Can smooth muscle represent a useful target for the treatment of rapid ejaculation?

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Rapid ejaculation is probably the most common form of male sexual dysfunction. Current research into the treatment of the condition has focused on centrally acting or topical desensitizing agents; however, no treatment has yet been approved. An alternative approach could be to develop drugs that act directly upon the target organ itself and our increasing knowledge of the molecular biology of the accessory sex organs makes this a realistic possibility. This review analyzes the information in the literature that would support such a hypothesis. Particular emphasis has been placed on articles that have investigated smooth muscle cell relaxation. A critical review of the literature has revealed that there are potentially a myriad of targets through which rapid ejaculation can be treated.

Most epidemiological studies have suggested that rapid ejaculation (RE) could be the most common male sexual dysfunction, with prevalence ranging from <5% to >30% [1,2]. In this condition, emission and ejaculation proper occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners [2] and this is due to a hyperactive ejaculation reflex [3]. The condition can be treated with various strategies such as behavioural therapy, topical anaesthetics, antipsychotics, tricyclic antidepressants and selective serotonin re-uptake inhibitors (SSRIs). Of the drugs used for the treatment of RE, SSRIs are the most frequently prescribed [4], however, to date no pharmaceutical agent has been approved for this indication

Recent advances in basic science have led to a better understanding of the molecular events regulating the contraction and/or relaxation cycle of smooth muscle cells (SMCs) of accessory sex organs (ASOs). Although SMCs are a target for many drugs used successfully to treat erectile dysfunction, treatment of RE using drugs affecting SMC function remains somewhat neglected. This review attempts to analyze the various options available for the targeting of SMCs. Discussion will be largely confined to human data, drawing on animal data mainly to fill gaps where human experimentation is either impractical or yet to be carried out, or where there appears to be supporting data or major species differences.

Regulation of SMC contractility

Ejaculation actually involves two coordinated processes, emission and ejaculation proper. The structures involved in emission and ejaculation include the vas deferens (VD), the seminal vesicle (SV), the ejaculatory ducts, the bladder neck, the prostate and the muscles of the perineal floor (i.e. the ischiocavernosus and bulbocavernosus). 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 [5] .Emission begins with bladder neck closure. Following this, propulsive contraction of the smooth muscles of the

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VD and prostate act together to expel their contents into the prostatic urethra. Forcible expulsion of the contents of the SV follows. Finally, the ejaculate is expelled from the urethra in a series of spurts caused by rhythmic contractions, 0.8 s apart, of the ischiocavernosus, bulbospongiosus and other associated perineal muscles [6]. The predominant functional receptor responsible for mediating the contractile response of human ASO has the pharmacological characteristics of the α_{1A} adrenergic receptor (AR) subtype [7,8].However, the α_{1L}-AR subtype predominates in longitudinal muscle and the α_{1A} subtype in the circular muscle of human VD [7]. In addition, numerous substances have the ability to enhance or modulate the action of norepinephrine. These include neurotransmitters and local endogenous factors such as acetylcholine, vasopressin and neuropeptide-Y [9,10].

The primary regulatory sequence

The first sequence of events in SMC contraction includes the binding of endogenous substance(s), such as neurotransmitters (mainly norepinephrine) and hormones, to their specific receptors. This activates various types of guanosine 5′-triphosphate- (GTP-) binding proteins, which are coupled to various ion channels and enzymes, modulating their activities .These enzymes include phospholipase C (which hydrolyses phosphatidylinositol, PIP2, to inositol 1,4,5-trisphosphate, Ins(1,4,5)P_3, and diacylglycerol, DG) and adenylate cyclase (which metabolizes adenosine 5′-triphosphate, ATP, to produce cyclic adenosine 3′,5′-monophosphate, cAMP). Some receptors are directly coupled to guanylate cyclase, such as atrial natriuretic peptide, which metabolizes GTP to produce cyclic guanosine 3′,5′-monophosphate, c GMP) [8].

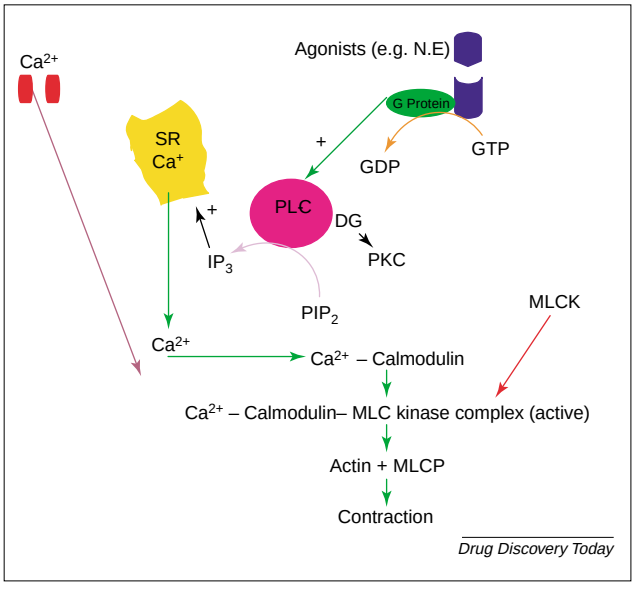

FIGURE 1

The mechanisms of contraction of smooth muscle. Contraction is initiated by an increase of Ca^{2+} in the myoplasm; this happens in one of two ways: Ca^{2+} can enter from the extracellular fluid through channels in the plasmalemma or, following agonist-induced receptor activation, Ca^{2+} can be released from the sarcoplasmic reticulum (SR). In this pathway, the activated receptor interacts with a G-protein (G) which in turn activates phospholipase C (PLC). Ca^{2+} combines with calmodulin (CaM) and the Ca^{2+}–CaM complex activates MLCK, which in turn phosphorylates light chain .The phosphorylated myosin filament combines with the actin filament and the muscle contracts. Abbreviations: Ca, calcium ;DG, diacylglycerol ;GDP, guanidine diphosphate ;GTP, guanidine triphosphate ; IP3, inositol triphosphate; MLCK, myosin light chain kinase ;NE, norepinepherine ;PIP2, phosphotidylinositol ; PL-c, phospholipase-c; PKc, protein kinase c; P, phosphorus ;SR, sarcoplasmic reticulum;+, stimulation.

The secondary regulatory sequence

The second regulatory sequence is related to changes in the intracellular Ca^{2+} concentration [7,9,10]. Ca^{2+} influx is the major mechanism by which the intracellular Ca^{2+} concentration is increased; however, release of Ca^{2+} from intracellular stores, such as the sarcoplasmic reticulum (SR), can contribute to elevation of intracellular Ca^{2+}, albeit at a lower level. Ca^{2+} in the cytosolic compartments exerts its effects by regulating contractile elements [9]. This is followed by changes in myosin light chain (MLC) kinase activity as a third regulatory sequence.

The tertiary regulatory sequence

The activation of MLC kinase by Ca^{2+} and calmodulin leads to phosphorylation of MLC. Phosphorylated myosin interacts with actin to induce contraction. It is generally believed that light chain phosphorylation and dephosphorylation controls the contraction and relaxation cycle of SMC, respectively (Figure 1) [11,12]. Although SMCs share many common properties, there exists a large heterogeneity in contractile properties within the SMC family. For example, Phasic SMCs, as in the case of VD, are characterized by relatively rapid rates of force activation and relaxation, high myosin ATPase activity, and a fast maximum velocity of muscle shortening. It has been reported that protein kinase C-induced contraction in phasic SMC of rabbit VD with high MLC protein content has a reduced sensitivity to Ca^{2+} compared with tonic SMC [13].

On the other hand, inhibition of the contractile process might be clinically relevant in reducing the SMC tone of ASOs in cases of RE. SMC relaxation occurs either as a result of removal of the contractile stimulus (e.g. blocking of α_1 AR) [14,15] or by the direct action of a substance that stimulates inhibition of the contractile mechanism. These include inhibition of kinases, inhibition of phosphodiesterases (PDEs), blocking of Ca^{2+} channels, K^+ channel opening and so on (Figure 2) [3,16–19].

Blocking of α_1 ARs

Few studies have demonstrated the therapeutic advantage of either selective (alfuzosin and terazosin) [15] or nonselective (phenoxybenzamine) [20,21] α_1 AR antagonists over placebo in the treatment of RE . Although selective α_1 AR antagonists are reasonably safe, efficacious drugs, the response rate was only ~50%. In the case of phenoxybenzamine,

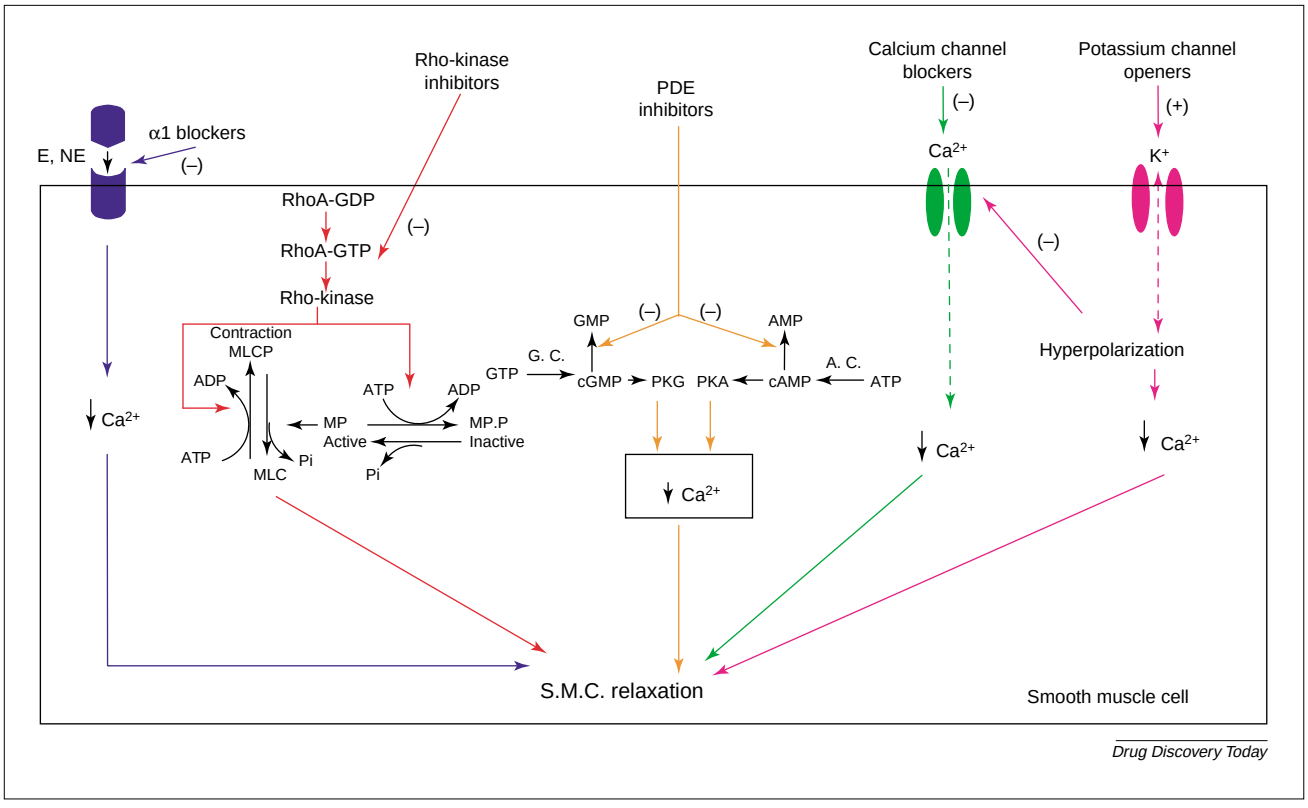

FIGURE 2

Mechanisms of peripherally acting agents for the treatment of rapid ejaculation. The primary mechanism proposed for relaxation of SMC is reduction of free cytosolic calcium concentrations. Five mechanisms are depicted for SMC relaxation. These include blocking of α1 adrenergic receptors, inhibition of Rho-Kinase, inhibition of PDE, blocking of Ca^{2+} channels and opening of K^+ channels. Abbreviations: AC, adenylate cyclase ; ADP, adenosine diphosphate ; AMP, adenosine monophosphate ; ATP, adenosine 5′-triphosphate; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; E, epinepherine; GDP, guanosine diphosphate ; GMP, guanosine monophosphate; GTP, guanosine 5′-triphosphate; MLC, myosin light chain; MP, myosin phosphatase; NE, norepinephrine; PDE, phosphodiesterase enzyme; Pi, phosphorus; PKA, protein kinaseA; PKG, protein kinase G; (–), inhibition; (+), stimulation.

the primary limitation was the incidence and severity of adverse reactions.

The sites of action of the currently used α_1 AR antagonists effective in relieving RE have not yet been established, but it seems clear that their effects on ASOs are important. The α_1 AR receptors of these organs, the ganglia and nerve terminals and also the central nervous system (CNS) can all influence ejaculation and the clinical effects of α_1 AR antagonists in this condition. However, the relevance of α_1AR subtype selectivity for the clinical utility has yet to be established. Researchers have observed a tissue-specific distribution of α_1 adrenergic receptor subtypes. The human VD is rich in α_1 ARs with the α_{1l} subtype predominating in longitudinal and the α_{1a} subtype in circular muscles [22], whereas the α_{1a} subtype predominates in the human prostate and urethra [23] and rat SV [24]. By contrast, human detrusor (which is responsible for bladder neck closure during ejaculation) showed a predominance of the α_{1d} subtype [25]. This distribution of α_1 AR subtypes in the genital tract could explain the occurrence of ejaculatory dysfunction in 4–18% of patients being administered the selective α_1 AR antagonist, tamsulosin [14,26] for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. Although the blockade of α_{1a} and α_{1d} receptors might be necessary for optimal clinical benefit in the relief of the SMC tension within the prostate and bladder neck, blocking α_{1d} ARs could be associated with retrograde ejaculation as commonly reported with tamsulosin, due to excessive relaxation of the bladder neck [27]. In addition, inhibition of α_{1a}AR induces SMC relaxation of the VD, SV and prostate, leading to the possibility of delayed ejaculation or even anejaculation [28].

Can selective α_1 adrenergic receptor antagonists be useful in the treatment of RE?

It has been reported that selective α_1 AR antagonists (prazosin, terazosin, alfuzosin and tamsulosin) exhibit inhibitory effects on the contractile responses of rat SV and VD to electrical stimulation. These effects were recorded *in vivo* through measurement of intraluminal pressures [14,29]. Furthermore, tamsulosin inhibited isolated human VD contraction at significantly lower concentrations than prazosin [30]. As data continue to emerge with respect to the distribution of α_1 AR subtypes in the ASOs, especially VD and SV, it is hoped that the role of α_1 AR

subtype-specific antagonists in RE will be further elucidated. At present, poor organ selectivity and side effects limit the therapeutic utility of currently available drugs.

Based on previous data, it would be expected that drug discovery efforts in this area would be most productive in the development of antagonists of specific α_1 AR subtypes, which would spare detrusor muscle and provide mild to moderate relaxation of the smooth muscle of VD, SV and prostate of short duration, which would be expected to avoid anejaculation . Should this class of 'genitoselective' agents be developed, a key requirement would be a high degree of selectivity over α_{1b}AR to avoid effects on blood pressure. In addition, it would be desirable if such drugs were unable to cross the blood brain barrier [31]. A recently developed uroselective α_1 AR antagonist, REC15/2739, was fused with nitrooxy and furoxan nitric oxide (NO)-donor moieties to give new NO-donor α_1 AR antagonists. Members of this series were able to antagonize noradrenaline-induced contraction of the prostatic portion of rat VD as a result of the combination of their α_{1A} antagonist and NO-donor properties [32].

Inhibition of Rho kinase

Rho kinases are the downstream effectors of Rho, one of a family of small GTP-binding proteins that are structurally and functionally related to Ras [33]. Rho family members are G-proteins that cycle between an inactive GDP-bound form and an active GTP-bound form. Activated Rho binds to target proteins to regulate diverse functions in the cells including morphology, cytoskeletal function, secretion and SMC contraction. Evidence has accumulated in the last two decades suggesting that changes in cytosolic Ca^{2+} alone cannot account for the extent of contraction observed in SMC [34]. In other words, other factors capable of modifying the sensitivity of contractile and regulatory proteins to Ca^{2+} in the face of constant cytosolic Ca^{2+} levels are necessary to produce the observed levels of contraction. One of these mechanisms might be the Rho kinase pathway, which has been proposed as a major Ca^{2+} sensitization mechanism in SMCs [35]. Also, the Rho kinase pathway modulates the level of phosphorylation of the MLC of myosin II, mainly through inhibition of myosin phosphatase [16]. Inhibition of RhoA-induced activation of Rho kinase therefore inhibits SMC contraction.

More recently, it has been reported that Rho kinase protein is expressed in the mouse VD and in human and rat prostatic SMC [16,17].Furthermore, the Rho kinase pathway is proposed to be one of the sensitizing mechanisms responsible for induction of SMC contraction in mouse VD [15] and rat prostate [17] by increasing Ca^{2+} sensitivity without necessarily changing Ca^{2+} levels. Moreover, specific Rho kinase inhibitors have been shown to relax SMCs of the mouse VD [16] and rat prostate [17], possibly through inhibition of the Ca^{2+}-sensitizing mechanism.

The expression pattern of some molecules or enzymes differs between phasic SMCs (such as in the case of VD) and that of tonic SMC (e.g. vascular SMC). For example, rabbit VD phasic muscles contain more MLCP myosin-targeting subunit, which is phosphorylated via the RhoA–Rho-kinase pathway, than tonic tissues. By contrast, the phasic VD SMCs possess ~8 times less cellular CPI-17 (the MLCP inhibitor phosphoprotein) than tonic SMC [18]. In the future, additional research studies might reveal distinct isoforms of RhoA or Rho-kinase proteins in the human VD, SV and prostate. Drugs developed to target these isoforms might be useful in the modulation of the contractility of these organs. In addition, other approaches to inhibit RhoA–Rho-kinase signalling could include altering the activity of associated molecules (guanine nucleotide dissociation inhibitors, GDI and guanine nucleotide exchange factors, GEF), which are essential for activity of this pathway. Such compounds might be potentially useful in the modulation of ejaculation and in the treatment of RE and therefore should warrant further investigation.

Inhibition of PDEs

The intracellular levels of cAMP and cGMP are tightly controlled both by their rates of synthesis (by adenylyl and guanylyl cyclases, respectively) in response to extracellular signals, and by their rate of hydrolysis (by cyclic nucleotide PDEs). There are 11 isoforms of the cyclic nucleotide PDE superfamily, catalysing the breakdown of cAMP and cGMP. Because of their central roles in SMC tone regulation and their considerable species and tissue diversity, PDEs have become an attractive target for drug development since the demonstration of the efficacy of sildenafil citrate for the treatment of erectile dysfunction. The presence of PDE 5 mRNA in human VD has been demonstrated, but at levels 10-fold less than in corpora cavernosa [36]. PDE5 was immunolocalized in all the muscular layers of human and rabbit VD and was found to be negatively involved in the regulation of nitric oxide- (NO-) induced relaxation. The authors noted the presence of PDE5 mRNA in human prostate at a level more or less equal to the expression found in human VD. Although the rate of cGMP metabolism was higher in corpora cavernosa than in VD, both tissues had similar sensitivity to a broad panel of cGMP-related PDE inhibitors: sildenafil, tadalafil, dipyridamole, zaprinast, vinpocetine, and cilostamide. Furthermore, mRNA transcripts encoding for PDEs 1–5,7–9 and 10 in various anatomical regions of human prostate have been detected [37] and a physiological role for the NO–cGMP pathway in human SV has been demonstrated [38]. The rationale for the use of PDE 5 inhibitors in RE might be due to their central effects, involving reduced sympathetic tone; SMC relaxation of the VD, prostate and SV; increasing the total duration of erection and induction of a state of peripheral analgesia [3].

The bulk of available clinical evidence for the efficacy of PDE5 inhibitors in RE comes from studies that have not been placebo-controlled [39–41] compared with that from prospective, randomized, placebo-controlled studies [42,43]. Preliminary reports from the first double-blind placebo–controlled trial of sildenafil for RE indicated no significant difference in the intravaginal ejaculation latency time (IELT) of sildenafil compared with placebo but demonstrated significant improvements in the ejaculatory control domain and the ejaculatory function global efficacy question [42]. In the second study, Ekmekçioðlu *et al.* [43] evaluated whether sildenafil citrate prolongs ejaculation latency time when vibratory stimulation is applied after exposure to audiovisual sexual stimulation in a laboratory setting in a group of 30 normal volunteers. They noted significant prolongation in IELT of sildenafil citrate compared with placebo (3.89 and 2.23 min respectively, p=0.01). Further results from double-blind placebo-controlled multicenter trials are needed to determine whether selective PDE 5 inhibitors will have a place in the treatment of RE. It has long been appreciated that smooth muscle tissues display considerable diversity with respect to their basic contractile properties as well as their response to modulating signals. For example, as the NO–cGMP-mediated relaxation pathway was elucidated, it was also appreciated that smooth muscle tissues differ in their sensitivity to this pathway. The molecular basis of this SMC functional diversity is not well understood [44]. Future studies should examine the sensitivity of SMC of the human VD and prostate to the NO–cGMP and cAMP pathways. In addition, it will be of great importance to investigate the expression of the various PDE isoforms expression in human VD and SV in the search for highly selective therapies.

Blocking Ca^{2+} channels

The process of SMC relaxation requires a decrease in the intracellular concentration of Ca^{2+} and a concomitant increase in MLC phosphatase activity. The mechanisms that sequester or remove intracellular Ca^{2+} might involve the sarcoplasmic reticulum and the plasma membrane. Ca^{2+} uptake into the sarcoplasmic reticulum is dependent on ATP hydrolysis. Calcium efflux from the cell through the plasma membrane occurs via the $3Na^{+}$–Ca^{2+} exchanger. The plasma membrane also contains Ca^{2+}- and Mg^{2+}-ATPases, providing additional mechanisms for reducing the concentration of activator Ca^{2+} in the cell [9,10]. It has been reported that the plasma membranes of SMC human VD [45], prostate [46] and guinea-pig SV [47] contain voltage-operated Ca^{2+} channels that are important in Ca^{2+} influx and SMC contraction. Inhibition of these channels can elicit relaxation. Ca^{2+} channel antagonists (CCBs) such as the dihydropyridines, phenylalkylamines and benzothiazepines bind to distinct sites on the channel protein and remotely inhibit Ca^{2+} entry into SMCs.

The effects of the CCBs nifedipine, verapamil and diltiazem were studied on contractions induced by electrical field stimulation in isolated preparations of the human VD [48]. The investigators noted that electrically-induced contractions were abolished by exposure to Ca^{2+}-deficient medium. Furthermore, every drug was able to abolish electrically induced contractile responses. These contractions could be completely blocked at high concentrations of verapamil and diltiazem but only partially (~40%) by nifedipine, even at high doses. This difference in effect is probably not due to verapamil and diltiazem being more effective CCBs than nifedipine, but that factors other than their CCB properties are involved in the antagonism of the contractile response. Some evidence supporting the premise that other factors other than CCB activity were involved in inhibition of the contractile response came from the same study, which showed that the drugs were also capable of abolishing K^{+}-induced contractions. In addition, other studies have shown that nifedipine was capable of suppressing noradrenaline-induced rhythmic contractions and reducing the underlying tonic response in circular and longitudinal SMC of vasectomy specimens of human VD [19]. Furthermore, nifedipine inhibits depolarization of circular SMC membrane of guinea-pig SV induced by noradrenaline [47]. This effect was associated with reduced amplitude of Ca^{2+} transients. A similar response was noted with verapamil in the KCl-induced contractions in the rat isolated SV [49]. In addition, nifedipine can completely abolish the inward current of SMC isolated from guinea-pig prostate [50]. This effect was attributed to the CCB activity of nifedipine.

To the best of my knowledge, the clinical efficacy and safety of different CCBs in the treatment of RE have not been studied. However, the SSRIs sertraline and fluoxetine were demonstrated to inhibit human VD motility *in vitro* through inhibition of Ca^{2+} entry, with no effect on the ARs [51]. This Ca^{2+} channel-blocking activity of SSRIs has been also noted with paroxetine [52]. This effect could explain, at least partially, the clinical efficacy of these drugs in RE and the peripheral inhibitory effects on contraction of human VD *in vitro* [53]. Collectively, these data demonstrate that CCBs have the potential to modulate SMC of VD and prostate.

First-generation CCBs were originally developed to treat ischemic heart disease and later were used to treat hypertension. However, they are a chemically and pharmacologically heterogeneous group of drugs, yet physiologically they all share the ability to selectively inhibit the Ca^{2+} transit. In future, better characterization of the physiological and pharmacological properties of Ca^{2+} channels in human ASOs will provide more information to develop new generations with negligible effect on cardiac and vascular SMCs and increased ASOs selectivity.

Opening of K^{+} channels

Visceral smooth muscle is an excitable tissue that relies on the maintenance of a membrane potential for its function.

BOX 1

Future challenges for the establishment of ASO smooth muscle cells as a viable target for the treatment of RE and steps required to develop drugs for this target

- Identify predominant a AR subtypes in human SV and to confirm previous findings regarding the same receptors in human VD.
- Develop future class of selective a1 blockers with minimal affinity for the a 1b and a 1d ARs (to avoid blood pressure changes and retrograde ejaculation respectively), as well as absence of the ability to penetrate the blood brain barrier.
- Determine the distinct isoforms of RhoA or Rho-kinase proteins in the human VD, SV and prostate.
- Identify the effect of available Rho-kinase inhibitors on SMC of human VD, SV and prostate.
- Determine the PDE isoform expression in human VD and SV.
- Examine the sensitivity of smooth muscle cells of the human VD, and prostate to the NO–cGMP and cAMP pathways as well as confirmation of that previously noted with human SV.
- Determine whether selective PDE 5 inhibitors will have a place in treatment of RE through double-blind placebo-controlled multicentre trials.
- Determine the predominant voltage-operated Ca^{2+} channels subtypes in the plasma membrane of SMC of human VD, SV and prostate.
- Characterize the different K^+ channel subtypes in human ASOs as well as the human genes encoding these channels in the primary lifelong RE patients and normal persons.
- Identify the predominant subtype(s) of K^+ channels responsible for K^+ currents in human ASOs.
- Examine the effects of different KCOs on human SMC of VD, SV and prostate.

The membrane potential in its component cells is largely derived from the differences in concentration of extracellular and intracellular K^+. Movement of K^+ into and out of SMC occurs through K^+ channels, membrane proteins that selectively conduct K^+ across the cell membrane. Agents that increase the permeability to K^+ (K^+ channels openers, KCOs) hyperpolarize the cell membrane and thereby close the voltage-dependant Ca^{2+} channels and inhibit SMC contractile activity. In turn, an increase in intracellular Ca^{2+} can inhibit voltage-dependant K^+ channels and evoke membrane depolarization, leading to contraction of SMCs [54]. The recent development of molecular biological techniques has enabled the development of a genomic and structural classification for K^+ channels into several types and subtypes. The large conductance Ca^{2+}-activated K^+ channels (BKCa, also known as Maxi-K channels) and delayed rectifier components of the outward current (KDR) were identified and characterized in SMC of human VD [44]. These findings imply that K^+ channels have a role in regulation of SMC contractility of human VD. However, in rat VD SMC, when BKCa current was suppressed, A-type K^+ (KA) current and KDR current were identified [55]. These results could indicate a species difference between human and rat. In addition, BKCa [56], SK2 (S is for small conductance) and SK3 mRNA were detected in human prostatic SMCs [57]. In another study, active K^+_{ATP} channels were noted in cultured human prostatic stromal cells [58]. Moreover, KA and BKCa were detected in SMC of guinea-pig SV [59].

Several molecules are known to activate K^+ channels. Such compounds could have a wide therapeutic potential and a few are currently used as antihypertensive agents. Different chemical series of KCOs have been identified with different molecular sites of action and tissue selectivity [60]. That is to say, KCOs capable of opening one type or even subtype of K^+ channel might not be able to open other types. Tissue selectivity reduces the potential for unwanted side-effects.

Studies of VD tissues from animal species have demonstrated that the KCOs cromakalim and NS 1619 reduce spontaneous contractions [61] as well as contractions induced by electrical stimulation [62,63]. Another study showed that KCOs were also efficacious relaxants of the isolated normal canine prostate, producing ~80% inhibition of phenylephrine-induced contraction force ; with cromakalim more potent than diazoxide [64]. To our knowledge, neither the effects of different KCOs on human SMC of VD, SV and prostate nor the efficacy of available drugs in treatment of RE are studied.

In the coming years, further characterization of different types and subtypes of K^+ in human ASOs, as well as the human genes encoding these channels, could assist in the development of highly selective KCOs. Even if KCOs have inhibitory effects on the human VD, SV and prostate, it is still unclear whether K^+ channel dysfunction contributes to the pathogenesis of overactive ejaculatory reflex and consequently RE .This hypothesis has not yet been investigated; however, it has been demonstrated recently that BK_{Ca} channel dysfunction, caused by deletion of the gene *mSlo1* for the pore-forming subunit of the BK_{Ca} channel, leads to overactive bladder and urinary incontinence in mice [65]. Urinary bladder and VD both contain phasic SMCs .This could explain the growing evidence supporting the potential use of KCOs in the treatment of overactive bladder [66]. If this is the case in ASOs, this could also explain, at least partially, a mechanism underpinning primary lifelong RE .

Conclusions

The complex biology of SMC of ASOs is becoming clearer. Despite the mounting literature on the biochemistry, physiology and pharmacology of SMC in these organs, the clinical targeting of these cells for improved treatment of RE is still in its infancy. The search for novel agents for the treatment of RE has led to the exploration of many potential targets within the SMC. Before the ongoing pursuit of new agents targeting SMCs, much still remains to be defined regarding the biochemical, physiological, pharmacologic and genetic aspects of SMC of these organs as outlined in Box 1.

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