhibitors in RE

Sildenafil is the first oral PDE5 inhibitor approved by the FDA for treatment of ED. There are other PDE5 inhibitors under various stages of development.[85] PDE5 inhibitors act by inhibiting PDE5 hydrolysis of cGMP. Upon sexual stimulation (CNS or sensory), the nonadrenergic noncholinergic

Table II. Causes and possible mechanisms of the genesis of rapid ejaculation

Cause	Possible mechanisms	References
Primary	Increased penile sensitivity and/or excitability[a]	56-59
Secondary		
Anxiety	Activation of sympathetic nervous system[a]	60-63
Diabetes mellitus (early)	Hypersensitivity to actions of noradrenaline[a]	64-66
	Deficiency of NO production in peripheral nerves	67-69
Spinal cord injury	Interference with descending inhibitory pathways which control ejaculation	70-72
Alcoholism	Enhancement of sympathetic activity[a]	73-76
	Decrease in testosterone production	
Hypogonadism	Imbalance between estrogen and androgens leading to increased sympathetic activity[a]	77,78
	Estrogens antagonise NOS activity[a]	79,80
Chronic prostatitis	Alteration of ejaculatory reflex by inflammatory process	81
Drugs (e.g. desipramine)	Enhances the effects of noradrenaline on VD and SV[a]	82-84

a These mechanisms could be blocked by PDE5 inhibitors.

NO = nitric oxide; **NOS** = nitric oxide synthase; **PDE5** = phosphodiesterase type 5; **SV** = seminal vesicle; **VD** = vas deferens.

nerves release NO (produced by neural NO synthase [NOS]). This NO activates guanylate cyclase in the vascular smooth muscle, increasing the synthesis of cGMP which, in turn, leads to smooth muscle relaxation. The end result is that the helicine arterioles (which the cavernosal arteries feed) dilate, allowing an inflow of arterial blood and the trabecular smooth muscle of the corpus cavernosum begins to relax. There is also a change in the blood oxygen tension in the corpus cavernosum (from 25–40 to 90–100mm Hg erect) and this increase in oxygen tension, as well as some shear effects, may activate the endothelial NOS (eNOS), further contributing to NO production and increased cGMP.[86]

Six recent studies have suggested that the PDE5 inhibitor sildenafil could be beneficial in the treatment of RE, either as a single agent[87-89] or in combination with the SSRIs, paroxetine[90,91]and sertraline.[92]

In the study by Abdel-Hamid et al.,[87] 31 patients with primary RE went through a cascade of treatments, including clomipramine, sertraline, paroxetine, squeeze technique and sildenafil in a randomised crossover design. The dose of sildenafil was 50mg administered as needed 3–5 hours before planned intercourse. The authors found that sildenafil was superior to other modalities in terms of intravaginal ejaculation latency time (IVELT) and sexual satisfaction score. The success rate of sildenafil was 90.3%. Adverse events reported from sildenafil in this study included headache (6.5%), flushing (6.5%) and nasal congestion (3.2%). Chen et al.[88] evaluated the efficacy of sildenafil for treatment of severe RE in 58 men who failed other treatment modalities, such as behavioural therapy, topical lidocaine, tricyclic antidepressants and SSRIs. Sildenafil was taken 1 hour before sexual activity, 2–3 hours after a meal, in escalating doses of 25–100mg until satisfactory ejaculation was attained. The investigators concluded that sildenafil is beneficial in the treatment of RE and a trial of the drug is recommended for patients who have failed other remedies.

In an extension to the previous study, Chen et al.[90] noted that sildenafil plus paroxetine was shown to have a higher success rate (98%) than paroxetine alone in patients with severe RE. The therapeutic protocol involved taking paroxetine 20mg 7 hours before intercourse and sildenafil (25–100mg) 1 hour before sexual activity. In a well designed study, Salonia et al.[91] compared paroxetine alone with paroxetine and sildenafil as an oral therapy for men reporting RE. In the combination group, paroxetine was given as 10mg once daily for 20 days, followed by 20mg as needed subsequently, and sildenafil 50mg 1 hour before intercourse. This

study showed that the combination of paroxetine and sildenafil obtained better results in terms of IVELT and intercourse satisfaction than paroxetine alone. The combination treatment is associated with a mild increase in drug related adverse effects, such as headache (20%), nausea (15%) and flushing (15%). Despite the higher incidence of adverse effects associated with the combined therapy, the majority of patients (90%) were willing to continue therapy on an as-needed basis.

A study that included 38 patients with secondary RE (with various degrees of ED) who were treated with sildenafil 50–100mg alone found significant improvement in sexual satisfactory score (using a five-item International Index of Erectile Dysfunction) and prolongation of mean IVELT in 95% of patients.[89] The two patients (5%) who continued to report RE then received sertraline in addition to sildenafil with benefit. The most recent study[92] compared sildenafil 25–100mg plus sertraline 50mg versus sertraline 50mg alone and sildenafil 50mg alone in three different groups of RE patients (48, 51, 30 patients, respectively). The highest success rate was observed in the group receiving sertraline plus sildenafil (62.5%) followed by those receiving sertraline alone (56.8%) and lastly those who received sildenafil alone (40%).

3. Possible Mechanisms of Action of PDE5 Inhibitors in RE

Our understanding of the biological roles and cellular functions regulated by PDE5 is expanding rapidly. There are several possible mechanisms that could explain the efficacy of PDE5 inhibitors in the treatment of RE. Both peripheral and central mechanisms are likely to be important, with unknown contribution of each.

3.1 Possible Peripheral Mechanisms

3.1.1 Modulation of the Contractile Response of the Vas Deferens, Seminal Vesicles, Prostate and Urethra

PDE5 inhibitors could inhibit the contractile response of the VD, SV, prostate, urethra and even the skeletal muscles. Three possible mechanisms are thought to be involved in achieving modulation of the contractile response in these organs.

Firstly, the concept that NO/cGMP and NO/cyclic adenosine monophosphate (cAMP) signalling pathways may be involved in the therapeutic effect of PDE5 inhibitors in RE arose from several early and more recent observations.

- Expression of PDE activity has been reported in the prostate,[21,23] SV[20] and skeletal muscles.[22] PDE expression in VD is not yet studied.
- Nitrergic innervation and NOS activity have been detected in human VD, SV,[13,15,16] prostate,[15] urethra[17] and skeletal muscles.[18]
- NO seems to be the predominant inhibitory neurotransmitter in genitourinary organs.[12,28,29]
- NO and NO donating agents were reported to inhibit seminal emission in male rats.[44] Furthermore, NO inhibitors increase the number of ex-copula seminal emissions and decrease the latency to seminal emission in these rats.[45]
- The cyclic nucleotides, cAMP and/or cGMP act as relaxants in the smooth muscle of the rat[30] and guinea pig VD.[27,31,32] In addition, cross talk regulation of cGMP and cAMP systems in smooth muscles has been reported.[93] Furthermore, sildenafil citrate and JPM8 (a novel PDE5 inhibitor) have been shown to increase the concentration of both cGMP and cAMP in cavernous and cardiac smooth muscles.[94,95] Moreover, human SV smooth muscle relaxation and hence modulation of ejaculation are regulated, in part, by increases of intracellular cGMP.[32] Recently, it has been demonstrated that the cAMP increasing agent forskolin, and NO-donating agents, reduce the contractile response of guinea pig VD[27]

and human SV,[24] respectively. Lastly, the increase in cGMP levels in the rat VD could induce smooth muscle relaxation.[30]

- Sildenafil, the PDE5 inhibitor, causes potent and selective potentiation of nitrergic transmission in the urogenital muscle in male mice.[96]
- Other PDE inhibitors such as isobutyl methylxanthine and RO-201724 have been shown to augment the relaxant response of the VD in laboratory animals.[31,97,98]

Secondly, PDE5 inhibitors are thought to inhibit adrenergic neurotransmission in accessory sex organs. It has been reported that adrenergic tension in human prostatic strip preparations could be reversed by PDE5 inhibitors.[25] Moreover, sildenafil could inhibit adrenergic neurotransmission in human VD *in vitro*.[99] Furthermore, NO-donating agents were shown to blunt the adrenergic response in human SV *in vitro*[100] and in guinea pig VD.[101,102] This modulation of adrenergic response may occur in a paracrine (NO being generated in nitrergic nerves adjacent to the sympathetic nerves) or in a autocrine (NO being an atypical co-transmitter in sympathetic neurons themselves) fashion.[102]

Lastly, sildenafil has been shown to exhibit a direct inhibitory action on smooth muscles of human VD, possibly through activation of the opening of pre-junctional K^+ channels. The K^+ channel involved in the effect of sildenafil appears to be a large conductance Ca^{2+}-activated K^+ channel.[99]

3.1.2 Induction of Peripheral Analgesia

Sildenafil has been shown to induce a state of peripheral analgesia via activation of the NO/cGMP signalling pathway in laboratory animals.[103-105] This effect could be of value in alleviating the penile hypersensitivity that may be found in some patients with RE[57] and may mimic the success of topical anaesthetics in the treatment of some patients.[106]

3.1.3 Prolongation of the Total Duration of Erection

The ability of PDE5 inhibitors to augment the total duration of both sexually stimulated[107-111] and sleep-related[112,113] erections is now well established. It has been reported that administration of PDE5 inhibitors resulted in clinically significant improvement in the total duration of erection when evaluated either by sexual function questionnaires[107,109] or by Rigiscan during visual sexual stimulation.[107,108,111,114] In Rigiscan studies, the mean duration of rigidity were 42.9 and 49.3 minutes for vardenafil 20 and 40mg, respectively,[108] compared with 31.8 minutes for sildenafil 50mg in one trial[114] and 19.5 minutes in another study.[111] Moreover, monitoring of sleep-related erections after administration of sildenafil 50mg[113] or 100mg[112] at bedtime revealed a significant increase in the total duration of rigidity. PDE5 inhibitors improve the duration of erection possibly because of enhancement of penile tissue oxygenation.[112,113] Since the ejaculation latency time was reported to be dependent on the duration of erection, the longer the duration of erection the more prolonged the ejaculation latency time,[115] and so, it is anticipated that PDE5 inhibitors could increase the ejaculation latency time.[87,90]

3.2 Possible Central Mechanisms

3.2.1 Central Role of the Nitric Oxide/Cyclic Guanosine Monophosphate Pathway

Evidence indicates that PDE5 inhibitors may have CNS effects in patients with RE. This evidence includes the following: (i) sildenafil crosses the blood brain barrier and exerts various biochemical and physiological effects in the brain;[116,117] (ii) PDEs including PDE5 have been demonstrated in the CNS;[33-37] (iii) NOS and guanylate cyclase are present at higher activities in areas of the CNS responsible for behaviour and sex drive;[38-43] and (iv) modulation of a variety of CNS functions has been ascribed to NO/cGMP pathway,[42] including various aspects of sexual physiology.[40-42,118] However, the central role of NO-stimulated guanylate cyclase activity is more complex than previously assumed and associated with a diversity of cellular responses.[119,120] Overall, previous data may indicate a potentially important role of the CNS NO/cGMP pathway on ejaculatory function, but provide

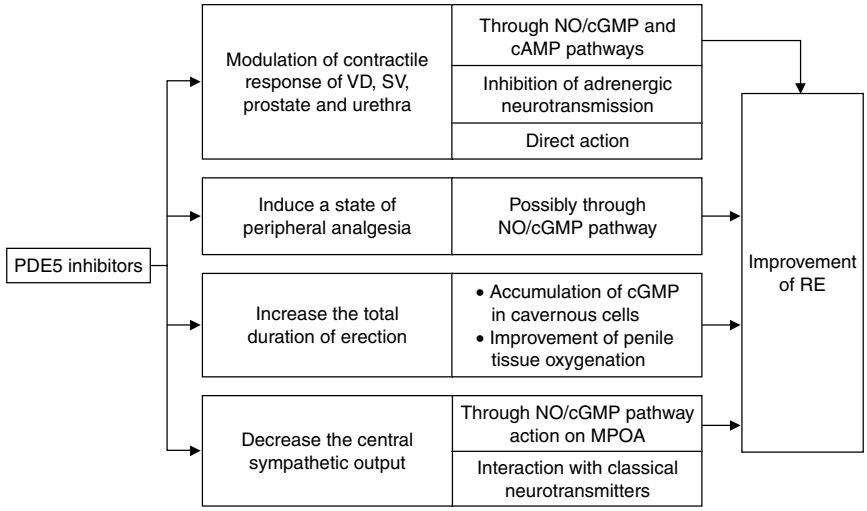

Fig. 1. Schematic diagram of potential mechanisms of phosphodiesterase (PDE) 5 inhibitors in rapid ejaculation (RE). **cAMP** = cyclic adenosine monophosphate; **cGMP** = cyclic guanosine monophosphate; **MPOA** = medial preoptic area of hypothalamus; **NO** = nitric oxide; **SV** = seminal vesicles; **VD** = vas deferens.

no information concerning the quality and magnitude of the changes in this pathway required to affect the function of the VD, SV, prostate and urethra.

3.2.2 Lessening of the Central Sympathetic Output

It has been suggested that NO activity in the medial preoptic area (MPOA) tonically inhibits ejaculation by decreasing the sympathetic tone,[46] since NO is known to play a role in sympathetic regulation by decreasing the central sympathetic output to the periphery in different species including humans[121-124] and this effect may be induced through cGMP-dependent mechanism or via interactions with the classical neurotransmitters.[125] In addition, NO donors have been demonstrated to increase cGMP levels in the hypothalamus.[118] It has been noted that intrathecal administration of sildenafil in rats increases the cGMP and NO levels in the medial preoptic area of the hypothalamus.[126] In addition, cGMP measured in rat hippocampal slices increases when incubated with a high concentration of vardenafil.[127] Furthermore, sildenafil users reported statistically significant improvement in general mental health and emotional well being.[128] Moreover, sildenafil treatment reduced the anxiety score in patients with RE compared with baseline.[87] The action of sildenafil in the CNS appears similar to its presumed role in the peripheral nervous system.[126] Figure 1 shows a schematic description of the possible mechanisms of action of PDE5 inhibitors in RE.

4. Evidence from Knockout Mice

4.1 Mice Lacking the Gene for Endothelial Nitric Oxide Synthase

Available data suggest that NOS and heme oxygenase-2 (HO-2), which catalyses carbon monoxide (CO) production, are co-localised in the nerve fibres of human VD and SV,[11] suggesting that both NO and CO may have a role both as directly acting transmitters or as modulators of the efferent neurotransmission.[129] Theoretically, we propose that NO released from the nerves of VD, SV and prostate during sexual stimulation could be one factor keeping these organs relaxed during initiation and maintenance of erection. This hypothesis could explain the occurrence of regional sympathetic depression during erection suggested by Ertekin et al.[130] It has been demonstrated that mice lacking the gene for

eNOS (eNOS−/−) need less stimulation to elicit ejaculation compared with genetically intact mice and ejaculate after a shorter latency time, a picture that is similar to RE.[131] The absence of the eNOS control mechanism in eNOS−/−mice may thereby account for overactive sympathetically mediated ejaculatory responses in these mice.[132] Since the NO/cGMP pathway is, in part, responsible for relaxation in human SV,[24] PDE5 inhibitors could be of value in treatment of RE.

4.2 Mice Lacking the Gene for Heme Oxygenase-2

Considering the co-localisation of NOS and HO-2, an interaction or crosstalk between NO and CO contributing to modulation of the ejaculatory function may be expected. In laboratory animals, it has been demonstrated that CO blocks the NO-mediated cGMP increase and inhibitors of CO production potentiate the NO-mediated cGMP increase, indicating that CO generated by HO-2 can bind and inactivate NOS.[133-135] Some authorities consider HO-2 as an intracellular 'sink' for NO.[136] However, CO and NO can modulate each other's activity.[134] These previous findings could explain the occurrence of delayed or anejaculation, and decreased bulbospongiosus activity in genetically altered mice in which HO-2 is knocked out.[137] The defective or absent HO-2 in these animals allows NO to work unrestricted, leading to severe smooth muscle relaxation and inhibition of sympathetic activity.

5. Contradictory Evidence and Speculation

Contradictory findings against the efficacy of PDE5 inhibitors in the treatment of RE have arisen in three areas: (i) sildenafil was reported to reduce the ejaculation latency time and mount frequency in male rats, possibly because of cGMP/PDE5 and dopamine co-localisation in several brain areas;[138,139] (ii) cGMP-elevating agents such as sodium nitroprusside (SNP) and atrial natriuretic factor have been shown to elevate cGMP without inducing relaxation of rat and guinea pig VD, indicating that the VD is a non-responsive tissue;[140-142] and (iii) elevation of extracellular NO in the MPOA facilitates male copulatory behaviour of rats, whereas the decrease of NO reduces their copulatory behaviour.[41]

The possibility that sildenafil facilitates rather than delays copulatory function of male rats has not been confirmed by other groups of investigators. In these reports,[138,139] categorisation of rats into sluggish or normal ejaculators was arbitrary and the conclusion depends on observation of copulatory behaviour of male rats once, after a single dose of sildenafil 1 mg/kg. In addition, to the best of our knowledge, this effect has not been reported clinically and, in contrast, sildenafil was demonstrated to improve both the total duration of erection[107,111,114] and RE.[87,88,91] Furthermore, it has been reported that sildenafil could induce priapism.[143,144] Lastly, the only situation in which PDE5 inhibitors appear to enhance the contractility of smooth muscles is after chronic exposure to these agents. This leads to enhanced sensitivity to contractile stimuli, a mechanism which appears to be cAMP dependant,[145] or sildenafil may be associated with increased generation of superoxide anions. These anions may compromise the relaxing potential of the cGMP by reducing the bioavailability of NO[146] and this could explain the reported tachyphylaxis with sildenafil.[147,148]

Regarding the effects of SNP on the VD, it has been reported that the response to SNP differs between species.[149] For example, SNP has no effect on the neurogenic contraction of a ring segment of human VD nor does it affect the contraction induced by norepinephrine (noradrenaline).[99] Furthermore, it has been reported that SNP could attenuate the adrenergic tension of human SV *in vitro*.[100] In addition, SNP may not be an acceptable NO donor.[149] SNP-induced contractility in rat and guinea pig VD could be attributed to the sodium content of SNP. Sodium was reported to potentiate the contrac-

Table III. Evidence for and against PDE5 inhibitor therapy in rapid ejaculation (RE)

For	Against
Clinical	
Success of PDE5 inhibitors in the treatment of RE in six studies alone or in combination	
PDE5 inhibitors prolong total duration of erection in many studies	
Anatomical and physiological	
Demonstration of PDE activity in the SV, prostate, skeletal muscles and CNS	
Demonstration of NANC-mediated relaxation in human SV, prostate and urethra, and guinea pig VD	
Co-localisation of NOS and HO-2 in human SV and VD	
NO and CO modulate each other's activity	
Pharmacological	
Sildenafil inhibits adrenergic activity in human VD and prostate	Sildenafil reduces ejaculation latency and mount frequency in male rats
Sildenafil has direct relaxing effect on human VD *in vitro*	
PDE inhibitors (IBMX, RO-201724) augment relaxation of VD in laboratory animals	Elevation of extracellular NO in MPOA facilitates male copulatory behaviour in rats
Sildenafil induces peripheral analgesia in animals	SNP and atrial natriuretic factor elevate cGMP without relaxation of smooth muscles of rat and guinea pig VD
NO and NO-donating agents inhibit adrenergic tension in human SV and seminal emission in rats	
NO activity in MPOA decreases the central sympathetic output	
cGMP act as relaxant in human SV, and rat and guinea pig VD	
Genetic	
Mice lacking gene for eNOS develop a picture similar to RE	
Mice lacking gene for HO-2 develop a picture similar to delayed or anejaculation	

CNS = central nervous system; **CO** = carbon monoxide; **eNOS** = endothelial nitric oxide synthase; **cGMP** = cyclic guanosine monophosphate; **HO-2** = hydrogen peroxide 2; **IBMX** = 1-methyl-3-isobuttylxanthine; **MPOA** = medial preoptic area of hypothalamus; **NANC** = nonadrenergic noncholinergic; **NO** = nitric oxide; **NOS** = nitric oxide synthase; **PDE** = phosphodiesterase; **PDE5** = phosphodiesterase type 5; **SNP** = sodium nitroprusside; **SV** = seminal vesicle; **VD** = vas deferens.

tile response in guinea pig VD.[150,151] Finally, atrial natriuretic factor was reported to inhibit the release of norepinephrine from adrenergic nerves in rabbit VD.[152]

Although it is generally accepted that NO is an important inhibitory mediator in nonadrenergic, noncholinergic nerves in urogenital smooth muscles, the role of NO in neurotransmission seems to be complex, implying the existence of hitherto unknown regulatory factors. For example, NO synthesised by eNOS seems to have exclusively physiological actions, whereas NO produced by neural NOS and inducible NOS may be pathological.[153] Moreover, the level of NO may undergo diurnal variations[118] and drug administration changes.[128] Furthermore, the sexual response cycle in males has four successive stages; one of them is ejaculation. It has been reported that these stages relate to corresponding biochemical changes in the brain, blood and cavernous tissues.[154-157] NO/cGMP pathway changes during this cycle await verification. Table III lists the evidence for and against of PDE5 inhibitor therapy in patients with RE.

6. Conclusions and Future Directions

Review of the literature suggests the potential usefulness of PDE5 inhibitors in the therapy of RE. In the relatively small number of patients investigated, sildenafil was superior to other modalities (pause-squeeze, tricyclic antidepressants and SSRIs), treated patients with severe RE who had failed other treatment modalities (topical lidocaine, tricy-

clic antidepressants and SSRIs) and improved secondary RE associated various degrees of ED. In the three other investigations, sildenafil combined with paroxetine or sertraline was shown to have a higher success rate than paroxetine alone or sertraline alone. The place of PDE5 inhibitors in the therapy of RE awaits larger patient samples and placebo-controlled studies to confirm these encouraging results. Available evidence indicates that PDE5 inhibitors may exhibit multiple mechanisms of action in the treatment of RE. Future studies should examine these possible mechanisms of action. The clinical utility of PDE5 inhibitors in the treatment of RE may be improved through focussing on the exact PDE isoform expressed in human VD and SV. The effects of different PDE5 inhibitors on the contractility of the seminal tract *in vivo* should also be investigated. Finally, the changes in the central NO/cGMP and NO/cAMP signalling pathways in different areas of the brain and their corresponding functional effects in the VD, SV and prostate after administration of PDE5 inhibitors should be studied.

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