Role of the serotonergic system in urethral continence reflexes during sneezing in rats

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Introduction and Objective:

The spinal serotonergic pathways are reportedly involved in the control of urethral continence reflexes that prevent stress urinary incontinence (SUI). Previous studies described that serotonin (5-HT) receptor subtypes, 5-HT_{1A} and 5-HT_{2C}, respectively reduce and enhance the urethral continence reflex during sneezing in rats [1]. However, because there are other multiple excitatory and inhibitory 5-HT receptors, the overall effects of the 5-HT system on the urethral function remain to be elucidated. Therefore, in this study, we examined the effects of 5-HT depletion induced by *p*-chlorophenylalanine (PCPA) that inhibits 5-HT synthesis and 5-HT_{2C} or 5-HT_7 subtype agonists on urethral baseline activity and reflex contractions during sneezing in rats.

Materials and Methods:

We investigated the effects of intraperitoneal application of PCPA (200 mg/kg/day), and intravenous application of a 5-HT_{2C} agonist (CP-809101) or a 5-HT_7 agonist (LP44) on neurally evoked urethral continence reflexes during sneezing (Figs. 1 and 2). Female Sprague-Dawley rats (12 weeks old) were divided into two groups; either Normal group (n = 6) or PCPA-treatment group without (n = 5) or with 5-HT drug administration (n=21). The PCPA-treatment + drug administration group received intravenous injection of; (1) a 5-HT_{2C} agonist without (n = 4) or with a 5-HT_{2C} antagonist (n = 4) or (2) a 5-HT_7 agonist without (n = 7) or with a 5-HT_7 antagonist (n = 6). In the PCPA-treatment + 5-HT_7 agonist group, a 5-HT_{1A} antagonist (WAY-100635) was also administered before LP44 administration to suppress the partial 5-HT_{1A} agonistic effect of LP44. Using a microtransducer-tipped catheter inserted to the mid-urethra, we assessed amplitudes of urethral pressure responses during sneezing (A-URS) and urethral baseline pressure (UBP) under urethane anesthesia (Figs. 3 and 4). To evaluate the induced sneeze intensity, abdominal pressure during sneezing (Pabd) was also measured via an intraabdominal balloon catheter.

Results:

5-HT depletion by PCPA treatment significantly decreased A-URS from 71.8 to 36.7 cmH_2O ($p < 0.01$), and also UBP from 31.1 to 17.8 cmH_2O ($p < 0.01$) compared to normal rats (Figs. 3 and 5A). On the other hand, in PCPA-treated rats, CP-809101 alone or LP44 with WAY-100635 significantly increased A-URS from 42.1 to 66.2 cmH_2O ($p < 0.01$) or from 30.0 to 50.5 cmH_2O ($p < 0.01$) as well as UBP from 17.3 to 32.4 cmH_2O ($p < 0.05$) or from 15.2 to 26.6 cmH_2O ($p < 0.01$). respectively (Figs 3, 5B and 5C). The enhancing effects of 5-HT_{2C} or 5-HT_7 agonist on A-URS and UBP were antagonized by respective 5-HT receptor antagonist.

Fig. 1

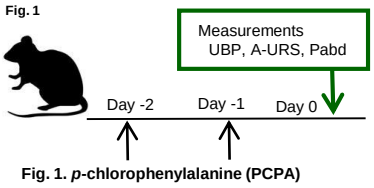


Fig. 1. *p*-chlorophenylalanine (PCPA)

PCPA depletes brain 5-HT by synthetic inhibition. Systemic pretreatment for 2 days resulted in 95 % depletion in hypothalamic 5-HT [2].

Fig. 3 Representative traces of urethral pressure responses

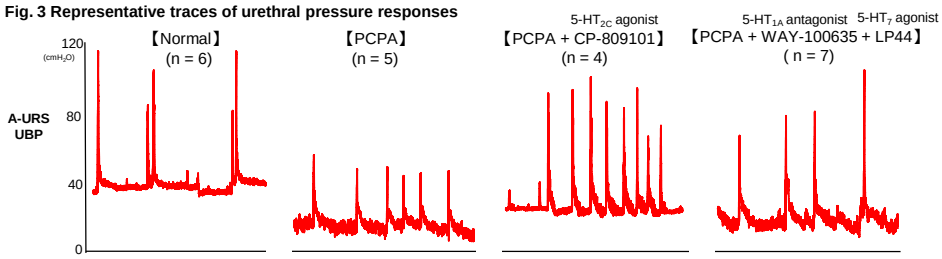


Fig. 2

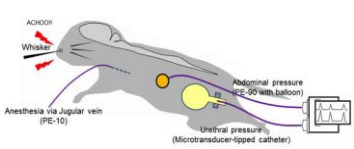


Fig. 2. Surgical procedure and protocols

- Isoflurane anesthesia
- Insert a jugular vein catheter
- Cut bilateral ureters
- Cut bilateral visceral branch of pelvic nerves
- Insert a balloon catheter (for measuring Pabd)
- Urethane anesthesia (1.0-1.2 g/kg)
- Insert a microtransducer-tipped catheter (for measuring UBP, A-URS)

Fig. 4

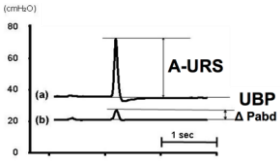
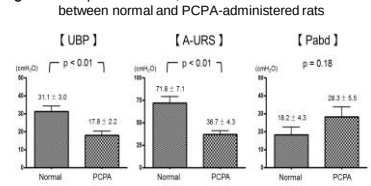


Fig. 4. Measurements of urethral baseline pressure (UBP), amplitude of urethral responses during sneezing (A-URS) (a) and abdominal pressure (Pabd) (b)

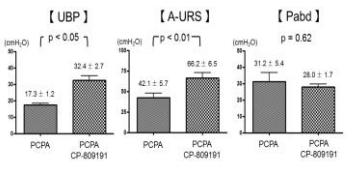
A-URS represents the maximal pressure change in cmH_2O from the baseline. The averaged UBP was obtained from a plateau section of pressure recording just before the sneeze response [3].

Fig. 5A Comparison of UBP, A-URS and Pabd between normal and PCPA-administered rats



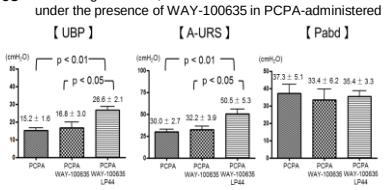
Mean ± SEM (cmH_2O); Unpaired t-test

Fig. 5B The changes of UBP, A-URS and Pabd after CP-809101 administration in PCPA-administered rats



Mean ± SEM (cmH_2O); Paired t-test

Fig. 5C The changes of UBP, A-URS and Pabd after LP44 administration under the presence of WAY-100635 in PCPA-administered rats



Mean ± SEM (cmH_2O); One-way analysis of variance followed by Bonferroni's multiple comparison tests

Discussion:

In the present study, 5-HT depletion by PCPA decreased A-URS and UBP, indicating that the overall 5-HT system plays a facilitatory role in the urethral continence function. Furthermore, both 5-HT_{2C} and 5-HT_7 agonists increased A-URS and UBP, indicating that not only 5-HT_{2C}, but also 5-HT_7 receptor subtypes can enhance the urethral continence reflex. In addition, previous studies reported that intrathecal application of a 5-HT_{2C} agonist, mCPP, increased A-URS without affecting UBP in rats without 5-HT depletion [1], suggesting that endogenous 5-HT may influence the 5-HT_{2C} receptor-mediate effect on UBP. The site of the action of 5-HT is likely to involve the Onuf's nucleus of the lumbosacral spinal cord, where dense 5-HT-containing nerve terminals onto urethral rhabdosphincter motoneurons are identified [4].

Conclusion:

These results indicate that activation of 5-HT receptors such as 5-HT_{2C} and 5-HT_7 enhances the active urethral closure reflex during sneezing. Activation of these excitatory 5-HT receptor subtypes could be effective for the treatment of SUI.

References:

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Conflict of interest:
None

Source of funding:
NIH R01DK107450