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EFFECTS OF DULOXETINE, NOREPINEPHRINE AND SEROTONIN REUPTAKE INHIBITOR, ON THE SNEEZE-INDUCED URETHRAL CONTINENCE REFLEX IN RATS

Hypothesis / aims of study

Stress urinary incontinence (SUI) is the most common type of urinary incontinence in women. Duloxetine, a norepinephrine (NE) and serotonin reuptake inhibitor, has demonstrated clinical efficacy in the treatment of SUI,[1] but the precise mechanisms for improving continence during stress conditions has not been fully clarified. We have previously established a rat model that can examine the active urethral closure mechanism during the sneeze reflex that is mediated by somatic nerve-induced reflex contractions of external urethral sphincter and pelvic floor striated muscles.[2] We therefore investigated the effect of duloxetine on the sneeze induced continence reflex using this model. Further, in order to clarify the role of noradrenergic and serotonergic pathways in the active pressure responses preventing SUI during sneeze, we investigated the effect of duloxetine followed by intrathecal (i.t.) prazosin, a selective α_1-adrenoceptor antagonist, and/or methiothepin maleate, a non selective 5-hydroxytryptamine $(5\text{-HT})_2$ antagonist.

Study design, materials and methods

(1) Effects of duloxetine on mid-urethral pressure responses

Normal female rats and rats with simulated birth trauma induced by vaginal distension (VD) were used. In VD rats, the vagina was distended with 4 ml balloon catheter for 3 hours 4 days before the experiment. Both in normal and VD rats, the bladder was emptied and bilateral pelvic nerve was transected to suppress reflex bladder contractions. Then, sneezes were induced by a rat's whisker cut and inserted into the nostril under urethane anesthesia in supine position. Urethral responses were measured using a microtip transducer catheter inserted to the middle urethra from the urethral orifice. At least ten sneeze-induced urethral responses were measured before and after intravenous (i.v.) injection of duloxetine (1 mg/kg), and changes in amplitude of urethral responses and urethral baseline pressure during sneeze after duloxetine treatment were evaluated.(2) Effects of i.t. application of prazosin and/or methiothepin maleate on duloxetine-induced changes in urethral pressure responses In normal rats, after i.t. administration of prazosin (0.02 nmol) and/or methiothepin maleate (6 nmol) at the level of L6-S1 spinal cord, the effect of duloxetine (1 mg/kg i.v.) on sneeze-induced urethral responses as well as urethral baseline pressure at the mid urethra was evaluated. (3) Effects of duloxetine on sneeze leak point pressure Both in normal and VD rats, changes in pressure of the bladder filled with 0.4 ml saline were recorded to examine whether urinary leakage from the urethral orifice was induced during sneezing. The maximal intravesical pressure was measured in each sneeze event and the lowest pressure value that induced fluid leakage from the urethral orifice was defined as the sneeze leak point pressure (S-LPP). Duloxetine (1 mg/kg) was injected (i.v.) and changes in S-LPP were evaluated in normal and VD rats.

Results

(1) Effects of duloxetine on mid-urethral pressure responses The amplitude of mid-urethral pressure responses during sneezing in VD rats was significantly lower than in normal rats (11.5 ± 1.3 vs. 34.5 ± 3.6 cmH_2O). In both normal and VD rats, amplitude was increased by 33-34% to 45.9 ± 4.5 and 15.5 ± 2.3 cm H_2O, respectively, by duloxetine. The urethral baseline pressure was also increased by 5.3 ± 1.2 cm H_2O in normal rats and 4.8 ± 1.0cm H_2O in VD rats after duloxetine treatment. (2) Effects of prazosin and/or methiothepin maleate Methiothepin maleata (i.t.) alone did not affect duloxetine-induced increases in sneeze response amplitude at the mid-urethra (amplitude before/after duloxetine: 40.5 ± 3.5 cm H_2O/55.1 ± 7.4 cm H_2O, respectively). However, prazosin (i.t.) suppressed duloxetine-induced increases in the sneeze response amplitude at the mid-urethra because the amplitude before and after duloxetine (51.7 ± 6.7 and 56.0 ± 5.3 cm H_2O, respectively) was not different in the presence of prazosin. Further, simultaneous application of methiothepin maleata and prazosin (i.t.) inhibited duloxetine-induced increases in sneeze response amplitude at the mid-urethra and further decreased the sneeze-induced response (amplitude before/after duloxetine: 40.9 ± 6.4 cm H_2O/26.9 ± 6.5 cm H_2O, respectively). Prazosin and/or methiothepin maleate (i.t.) also suppressed duloxetine-induced increases in urethral baseline pressure. (3) Effect of duloxetine on sneeze leak point pressure. In normal rats, no sneeze-induced leakage was observed before and after duloxetine injection. In 7 of 8 VD rats, leakages were observed during sneezing before duloxetine injection. However, after the duloxetine treatment (i.v.), incontinence during sneeze disappeared in two rats, and S-LPP was increased in other 5 incontinent rats from 37.5 ± 4.3 cm H_2O to 92.3 ± 15.8 cm H_2O.

Interpretation of results

Duloxetine prevented sneeze-induced SUI in a rat SUI model due to an enhancement of the active urethral closure reflex during sneezing and an increase in baseline pressure at the mid-urethra. Because simultaneous administration of methiothepin maleate and prazosin (i.t.) suppressed duloxetine-induced increases in sneeze response amplitude and further reduced the amplitude of duloxetine-induced sneeze responses at the mid-urethra, it is assumed that duloxetine can prevent SUI by enhancing the sneeze-induced active urethral closure mechanism at the spinal level and that synergic activation of spinal noradrenergic and serotonergic systems is important to maintain the urethral continence reflex during sneezing. In addition, our previous study has demonstrated that increases in urethral baseline pressure after administration of a NE reuptake inhibitor are induced by activation of sympathetic pathways innervating the urethral carried through the hypogastric nerve.[3] In the present study, i.t. application of prazosin and/or methiothepin maleate suppressed duloxetine-induced increases in urethral baseline pressure. Thus, it is possible that

duloxetine can activate sympathetic outflow to the urethra via α_1-adrenoceptors and 5-HT_2 receptors in the spinal cord to increase urethral baseline pressure and that administration of prazosin and/or methiothepin maleate (i.t.) reached the spinal levels, where the sympathetic outflow to the urethra originates, to suppress the duloxetine effects on baseline pressure.

Concluding message

The results in this study indicate that duloxetine, a NE and serotonin reuptake inhibitor, is effective to enhance the active continence reflex under stress conditions such as sneezing, thereby preventing SUI, and can exerts its effects via activation of both α_1-adrenoceptors and 5-HT_2 receptors in the spinal cord. These mechanisms could contribute to the clinical efficacy of duloxetine in the treatment of SUI.

References

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