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ORIGINAL BASIC SCIENCE ARTICLE

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Effect of a 5-HT2c receptor agonist on urethral closure mechanisms in female rats

Mifuka Ouchi RPT, MS[1,2] | **Takeya Kitta MD, PhD[1]** | **Yukiko Kanno MD, PhD[1]** | **Madoka Higuchi MD[1]** | **Mio Togo MLT[1]** | **Kimihiko Moriya MD, PhD[1]** | **Nobuo Shinohara MD, PhD[1]**

[1] Department of Renal and Genitourinary Surgery, Graduate School of Medicine, Hokkaido University, Sapporo, Japan

[2] School of Rehabilitation Sciences, Health Sciences University of Hokkaido, Tobetsu, Japan

Correspondence
Takeya Kitta, MD, PhD, Department of Renal and Genitourinary Surgery, Graduate School of Medicine, Hokkaido University, Sapporo, Japan.
Email: kitta@fb3.so-net.ne.jp

Aims: The serotonin (5-HT2c) receptor is known to be involved in the mechanism of urethral closure in a model of stress incontinence. Lorcaserin (Belviq®) has received Food and Drug Administration approval for the treatment of obesity. However, it is unclear whether this selective 5-HT2c receptor agonist enhances urethral closure in stress urinary incontinence (SUI) models. Therefore, we investigated whether lorcaserin could enhance urethral closure in female rats with vaginal distention (VD).

Methods: Normal female rats and rats with stress incontinence induced by VD were tested. We evaluated the effect of a single dose of lorcaserin (0.03, 0.3, or 0.9 mg/kg with cumulative administration) on the urethral pressure amplitude during electrical stimulation (A-URE) and on the urethral baseline pressure (UBP). The manual compression-induced leak point pressure (LPP) was also measured.

Results: In VD rats, a single intravenous injection of lorcaserin (0.3 and 0.9 mg/kg) significantly increased both A-URE and LPP compared to saline ($P < 0.05$). In normal rats, intravenous lorcaserin (0.3 and 0.9 mg/kg) also significantly increased A-URE and LPP compared to saline ($P < 0.05$). The changes of A-URE and LPP, which are parameters of active urethral closure, were significantly larger in normal rats than in VD rats.

Conclusions: We showed that lorcaserin can activate the external urethral sphincter and pelvic floor muscles, suggesting an influence on active closure mechanisms. 5-HT2c receptors agonists may have dual effects in patients with SUI, not only by reducing obesity but also by enhancing active urethral closure.

KEYWORDS
5-HT2c receptor agonist, active urethral closure mechanism, lorcaserin, stress urinary incontinence

Karl-Erik Andersson led the peer-review process as the Associate Editor responsible for the paper.

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1 | INTRODUCTION

Stress urinary incontinence (SUI) is defined as involuntary leakage of urine related to an increase of the intra-abdominal pressure by effort, exertion, or sneezing during the storage phase. Twenty-five percent of women over 20 years old have urinary incontinence, with half of them having SUI alone and 36% having SUI combined with urge incontinence.[1] Thus, SUI is the most common type of urinary incontinence. Overweight and obesity are important risk factors for urinary incontinence according to an epidemiological study,[2] and weight loss achieved by surgical or conservative approaches is effective for incontinence symptoms. However, an effective treatment for SUI has not yet been found. A recent review focusing on neurophysiological mechanisms in the control of urethral closure provided information suggesting there may be potential pharmacological approaches to treatment of SUI.[3] Noradrenergic and serotonergic pathways are considered to play an important role in maintaining urethral closure.[4] 5-Hydroxytryptamine 2c (5-HT2c) receptors are distributed in the central nervous system, and 5-HT2c receptor agonists have been used for regulation of substance abuse and food intake.[5,6] Interestingly, serotonergic pathways enhance the activity of excitatory spinal interneurons that form synapses with motoneurons in Onuf's nucleus, or directly activate motoneurons in Onuf's nucleus via 5-HT2c receptors to maintain active urethral closure (Figure 1).[7] In 2012, lorcaserin (Belviq®) received approval from the United States Food and Drug Administration (FDA) for treatment of obesity. The 5-HT2c receptor is also one of the potential targets for pharmacotherapy in SUI.[3] Previous research has revealed that motoneurons are directly activated through the 5-HT2c receptor to maintain active urethral closure.[7] However, whether 5-HT2c agonists enhance urethral closure by stimulating pudendal nerves via 5-HT2c receptors in Onuf's nucleus remains unknown. Therefore, this study was performed to investigate whether lorcaserin enhances urethral closure in female rats with vaginal distention (VD).

2 | MATERIALS AND METHODS

2.1 | Animals

A total of 31 Sprague-Dawley female rats (12-14 weeks old and weighing 252-302 g) were used. Rats were randomly assigned to the following groups: VD rats ($n = 7$) and normal rats ($n = 9$) for measurement of LPP, as well as VD rats ($n = 9$) and normal rats ($n = 6$) for urethral pressure measurements. Animals were treated in accordance with the National Institutes of Health animal care guidelines. All experiments were approved by our institute Animal Experimentation Committee.

2.2 | Vaginal distention

The following experiments were carried out to study the acute effects of lorcaserin on urethral closure mechanisms. Rats were injected intraperitoneally with pentobarbital (30 mg/kg) before undergoing VD.[3] Then a 14-Fr Foley balloon catheter (Cliny, Yokohama, Japan) with the tip cut off was inserted into the vagina, and the vaginal orifice was closed with a suture to prevent the catheter from slipping out. The balloon was dilated with 4 mL of water for 4 h to cause impairment of urethral closure.[8]

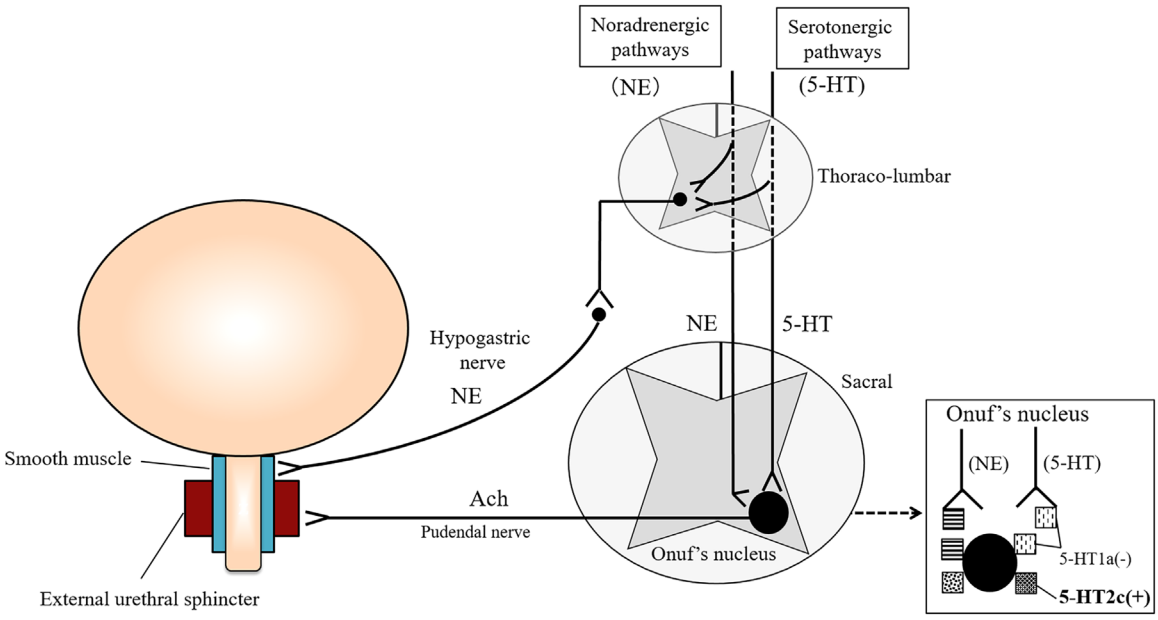


FIGURE 1 The noradrenergic and serotonergic pathways from Onuf's nucleus involved in urethral closure

2.3 | Urethral pressure measurement

The surgical procedures for assessment of urethral function were similar to those described previously.[9] Four days after VD, urethral pressure measurement was conducted. Both ureters were ligated, and the vesical branches of the pelvic nerves were transected bilaterally near the internal iliac vessels to abolish reflex bladder contractions. A 3.5 Fr nylon SPR-524 catheter (Millar Instruments, Houston, TX) with a side-mounted microtransducer 1 mm from the tip was inserted into the middle urethra at 12.5-15 mm from the urethral orifice. This microtransducer-tipped catheter was connected to a pressure control unit (PCU-2000, Millar Instruments). Urethral responses were recorded on a computer system with chart data acquisition software at a sampling rate of 400 Hz using a Power Lab® analog-to-digital converter (AD Instruments, Nagoya, Japan). The catheter position was monitored throughout the experiments to confirm that the transducer did not move. The exposed oblique abdominal muscles were stimulated with an electrical stimulator (SEN-3301; Nihon Kohden, Tokyo, Japan) and an isolator (SS-104J; Nihon Kohden). Electrical stimulation with a duration of 0.5 ms at 20 ms intervals was repeated every 10 s, with a stimulus intensity of 5 V (Figure 2). In preliminary study, there was no significant change of abdominal pressure during electrical stimulation (data not shown). The amplitude of the urethral response to electrical stimulation (A-URE) was measured, as well as the urethral baseline pressure (UBP). A-URE was determined as the maximal pressure change from baseline in cmH_2O. UBP was determined from a flat section of the pressure recording just before the response to electrical stimulation.[10] To insert the electrodes for electrical stimulation, bilateral incisions were made near the 11-13th ribs to provide access to the oblique abdominal muscles. During measurement, rats were placed in the supine position and were under anesthesia with urethane (Wako Pure Chemical Industries, Ltd., Osaka, Japan). After administration of 1.1 g/kg intravenously, additional doses of the anesthetic (0.1 g/kg) were administered as required before electrical stimulation to achieve a sufficient depth of anesthesia, as confirmed by a negative toe pinch reflex response. The final dose of urethane was 1.1 g/kg.

2.4 | Measurement of LPP

Four days after VD, we evaluated urethral function by measuring the leak point pressure (LPP).[10] PE-50 polyethylene tubing (Becton Dickinson™) was inserted into the bladder dome and the bladder dome was ligated around the tubing with 4-0 nylon sutures. Then the tubing was connected to a pressure transduce to record the intravesical pressure. The ureters and pelvic nerves were treated by the same procedure as for measurement of the urethral pressure response. After the bladder was emptied, 0.4 ml of saline solution containing Evans blue (Wako Pure Chemical Industries, Ltd.) (100 μg/ml) was inserted. The LPP was measured ten times in each rat by using manual abdominal compression. Pressure was slowly applied to the abdominal wall manually until leakage occurred at the urethral orifice, and then compression was immediately stopped. The peak pressure was measured by the intravesical catheter.[11] The increase of LPP was assessed on a computer system with chart data acquisition software at a sampling rate of 400 Hz, employing a PowerLab® analog-to-digital converter and an amplifier (AP-601G; Nihon Kohden).

2.5 | Injection of lorcaserin

Lorcaserin (Belviq®, Eisai Inc.) was dissolved in 0.9% saline (0.03, 0.3, or 0.9 mg/kg) before use. Saline (1 ml/kg) was

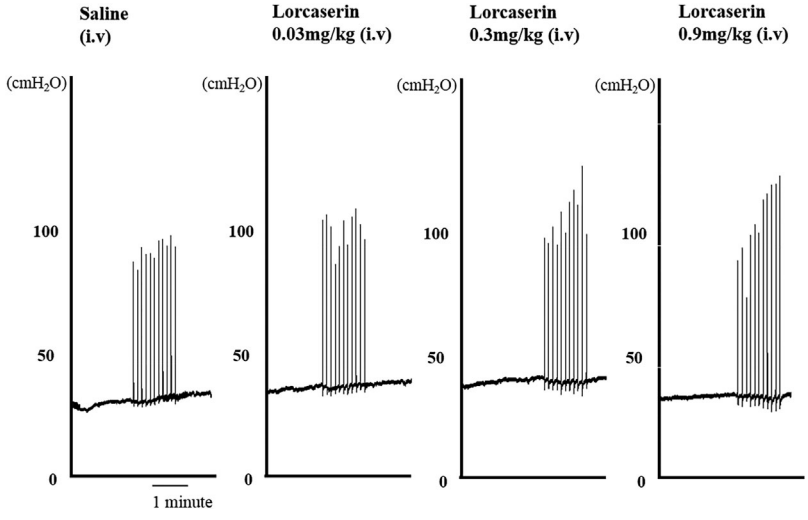


FIGURE 2 Representative traces of changes in the urethral pressure amplitude during electrical stimulation (A-URE) and changes of the baseline urethral pressure (UBP) induced by sequential intravenous administration of saline and lorcaserin (0.03, 0.3, and 0.9 mg/kg)

administered as the vehicle control. A polyethylene catheter (PE-50) was inserted for intravenous injection of the test drugs. Lorcaserin was injected cumulatively at 0.03, 0.3, and 0.9 mg/kg.[6] The A-URE, UBP, and LPP were measured at 5-10 min after administration of each dose.[12]

2.6 | Statistical analysis

Results are shown as the mean ± SE. Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS) 23.0J for Macintosh (IBM, Armonk, NY). The mean ± SE was calculated for each group of rats. Statistical analysis was carried out by using repeated measures ANOVA, followed by Tukey's multiple comparison test to compare changes of A-URE, UBP, and LPP at each dose of lorcaserin. In all analyses, $P < 0.05$ was considered significant.

3 | RESULTS

In VD rats, there was a significant decrease of all parameters, including A-URE, UBP, and LPP, compared to normal rats (all $P < 0.05$). A-URE showed a significant difference between VD rats and normal rats, being 14.4 ± 2.9 and 49.4 ± 4.7 cmH_2O, respectively ($P < 0.05$). UBP was 20.4 ± 1.2 cmH_2O in VD rats compared with 32.3 ± 1.7 cmH_2O in normal rats ($P < 0.05$). There was a significant reduction of LPP in VD rats compared to normal rats, 24.7 ± 4.2 cmH_2O versus 41.1 ± 2.4 cmH_2O, respectively ($P < 0.05$).

In 9 VD rats, a single intravenous injection of lorcaserin (0.3 and 0.9 mg/kg) significantly increased A-URE and UBP compared to injection of saline or lorcaserin at 0.03 mg/kg ($P < 0.05$) (Table 1). In VD rats, lorcaserin (0.3 mg/kg) significantly increased A-URE by 18.5%, compared to saline ($P < 0.05$). The high dose of lorcaserin (0.9 mg/kg) significantly increased A-URE by 21.6% compared to saline ($P < 0.05$).

In 7 normal rats, lorcaserin (0.3 and 0.9 mg/kg) significantly increased A-URE and UBP compared to saline or lorcaserin at 0.03 mg/kg ($P < 0.05$). In normal rats, lorcaserin (0.3 mg/kg) significantly increased A-URE by 30.1% compared to saline ($P < 0.05$). The high dose of lorcaserin (0.9 mg/kg) significantly increased A-URE by 43.2% compared to saline ($P < 0.05$).

In VD rats, the mean LPP after injection of saline or lorcaserin at 0.03, 0.3, or 0.9 mg/kg was 24.7 ± 4.2, 26.6 ± 3.5, 29.8 ± 3.2, and 31.3 ± 3.3 cmH_2O, respectively (Figure 3). There was a significant increase of LPP with lorcaserin at saline versus 0.3 and 0.9 mg/kg and the lowest dose of lorcaserin (0.03 mg/kg) versus 0.3 and 0.9 mg/kg ($P < 0.05$). In normal rats, mean LPP after injection of saline and each dose of lorcaserin was 41.1 ± 2.4, 42.6 ± 2.6, 51.3 ± 3.2, and 54.1 ± 2.7 cmH_2O, respectively. Lorcaserin (0.3 and 0.9 mg/kg) caused a significant increase of LPP compared to saline ($P < 0.05$).

4 | DISCUSSION

The present study showed that lorcaserin, a selective 5-HT2c receptor agonist, significantly increased both LPP and A-URE in a female rat VD model. These findings supported our hypothesis that the 5HT-2c receptor enhances active urethral closure in SUI model rats.

We found that the intravenous injection of lorcaserin (0.3 and 0.9 mg/kg) significantly increased the A-URE compared to saline (the vehicle) in VD rats. It was previously reported that 5-HT2c receptors in Onuf's nucleus are involved in the mechanism of active urethral closure in the serotonergic pathway for sneeze-induced urethral continence.[7] However, to our knowledge, there have been no investigations into the effect of 5-HT2c receptor agonists on urethral closure in an SUI model. There are seven main types of 5-HT receptor and fourteen different subtypes.[13,14] In rats and humans, serotonin-producing neurons in the raphe nuclei are distributed from the caudal pons to the caudal portion of the medulla oblongata, and send projections to the caudal brainstem and the spinal cord.[15,16] A previous study showed that a 5-HT2b/2c agonist increased the urethral pressure response during sneezing (A-URS) by 33.6% in normal rats, while a 5-HT2c antagonist reduced the response, suggesting that some 5-HT receptors subtypes, especially 5-HT2c, contribute to modulation of the sneeze-induced continence reflex.[7] Our present data suggest that a selective 5-HT2c receptor agonist could reinforce active urethral mechanisms for preventing leakage of urine.

We measured the LPP, which represents the threshold bladder pressure causing leakage of urine due to increased intra-abdominal pressure, to assess the integrity of urethral function. Similar to the A-URE, we showed that LPP was significantly increased by intravenous injection of lorcaserin (0.3 and 0.9 mg/kg) compared to saline in VD rats. In a previous study, the sneeze-induced LPP increased by 12.8 cmH_2O after injection of a 5-HT2b/2c agonist in VD rats.[7] Our results demonstrated that descending bulbo-spinal serotonergic pathways enhance the activity of spinal excitatory interneurons in Onuf's nucleus via the 5-HT2c receptor to promote active urethral closure.[4]

We found that A-URE was significantly lower in VD rats than in normal rats, and the LPP in response to manual compression was also significantly lower in VD rats compared to normal rats. The urethral pressure is mediated by contraction of the external urethral sphincter and the pelvic floor muscles under control of the pudendal nerves and somatic nerves.[8] The changes of A-URE and LPP observed in the present study were

TABLE 1 Changes of A-URE and UBP (mean ± SE) in VD rats and normal rats

	Mean ± SE A-URE (cmH_2O)	Mean ± SE UBP (cmH_2O)
VD		
Saline	14.4 ± 2.9	20.4 ± 1.2
Lorcaserin 0.03	14.6 ± 3.3	22.3 ± 1.7
Lorcaserin 0.3	17.0 ± 3.4[a,b]	24.9 ± 2.1[a]
Lorcaserin 0.9	17.5 ± 3.7[a,b]	25.4 ± 2.4[a]
Normal		
Saline	49.4 ± 4.7	32.3 ± 1.7
Lorcaserin 0.03	60.0 ± 5.6	33.8 ± 2.7
Lorcaserin 0.3	64.3 ± 3.4[a]	35.5 ± 2.7[a]
Lorcaserin 0.9	72.3 ± 4.6[a]	31.7 ± 2.1

[a]Significant difference versus saline in each group ($P < 0.05$).
[b]Significant difference versus lorcaserin at 0.03 mg/kg in each group ($P < 0.05$). A-URE, the urethral pressure amplitude during electrical stimulation; UBP, the urethral baseline pressure; VD, vaginal distention; SE, standard error.

consistent with previous reports,[4,17–19] confirming that our rat model of SUI was appropriate. It is assumed that VD reduced blood flow to the urethra and caused hypoxia of the urogenital organs, thus damaging the peri-urethral striated muscle[20] and resulting in decreased active urethral closure.

The maximum urethral closure pressure (MUCP) is 43% lower in SUI patients compared to women without urinary symptoms.[21] In the present study, the UBP was lower in VD rats than in normal rats, resulting in earlier leakage from the urethral orifice during manual abdominal compression. These findings were in accordance with a previous report that the urethral pressure of VD rats was decreased during sneezing.[8] VD can damage the urethral sphincter, ligaments, and nerves contributing to UBP, resulting in impaired static closure at the mid urethra in the present SUI model.

The changes of A-URE and LPP after lorcaserin injection were significantly larger in normal rats than VD rats. These results were consistent with our previous study, which indicated that combined administration of an alpha 2-adrenoceptor antagonist could enhance the efficacy of serotonin and norepinephrine reuptake inhibitors for SUI in rats.[9] In this model, muscular and neural damage around the urethra could impair the effects of neurotransmitters at synapses such as neuromuscular junctions.

In this study, we investigated the potential of applying lorcaserin, which has already been approved for weight loss in obese adults (BMI ≥ 30.0 kg/m^2) to treat patients with SUI. The hypothalamus is composed of several nuclei that integrate peripheral signals, such as those related to adiposity and calorie intake, to control food intake.[5] Lorcaserin is a selective 5-HT2c receptor agonist that was recently approved for weight loss.[22] Smith et al[22] conducted a double-blind clinical trial, which showed that 47.5% of overweight adults in the lorcaserin group lost 5% or more of their body weight at 1 year versus 20.3% of

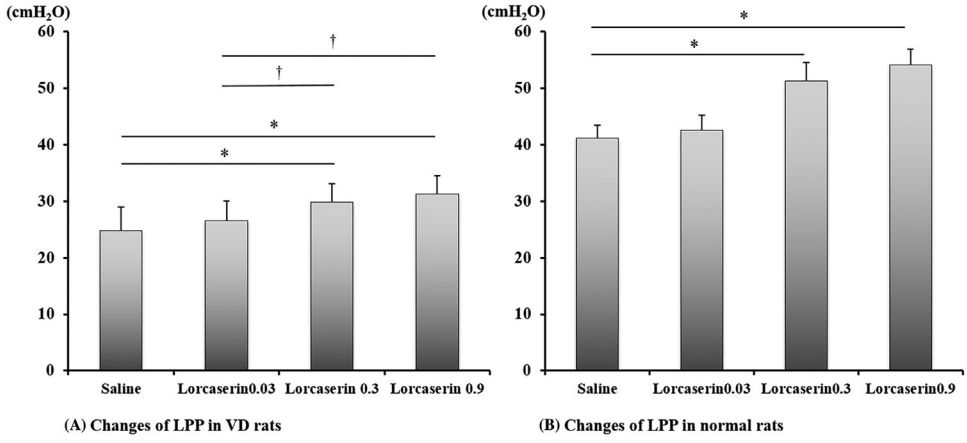


FIGURE 3 Changes of LPP after injection of lorcaserin in VD rats and normal rats. Significantly different versus saline in each group ($P < 0.05$). †Significantly different versus lorcaserin 0.03 in each group ($P < 0.05$). LPP, leak point pressure

the placebo group ($P < 0.001$).[23] Nausea and malaise are the main side effects reported for lorcaserin in clinical use, especially at supratherapeutic doses.[24] Provided consideration is paid to potential minor side effects, the antiobesity effect of lorcaserin could be advantageous in obese patients with SUI.

Considering other pharmaceutical agents that could act on urethral function, duloxetine or idazoxan (an alpha2-adrenoceptor blocker) and propiverine (a noradrenaline reuptake inhibitor) have been reported to improve urethral closure.[9,25] However, serotonin norepinephrine reuptake inhibitors (SNRIs) have adverse effects, including a higher risk of attempted suicide. Currently, duloxetine is not approved for SUI by the FDA. Thus other mechanisms may be effective for SUI, but an appropriate dose of lorcaserin could be used for SUI with fewer adverse effects.

The invasive surgical procedures are generally employed for correcting SUI, so more effective pharmacological approaches are needed. Lorcaserin improved the contractility of peri-urethral muscles in VD rats and normal rats, and seems to have favorable properties as an agent for treating SUI since it increased urethral resistance against intra-abdominal pressure. Lorcaserin may have two beneficial mechanisms for patients with SUI. First, lorcaserin can contribute to significant weight loss, which is important since obesity is the predominant risk factor for SUI.[22] Second, it can enhance active urethral closure in response to increased intra-abdominal pressure by activating pudendal nerves and somatic nerves via 5-HT2c receptors in Onuf's nucleus.

Some limitations of this study need to be considered. First, it is possible that supraspinal regions were influenced by lorcaserin. Second, we did not assess the long-term effect of lorcaserin on urethral function. Third, we did not examine if 5-HT2c antagonist inhibit lorcaserin-induce effects. Fourth, we could not determine precise location to be activated by lorcaserin. Further studies are needed in order to identify precise site actions, such as peripheral, lower spinal or supra spinal level.

5 | CONCLUSIONS

The 5-HT2c receptor agonist lorcaserin may have dual mechanisms of action on SUI, including an anti-obesity effect and promotion of active urethral closure. The present study suggested that lorcaserin increased contraction of the external urethral sphincter and pelvic floor muscles, suggesting an influence on active urethral closure mechanisms.

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CONFLICTS OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

MO contributed for data collection or management, data analysis, and manuscript writing/editing. TK contributed for protocol/project development, manuscript writing/editing. YK, MH, MT, KM, and NS contributed for manuscript writing/editing

ORCID

Mifuka Ouchi http://orcid.org/0000-0001-9535-1185

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