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-HT1A and 5-HT2C, 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-HT2C or 5-HT1A 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-HT2C agonist (CP-809101) or a 5-HT7 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-HT2C agonist without (n = 4) or with a 5-HT7 antagonist (n = 4) or (2) a 5-HT7 agonist without (n = 7) or with a 5-HT7 antagonist (n = 6). In the PCPA-treatment + 5-HT7 agonist group, a 5-HT1A antagonist (WAY-100635) was also administered before LP44 administration to suppress the partial 5-HT1A 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 cmH2O (p < 0.01), and also UBP from 31.1 to 17.8 cmH2O (p < 0.01) compared to normal rats (Figs. 3 and 4). 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 cmH2O (p < 0.01) or from 30.0 to 50.5 cmH2O (p < 0.01) as well as UBP from 17.3 to 32.4 cmH2O (p < 0.05) or from 15.2 to 26.6 cmH2O (p < 0.01), respectively (Figs. 3B and 5C). The enhancing effects of 5-HT2C or 5-HT7 agonist on A-URS and UBP were antagonized by respective 5-HT-receptor antagonist.

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-HT7 and 5-HT1A agonists increased A-URS and UBP, indicating that not only 5-HT2C, but also 5-HT7 receptor subtypes can enhance the urethral continence reflex. In addition, previous studies reported that intrathecal application of a 5-HT2C agonist, mCPP, increased A-URS without affecting UBP in rats without 5-HT depletion [1], suggesting that endogenous 5-HT may influence the 5-HT7 receptor-mediated effect on UBP. The site of the action of 5-HT is likely to involve the Onuf’s nucleus of the lumbarosacral spinal cord, where dense 5-HT-containing nerve terminals onto urethral rhabdosphincter motoneurons are identified [4].

Conclusion:
These results indicate that activation of 5-HT7 receptors such as 5-HT2C and 5-HT7 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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