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].

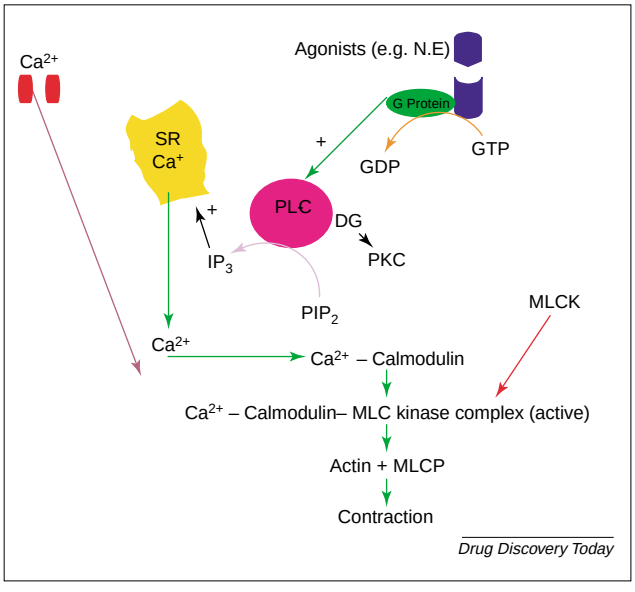

FIGURE 1

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,