

## THE EFFECT OF 5-HT<sub>2C</sub> RECEPTOR AGONIST ON URETHRAL CLOSURE MECHANISM IN FEMALE RATS AFTER VAGINAL DISTENSION

### Hypothesis / aims of study

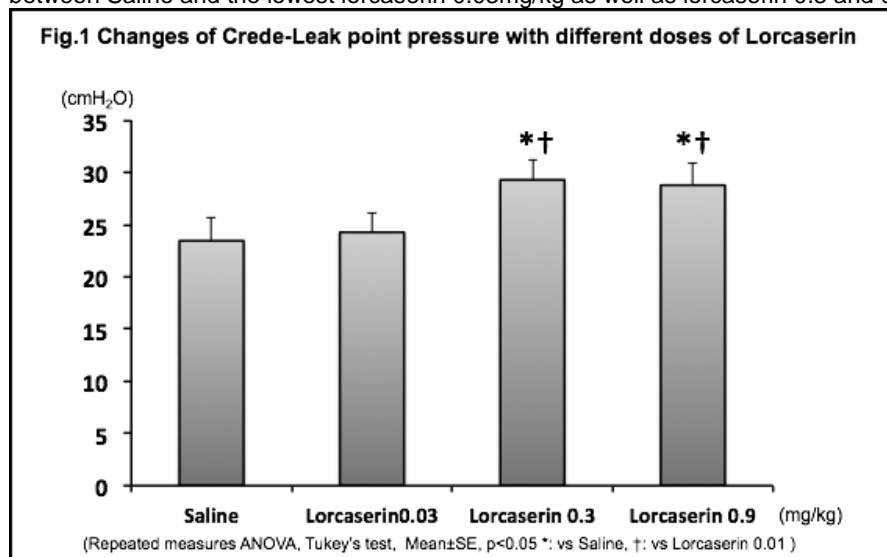
Stress urinary incontinence (SUI) is defined as the complaint of involuntary leakage on effort, exertion or sneezing to increase in intra-abdominal pressure during storage phase. SUI is the most common condition among urinary incontinence, and overweight and obesity are important risk factors for urinary incontinence from epidemiological studies. Weight loss by surgical and more conservative approaches is effective to decrease urinary incontinence symptoms. The more diversity of treatment to improve SUI is required to provide tailor-made pharmacological alternatives for heterogeneous population. Noradrenergic and serotonergic pathways is considered to play an important role in maintaining urethral resistance (ref 1). Urethral closure was enhanced activated motoneurons through alpha1-adrenergic and 5-(hydroxytryptamine: HT) 2C receptors which directly innervate external urethral sphincter and pelvic floor muscles in Onuf's nucleus. Pharmacological treatment the lorcaserin (Belviq) received Food and drug Administration approval for the treatment of obesity in the United States in 2012. Also a 5-HT<sub>2c</sub> agonist is currently used for patients with muscular hyperalgesia, several drug-self administration. The previous research revealed that directly activate motoneurons through 5-HT<sub>2c</sub> receptor, maintaining the active urethral closure mechanisms. However, the effect that 5-HT<sub>2c</sub> agonist enhances urethral closure mechanism due to stimulate pudendal nerve through 5-HT<sub>2c</sub> receptor at Onuf's nucleus remains unknown. The aims of this study is to investigate whether lorcaserin enhances urethral closure mechanism in female rats with vaginal distention (VD).

### Study design, materials and methods

Sprague-Dawley female rats (12 weeks old) weighing 258-291g were used. Rats randomly assigned to vaginal distention (n=4-5). The following experiments were carried out to study the effects of acute lorcaserin administration on urethral closure mechanism. Before VD (ref 2) operation, rats were injected pentobarbital anesthesia intraperitoneally (30mg/kg). 10-Fr Foley balloon catheter 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 off. The balloon catheter was dilated with 4mL water in the vagina for 3 hours for urethral closure dysfunction. Four days after VD, we evaluated urethral function with leak point pressure induced by manual abdominal compression (crede-LPP) (ref 3). After the bladder was emptied, 0.3ml saline solution containing Evans blue (100µg/ml) was injected. Manual pressure was slowly applied vertically to abdominal wall till the leakage occurred at urethral orifice, then removed immediately. Regarding drug preparation, lorcaserin was dissolved in saline (0.3mg/kg) before testing. Saline (1 ml/kg) was administrated as the control vehicle. In the experiment of the crede LPP, rats were placed under urethane anesthesia (1.1g/kg). A polyethylene catheter (PE-50) was inserted for the intravenous injection of Saline, lorcaserin 0.03, 0.3 and 0.9 mg/kg. Five minutes after injection, the crede LPP was measured. The data was shown as the mean ± SE. All data were analyzed using SPSS. Statistical analysis were carried out by using the repeated measures ANOVA and Tukey's test with p <0.05 considered significant.

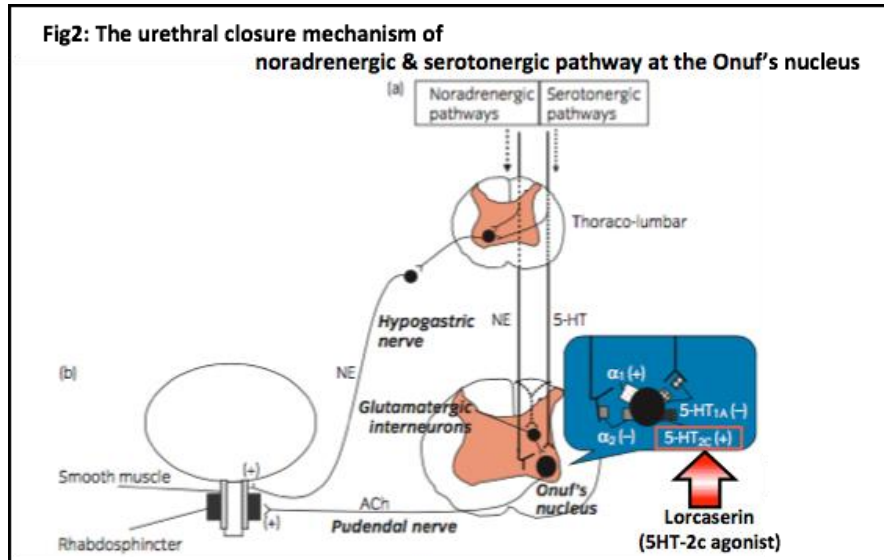
### Results

The changes of crede-LPP with different doses of lorcaserin were shown in Figure 1. The doses of injection were conducted in 4 conditions as follows: Saline (n=5) as control vehicle, lorcaserin 0.03 (n=5), 0.3 (n=5) and 0.9 mg/kg (n=4). Acute lorcaserin caused a significant effect increasing bladder pressure during manual compression with the 0.3 and 0.9 mg/kg compared with saline (\*: p<0.05) and lorcaserin 0.03mg/kg (†: p<0.05). The mean bladder pressure with saline, lorcaserin 0.03, 0.3, 0.9 mg/kg were 23.5 ± 2.2, 24.3 ± 1.9, 29.3 ± 1.8 and 28.8 ± 2.1 cmH<sub>2</sub>O in female rats, respectively. However, there were no differences between Saline and the lowest lorcaserin 0.03mg/kg as well as lorcaserin 0.3 and 0.9 mg/kg.



### Interpretation of results

Our results show that treatment with lorcaserin, a selective 5-HT<sub>2c</sub> agonist, significantly increased LPP in female rats after VD. Since the lorcaserin increased in LPP dose-dependently, it might suggest that 5-HT<sub>2c</sub> enhances the urethral closure mechanism in these rats. Lorcaserin is a selective 5-HT<sub>2c</sub> receptor agonist that recently received the FDA approval for weight loss. A previous study has also clarified 5HT receptors subtypes that contribute to the modulation of the sneeze-induced continence reflex. Figure 2 demonstrates that descending bulbo-spinal serotonergic pathways enhance activity of spinal excitatory interneurons in Onuf's nucleus through 5-HT<sub>2c</sub> receptors, thereby maintaining the sneeze-induced active urethral closure mechanisms, while 5HT<sub>1A</sub> receptor stimulation can inhibit activity (ref1). Therefore, the findings in the present study may suggest an important role for 5-HT<sub>2c</sub> receptors in active urethral mechanism. In addition, 5-HT<sub>2c</sub> may have double mechanisms for SUI patients. It is possible that 5-HT<sub>2c</sub> can contribute to not only losing body weight, but also enhancing active urethral closure at increased intra-abdominal pressure. Further research is warranted to determine the possible efficacy of lorcaserin on the urethral baseline pressure and the amplitude of urethral response in order to confirm the urethral function.



### Concluding message

We showed that lorcaserin may effect on the external urethral sphincter and pelvic floor muscles that are innervated by pudental nerve from Onuf's nucleus in female rat after VD, suggesting the involvement of 5-HT<sub>2c</sub> receptors in active closure mechanism.

### References

1. 2009. 297(4):F1024-31.
2. 2007. 292(4):F1229-37.
3. 2004. 287(3):F434-41.

### Disclosures

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