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EFFECTS OF NOREPINEPHRINE REUPTAKE INHIBITOR, NISOXETINE, ON THE SNEEZE-INDUCED URETHRAL CONTINENCE REFLEX IN RATS.

Hypothesis / aims of study

Norepinephrine (NE) and/or serotonin reuptake inhibitors have demonstrated clinical utility in the treatment of stress urinary incontinence (SUI), but the mechanism 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 activation of somatic nerves innervating urethral and pelvic floor striated muscles. We therefore investigated the effect of a NE reuptake inhibitor, nisoxetine, on active continence reflexes induced by sneezing in rats. The site of action (spinal vs. peripheral) of nisoxetine for the enhancement of sneeze-induced continence reflexes was also examined by intrathecal (i.t.) administration of a non-selective α-adrenoceptor antagonist, phentolamine.

Study design, materials and methods

(1) Effect of nisoxetine on sneeze leak point pressure

Normal female rats and rats with simulated birth trauma induced by vaginal distention (VD) were used. In VD rats, the vagina was distended with 4 ml balloon catheter for 3 hours 4 days before the experiment. Following bilateral pelvic nerve transaction, sneezes were induced by a rat's whisker cut and inserted into the nostrils under urethane anesthesia in supine position while recording changes in pressure of the bladder filled with 0.4 ml saline 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). Nisoxetine (1 mg/kg) was injected intravenously (i.v.) and changes in S-LPP were evaluated in both groups of animals.

(2) Effect of nisoxetine on mid-urethral pressure responses

Both in normal and VD rats, the bladder was emptied and the sneeze reflex was induced to measure urethral responses 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 nisoxetine injection, and changes in urethral baseline pressure and amplitude of urethral responses during sneeze after nisoxetine treatment were evaluated

(3) Effects of intrathecal application of phentolamine on nisoxetine-induced changes in urethral pressure responses.

After i.t. administration of phentolamine (20 μmol) at the L6-S1 spinal cord level, the effect of nisoxetine (i.v.) on sneeze-induced urethral responses as well as baseline urethral pressure was evaluated in normal rats.

Results

(1) Effect of nisoxetine on sneeze leak point pressure.

In normal rats, no sneeze-induced leakage was observed before and after nisoxetine injection. In 7 of 8 VD rats, however, leakages were observed during sneezing before nisoxetine injection. However, after the nisoxetine treatment, incontinence during sneeze disappeared in two VD rats, and S-LPP was increased in other 5 rats from 46.3 ± 6.4 to 61.5 ± 10.2 cmH_2O (mean ± SE) by nisoxetine.

(2) Effect of nisoxetine on mid-urethral pressure responses.

The amplitude of mid-urethral pressure responses during sneezing in VD rats was significantly lower than in normal rats (10.3 ± 1.8 vs. 35.6 ± 4.7 cmH_2O). In both normal and VD rats, the amplitude was increased by 13-18% to 40.1 ± 2.6 and 12.2 ± 2.3 cmH_2O, respectively, by nisoxetine. The urethral baseline pressure was also increased by 8.1 ± 1.0 cmH_2O in normal rats and 6.2 ± 0.8 cmH_2O in VD rats after nisoxetine treatment.

(3) Effects of phentolamine

Phentolamine (i.t.) suppressed nisoxetine-induced increases in the sneeze response amplitude at the mid-urethra (the amplitude before/after nisoxetine: 48.4 ± 9.3 / 48.0 ± 9.1 cmH_2O, respectively) in normal rats. However, phentolamine did not suppress the increase in

baseline pressure of the mid-urethra because baseline urethral pressure was still increased by 6.7 ± 1.1 cmH_2O after nisoxetine in phentolamine-treated rats.

Interpretation of results

Nisoxetine 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 i.t. administration of phentolamine blocked only the former response, it is assumed that nisoxetine can enhance the sneeze-induced active continence reflex via α-adrenoceptors in the spinal cord while increasing baseline urethral pressure by activation of peripheral adrenoceptors probably in urethral smooth muscles.

Concluding message

This study indicates that NE reuptake inhibitors such as nisoxetine is effective to enhance the active continence reflex under stress conditions such as sneezing, thereby preventing SUI, and can exerts their effects via activation of α-adrenoceptors at both spinal and peripheral sites. These mechanisms could contribute to the clinical efficacy of NE/serotonin reuptake inhibitors such as duloxetine in the treatment of SUI.

References

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