Investigation of the Effects of α_1-Adrenoceptor Antagonism and L-Type Calcium Channel Blockade on Ejaculation and Vas Deferens and Seminal Vesicle Contractility In Vitro

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ABSTRACT

Introduction. Premature ejaculation is one of the most common male sexual dysfunctions. Current pharmacological treatments involve reduction in penile sensitivity by local anesthetics or increase of ejaculatory threshold by selective serotonin reuptake inhibitors. α_1-Adrenoceptors (α_1-ARs) and L-type calcium channels are expressed in the smooth muscles of the male reproductive tract, and their activations play an important role in the physiological events involved in the seminal emission phase of ejaculation.

Aim. To evaluate if the inhibition of the contractility of the vas deferens and seminal vesicle by α_1-AR antagonism or the L-type calcium channel blockade can delay ejaculation.

Methods. The effects of the α_1-AR antagonist tamsulosin and of the L-type calcium channel blockers, nifedipine and (S)-(+)-niguldipine, on contractions induced by norepinephrine in the rat vas deferens and seminal vesicles in vitro and on the ejaculation latency of male rats in behavioral mating tests were evaluated.

Main Outcome Measure. Tension development of vas deferens and seminal vesicles in response to norepinephrine in vitro and behavioral mating parameters were quantified.

Results. Tension development of vas deferens and seminal vesicle to α_1-AR activation was significantly inhibited by tamsulosin, nifedipine, and (S)-(+)-niguldipine. Tamsulosin displayed insurmountable antagonism of contractions induced by norepinephrine in the rat vas deferens and seminal vesicle. Ejaculation latency of male rats was not modified by tamsulosin, nifedipine, or (S)-(+)-niguldipine; however, both the number and weight of the seminal plugs recovered from female rats mated with male rats treated with tamsulosin were significantly reduced.

Conclusion. Seminal emission impairment by inhibition of vas deferens or seminal vesicle contractility by L-type calcium channel blockade or α_1-AR antagonism is not able to delay the ejaculation. **de Almeida Kiguti LR and Pupo AS. Investigation of the effects of α_1-adrenoceptor antagonism and L-type calcium channel blockade on ejaculation and vas deferens and seminal vesicle contractility in vitro. J Sex Med 2012;9:159–168.**

Key Words. Premature Ejaculation; Vas Deferens; Seminal Vesicle; Ejaculatory Latency; α_1-Adrenoceptors; L-Type Calcium Channels

Introduction

Premature ejaculation is one of the most common male sexual dysfunctions affecting 5–40% of sexually active men [1–3]. According to the Committee for Definition of Premature Ejaculation of the International Society for Sexual Medicine, lifelong premature ejaculation is a male sexual dysfunction characterized by ejaculation that always or nearly always occurs before or within about 1 minute of vaginal penetration and the inability to delay ejaculation on all or nearly all vaginal penetrations, accompanied by negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy [4]. The pharmacological treatment of premature ejaculation targets the lengthening of the intravaginal ejaculatory latency time, and the current approaches involve the reduction in the penile sensitivity by topic local anesthetic application or the

modulation of ejaculatory threshold by selective serotonin reuptake inhibitors (SSRIs) [5–8]. As a result of the importance of serotonin in the control of the ejaculation, the SSRIs present the best results in the management of premature ejaculation [9,10].

Ejaculation is a complex reflex encompassing sympathetic, parasympathetic, and somatic outputs orchestrated by a spinal ejaculation generator at lumbosacral spinal cord [11]. The viscero-somatic events involved in ejaculation can be divided into two consecutive phases, the seminal emission and expulsion. During the seminal emission phase of ejaculation, the sperm stored in the cauda epididymis and secretions from sexual accessory glands are propelled into the urethra by contractions of the smooth muscles of cauda epididymis, vas deferens, seminal vesicle, and prostate. Then, in the expulsion phase, the semen deposited in the prostatic urethra is ejected through the urethral meatus as a result of rhythmic contractions of striated muscles of the pelvic floor partially triggered by the distention of the urethra [12].

The sympathetic nervous system plays a key role in the seminal emission by releasing norepinephrine, which controls the contractility of the cauda epididymis, vas deferens, prostate, and seminal vesicle through α_1-adrenoceptor (α_1-AR) activation [13]. The importance of α_1-ARs in the seminal emission is demonstrated by the ejaculation impairment resulting from knocking-out the three genes encoding α_1-ARs in mice and by ejaculatory dysfunctions observed during therapeutic management of benign prostatic hyperplasia with α_1-AR antagonists [14,15]. In addition, the contractions of vas deferens, seminal vesicle, and prostate from different species to several different pharmacological stimuli, including norepinephrine, are dependent on extracellular calcium influx through L-type voltage-dependent calcium channels [16–19]. L-Type calcium channels are members of voltage-dependent calcium channel family, which are pharmacologically recognized by their high sensitivity to blockade by a heterogeneous class of organic substances collectively known as calcium channel blockers [20,21].

Because of the involvement of α_1-ARs and L-type calcium channels in the contractions of the vas deferens and seminal vesicle in response to norepinephrine and the importance of these contractions in the physiological events that lead to the emission phase of ejaculation, we hypothesized that the pharmacological antagonism of α_1-ARs and L-type calcium channels would delay ejaculation by reducing the contractions of these organs, representing a potentially new therapeutic strategy for the treatment of premature ejaculation.

Aims

The aims of this study were to determine the effects of tamsulosin, a selective α_1-AR antagonist largely used in the management of low urinary tract symptoms associated with prostatic hyperplasia, and of the dihydropyridine-calcium channel blockers, nifedipine and (S)-(+)-niguldipine, in the contractions of the rat vas deferens and seminal vesicle to norepinephrine in vitro and on the ejaculation latency of male rats in behavioral mating tests. These drugs were particularly chosen to be investigated because it is known that tamsulosin presents an insurmountable-like antagonism of vas deferens contractions induced by norepinephrine in vitro, whereas it is known that (S)-(+)-niguldipine also presents high affinity for α_1-ARs in addition to interact with L-type calcium channels.

Materials and Methods

Animals

The experimental procedures were approved by the local Ethics Committee for the Use of Experimental Animals and are in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health).

Adult male (90–150 days old, 380–450 g) and female (90–120 days old, 200–220 g) Wistar rats were used in this study. Animals were maintained under controlled conditions (25°C, 30% humidity, 12/12-h light/dark cycle) with food and water available ad libitum.

In Vitro Contraction Studies

Adult male rats were killed by decapitation, and seminal vesicles or vasa deferentia were isolated, cleaned of adherent tissues, and mounted in 10-mL organ baths to record isometric tension development. Tissues were maintained under 9.8-mN resting tension in a nutrient solution with the following composition (mM): NaCl, 138; KCl, 5.7; $CaCl_2$, 1.8; NaH_2PO_4, 0.36; $NaHCO_3$, 15; and dextrose, 5.5, prepared in distilled water and maintained at 30°C, pH 7.4, constantly bubbled with 95% O_2/5% CO_2. This nutrient solution is a modified Tyrode's solution optimized to minimize erratic "spontaneous" contractions and, along with the organ bath temperature, improves the contractions of these two smooth muscles (Zuleika P. Picarelli, personal communication).