

ORIGINAL RESEARCH—BASIC SCIENCE

Contractile Changes of the Clitoral Cavernous Smooth Muscle in Female Rabbits with Experimentally Induced Overactive Bladder

Soon-Chul Myung, MD, PhD,* Moo-Yeol Lee, MD, PhD,[†] Shin-Young Lee, MD,*
Seung-Hee Yum, MD, PhD,[‡] Soo-Hyun Park, MA, and Sae-Chul Kim, MD, PhD

*Research Institute for Translational System Biomixs, Chung-Ang University, College of Medicine, Seoul, South Korea;

[†]Department of Physiology, Chung-Ang University, College of Medicine, Seoul, South Korea; [‡]Department of Urology, Chung-Ang University, College of Medicine, Seoul, South Korea

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ABSTRACT

Introduction. Recently, growing clinical evidence has suggested that sexual dysfunction is more prevalent in women with overactive bladder (OAB).

Aims. However, there has been no basic research to clarify the relationship between OAB and female sexual dysfunction. Therefore, we investigated this issue using a rabbit model of OAB.

Methods. Twenty-seven New Zealand white female rabbits were randomly divided into the OAB and control groups.

Main Outcome Measures. The contractile responses of clitoral cavernous strips to K⁺, phenylephrine (PE), Bay K 8644, and endothelin (ET)-1, and the relaxation responses of acetylcholine (ACh), sodium nitroprusside (SNP), and Y-27632 to PE-induced contraction by measuring isometric tension.

Results. The contractile responses to K⁺, PE, Bay K 8644, and ET-1 were significantly more increased in the OAB group in a dose-dependant manner than in the control group ($P < 0.05$), and the responses to ET-1 were more prominent than those to the remaining substances ($P < 0.01$). The increased contractile responses to ET-1 were blocked by BQ123 (ET_A receptor antagonist) but not by BQ788 (ET_B receptor antagonist). Clitoral cavernosal strips from the OAB group were more difficult to relax than those from the control group in terms of ACh- and SNP-induced relaxation ($P < 0.05$). The Y-27632-induced relaxant responses to PE- and ET-1-induced contraction were less prominent in the OAB group than in the control group.

Conclusions. The results of this study provide evidence that female OAB may deteriorate clitoral engorgement, which is associated with a greater force generation by increased calcium sensitization and subsequently decreased of relaxation. The activation of ET and Rho-kinase system may be crucial to negatively effect the clitoral smooth muscle relaxation in experimentally induced OAB animal model. But whether these vasomotor effects are revived in human clitoris is still debatable. **Myung S-C, Lee M-Y, Lee S-Y, Yum S-H, Park S-H, and Kim S-C. Contractile changes of the clitoral cavernous smooth muscle in female rabbits with experimentally induced overactive bladder. J Sex Med 2008;5:1088–1096.**

Key Words. Overactive Bladder; Sexual Dysfunction; Female

Introduction

Recently, growing clinical evidence has suggested a close association between voiding dysfunction and sexual dysfunction. Erectile dysfunction is more prevalent in benign prostate hyperplasia (BPH) patients with lower urinary tract symptoms (LUTS) than in the normal popu-

lations [1,2], and it has been reported that men with relatively mild BPH are more than two times more likely to perform normal coitus than those with severe BPH [3]. In women, abnormalities in sexual function have been closely associated with urinary incontinence and pelvic organ prolapse [4–6]. Some reports have shown that even a history of LUTS seems to enhance the likelihood of

experiencing both arousal and sexual pain disorder [7,8]. Recent data have indicated that OAB with or without incontinence negatively affects women's sexual health, reducing sexual desire and ability to achieve orgasm [9]. Also, OAB is defined as urgency, with or without urge incontinence, usually with frequency and nocturia. However, the causes of sexual derangement have not been elucidated regardless of whether it is due to physiological changes or psychological factors such as pain or anxiety resulting from voiding dysfunction.

An *in vitro* study using a male rabbit model of partial bladder outlet obstruction (PBOO) has proven that the corpus cavernous smooth muscle from rabbits with PBOO produced more force generation and was more difficult to relax than the controls [10]. This suggests that bladder outlet obstruction (BOO) induced by BPH may produce direct physiologic change of the corpus cavernous smooth muscle. However, there has been no basic research to clarify the organic relationship between female voiding dysfunction and sexual dysfunction. Although various factors including emotional and psychological environment have effects on female sexual responses, it is essential for satisfactory intercourse to evoke adequate sexual arousal responses. The clitoris may play a major role in enhancing female sexual responses because clitoral stimulation may induce local autonomic and somatic reflexes causing vaginal vasocongestion and subsequent lubrication of the introital canal, making a sexual act easier and also increasing the level of sexual arousal [11,12]. The neurovascular event that occurs in clitoral sexual responses is similar to penile erection. In the basal state, clitoral cavernous smooth muscles are under contractile tone by norepinephrine. After sexual stimulation, central nervous system activation leads to neurogenic and endothelial release of nitric oxide (NO) resulting in clitoral smooth muscle relaxation and engorgement [11–16].

It is probable that pathophysiologic changes of the female bladder may result in organic/functional changes of the clitoral cavernosal smooth muscle based on the results of a rabbit model with PBOO and neurophysiological similarities between clitoral engorgement and penile erection. This presumption is supported by the data which show a high incidence of sexual arousal disorders in female patients with urodynamic detrusor underactivity or BOO accompanied by combined large amount of residual urine [4].

Various mechanisms have been proposed regarding the association between LUTS and

male sexual dysfunction. These include autonomic hyperactivity/increased sympathetic tone, activation in the Rho-kinase/endothelin (ET) pathway, endothelial dysfunction (nitric oxide synthase [NOS], NO), atherosclerosis-induced pelvic ischemia, and age-related hormone imbalance [1]. However, to date, there has been no basic research to clarify the organic relationship between OAB and female sexual dysfunction while the evidence exists regarding the organic relationship between male BOO and erectile dysfunction.

The aim of this study was to investigate the clitoral vasomotor effects of experimentally induced OAB through the assessment of changes of vascular reactivity to various vasoactive agents in rabbit.

Materials and Methods

Animal Preparation and Induction of OAB

A total of 27 New Zealand white female rabbits (around 2.5 kg) were randomly divided into the control (N = 16) and OAB groups (N = 11). To develop bladder overactivity, we applied the same method described by Chuang et al. [17]. The intravesical administration of low-dose protamine sulfate (PS) compromised urothelial barrier, and subsequent potassium chloride (KCl) infusion produced irritative effects (intercontraction interval decreased) [17]. The bladder was catheterized with an 8-Fr Foley catheter under local anesthesia by intramuscular injection of ketamine (30 mg/kg) and xylazine (0.15 mg/kg). The OAB group was treated with an intravesical administration of 60 mL of 10 mg/mL PS for 1 hour, followed by 60 mL of 200 mM KCl for 1 hour. The control group was treated only with an intravesical instillation of 60 mL of normal saline for 1 hour. The same procedures were repeated six times at 3-day intervals for three consecutive weeks. A urothelial damage was confirmed by histology 12 hours after the last intravesical instillation of PS (Figure 1). The study received an Institutional Review Board approval from Chung-Ang University.

Isolation and Preparation of Rabbit

Clitoral Cavernosum

All strips were obtained within 2 days after the last treatment. Rabbit clitoris was removed with the surrounding tissue including the crus, and was placed in 100% oxygen-saturated 2-[4-(2-hydroxyethyl)-1-piperazinyl] ethanesulfonic acid (HEPES)-buffered physiological saline solution

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