

## TRAMADOL ENHANCES URETHRAL CONTINENCE REFLEX DURING SNEEZING THROUGH M-OPIOID RECEPTORS IN THE SPINAL CORD IN RATS

### Hypothesis / aims of study

Stress urinary incontinence (SUI) is the most common type of urinary incontinence in women. Because the efficacy of pharmacotherapy for SUI is generally unsatisfactory, so far surgery seems to be the best option for achieving long-term continence, so that there is a need to developing new effective drugs for SUI. Tramadol is widely used as an analgesic. It combines weak effects on  $\mu$ -opioid receptors with inhibition of serotonin and noradrenaline reuptake inhibitor.<sup>1</sup> This profile is of interest, since both effects may be useful principles for treatment of SUI, however, the efficacy of tramadol on SUI has not been fully understood. 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.<sup>2</sup> We therefore investigated the effect of tramadol on the sneeze induced continence reflex using this model.

### Study design, materials and methods

#### (1) Effects of tramadol on mid-urethral pressure responses

Normal female rats aged 3 months were used. 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 tramadol (3 mg/kg), and changes in amplitude of urethral responses and urethral baseline pressure during sneeze after tramadol treatment were evaluated.

#### (2) Effects of intrathecal (i.t.) application of cyprodime hydrochloride, a selective $\mu$ antagonist, on tramadol-induced changes in urethral pressure responses

In normal rats, after i.t. administration of cyprodime (0.1  $\mu$ g) at the level of L6-S1 spinal cord, the effect of tramadol (3 mg/kg i.v.) on sneeze-induced urethral responses as well as urethral baseline pressure at the mid urethra was evaluated.

#### (3) Effects of tramadol on tilt leak point pressure (tilt LPP)

Normal 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 3 days before the experiment. Both in normal and VD rats, urethral function was measured using the vertical tilt/intravesical pressure-clamp method.<sup>3</sup> Intravesical pressure was increased in 1–2 cmH<sub>2</sub>O increments via the suprapubic tube, by raising a reservoir with saline solution containing Evans blue. The pressure at which visible leakage from the urethral meatus occurred was defined as the LPP. The mean values of three or four estimates were analyzed. After control LPPs were obtained, tramadol (3 mg/kg) was injected intravenously and intravesical pressure was increased again to evaluate the effect of the drug on the LPP.

### Results

#### (1) Effects of tramadol on mid-urethral pressure responses

In normal rats, amplitude was significantly increased by 143% from  $53.22 \pm 6.2$  to  $76.6 \pm 5.0$  cm H<sub>2</sub>O by tramadol (3 mg/kg i.v.). The urethral baseline pressure was also increased by 135% from  $14.74 \pm 0.42$  to  $19.84 \pm 0.13$  cm H<sub>2</sub>O after tramadol treatment.

#### (2) Effects of tramadol in the presence of cyprodime

Cyprodime (0.1  $\mu$ g i.t.) alone did not affect sneeze response and urethral baseline pressure at the mid-urethra. However, in the presence of cyprodime, tramadol-induced increases in amplitude were suppressed, while those in urethral baseline pressure were not suppressed.

#### (3) Effect of tramadol on tilt LPP.

During passive intravesical pressure elevation, fluid leakage from the urethral meatus was observed at the LPP of  $31.50 \pm 0.79$  cmH<sub>2</sub>O in VD rats, which was significantly lower by 22.7% compared with normal rats ( $40.76 \pm 1.42$  cmH<sub>2</sub>O). Tramadol (3 mg/kg, i.v.) increased the tilt LPP both in normal and VD rats (Figure).

### Interpretation of results

Tramadol 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 in the presence of cyprodime, a selective  $\mu$  antagonist, tramadol-induced increases in sneeze response amplitude were reversed at the mid-urethra, it is assumed that tramadol can prevent SUI by enhancing the sneeze-induced active urethral closure mechanism at the spinal level. In addition, our previous study has demonstrated that increases in urethral baseline pressure after administration of duloxetine, a norepinephrine and serotonin reuptake inhibitor, are induced by activation of sympathetic pathways innervating the urethral carried through the hypogastric nerve. In accordance with the microtransducer-tipped catheter experiments, tramadol increased LPP, an overall urethral resistance, both in normal and VD rats.

### Concluding message

The results in this study indicate that tramadol, a  $\mu$ -opioid agonist with inhibition of serotonin and noradrenaline reuptake inhibitor, is effective to enhance the active continence reflex under stress conditions such as sneezing, thereby preventing SUI, and can exert its effects via activation of  $\mu$ -opioid receptors in the spinal cord. Tramadol is a potentially useful drug for the treatment of SUI.

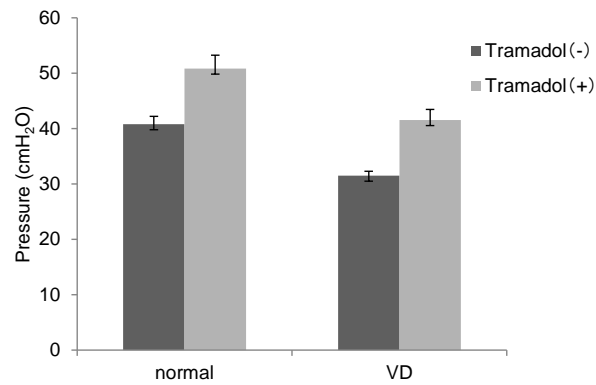


Figure. Tilt LPP in normal and VD rats before and after Tramadol (3mg/kg, i.v.).

#### References

1. Clinical pharmacology of tramadol. Clin Pharmacokinet. 43:879-923, 2004.
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3. Comparison of leak point pressure methods in an animal model of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct.16: 359-63, 2005.

#### Disclosures

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