

EFFECT OF SELECTIVE ANDROGEN RECEPTOR MODULATOR (SARM), GSK2849446A ON STRESS URINARY INCONTINENCE AND BLADDER ACTIVITY IN RATS WITH OVARIECTOMY-INDUCED ESTROGEN DEFICIENCY

Hypothesis / aims of study

Stress urinary incontinence (SUI) is common in post-menopausal women. Although the aetiology of SUI in women is multifactorial, estrogen deficiency due to menopause is one of the major causes of SUI that induces atrophic and degenerative changes in urethral and pelvic floor muscles. Selective androgen receptor modulators (SARMs) selectively stimulate anabolic pathways of the androgen receptor in muscle and bone while sparing the androgenic effects typically seen with steroidal androgens. In this study, we examined the effect of a SARM (GSK2849466A) on the urethral continence mechanisms in a rat model of SUI induced by bilateral ovariectomy (OVX).

Study design, materials and methods

Female nulliparous Sprague-Dawley rats with bilateral OVX were used. Rats were divided into 4 groups; sham operated (sham), vehicle-treated OVX (OVX-V), low dose GSK2849466A-treated OVX (0.005 mg/kg/day, p.o., OVX-low SARM) and high dose GSK2849466A-treated OVX (0.03mg/kg/day, p.o., OVX-high SARM) groups. At 2 weeks after OVX, vehicle or SARM treatments were started. After 4 weeks of treatments (6 weeks after OVX), rats were subjected to the evaluation of sneeze-induced continence reflex using microtransducer-tipped catheter methods, sneeze-induced leak point pressure (S-LPP) and continuous cystometry measurements. Histological analyses of urethral tissues using HE and Trichrome staining were performed only for the high dose group (OVX-high SARM).

Results

(1) At 6 weeks after OVX, rats had significantly greater body weight than age matched sham group. In contrast, OVX-V and OVX-low SARM groups had significantly lower uterine weight than the sham group (228, 266 and 636 mg, respectively), but uterine weight in the OVX-high SARM group was significantly higher (800 mg) than in the OVX-V and the OVX-low SARM groups. Bladder weight in the OVX-high SARM group was significantly higher than in the OVX-V group (140 vs. 96 mg).

(2) Urethral baseline pressure (UBP) was significantly decreased in the OVX-V group by 46%, compared to the sham group (19.8 ± 2.0 vs. 36.8 ± 4.8 cm H₂O). The amplitude of urethral responses during sneezing (A-URS) was also significantly decreased in the OVX-V group by 38% compared to the sham group (40.3 ± 5.4 vs. 65.3 ± 7.4 cm H₂O). In the OVX-low SARM group (n=6), UBP was significantly increased by 122% (44.1 ± 2.2 cm H₂O) compared to the OVX-V group. In the OVX-high SARM group (n=11), UBP and AURS were significantly increased by 96% (38.9 ± 5.4 cm H₂O) and 102% (81.7 ± 10.9 cm H₂O), respectively, compared to the OVX-V group. (Fig. 1A, B)

(3) In S-LPP measurements, the sham group did not leaked during sneezing. In this group, mean intravesical pressure was 110.7 ± 7.4 cmH₂O during sneezing. However, fluid leakage was observed with S-LPP values of 59.8 ± 9.5 cmH₂O during sneezing in all rats of the OVX-V group (n=8). In OVX-low SARM group, fluid leakage during sneezing was observed in 7 of 9 rats (78%) and mean S-LPP in these 7 incontinent rats was 67.4 ± 3.0 cm H₂O. In the OVX-high SARM group (n=8), only 1 rat (12.5%) showed fluid leakage during sneezing with the S-LPP value at 82.9 cm H₂O. (Fig. 1C)

(4) In the OVX-high SARM group, hypertrophy and reversal of atrophy of striated and smooth muscles in urethral transverse sections were observed compared to the OVX-V group.

(5) In cystometry measurements, there were no significant differences in any of parameters including maximum contraction pressure, intercontraction interval, voiding efficiency and bladder compliance among 4 groups.

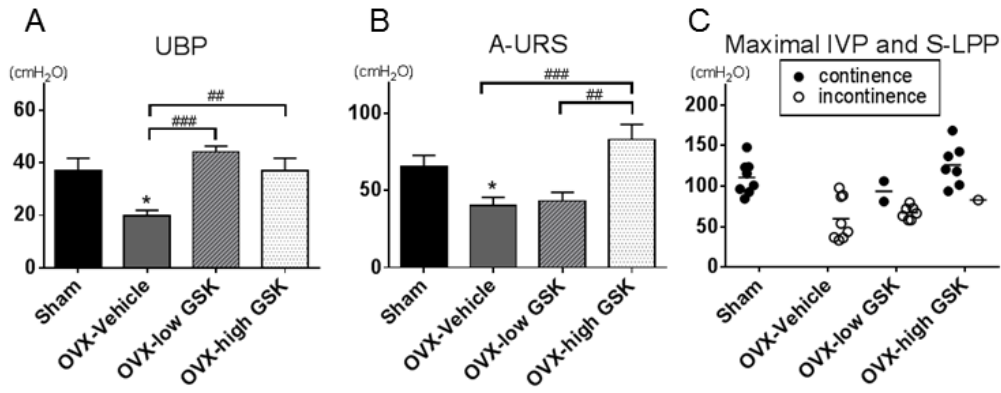
Interpretation of results

These results indicate that; (1) OVX significantly impairs urethral continence function after 6 weeks to induce SUI during sneezing, (2) the low-dose SARM treatment, which only restores the reduction in UBP without affecting A-URS, partially prevented SUI during sneezing, (3) the high-dose SARM treatment, which restores the reductions in UBP and A-URS accompanied with urethral muscle hypertrophy, more effectively prevented SUI during sneezing, and (4) SARM treatment does not affect bladder function in sham or OVX rats. Based on our previous studies, UBP and A-URS predominantly reflect urethral smooth and striated muscle activity, respectively, in rats [1]. Thus, these results suggest that the effects of SARM treatment are dose-dependent and have two phases to restore smooth muscle-related urethral function (=UBP) first at a low dose and then striated muscle-related urethral function (=A-URS) at a high dose.

Concluding message

The treatment with SARMs could be an effective modality for the treatment of SUI without affecting bladder function by enhancing smooth and striated muscle mediated urethral function under stress conditions such as sneezing.

Figure 1.



IVP: intravesical pressure

* p<0.05 vs. sham group. Dunnett's multiple comparisons test.

p<0.01, ### p<0.001. Tukey's multiple comparisons test.

References

1. Effects of ovariectomy and estrogen replacement on the urethral continence reflex during sneezing in rats. *Journal of Urology*, 186: 1517-1523, 2011

Disclosures

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