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ROLE OF SPINAL GLUTAMATERGIC MECHANISMS IN SNEEZE-INDUCED URETHRAL CONTINENCE REFLEX IN RATS

Hypothesis / aims of study

Urinary continence during stress conditions such as sneezing or coughing is mediated by activation of Onuf's nucleus in the sacral spinal cord that induces contractions of striated muscles of the urethral sphincter and pelvic floor. Norepinephrine (NE) and/or serotonin reuptake inhibitors, such as duloxetine, are reportedly effective for the treatment of stress urinary incontinence (SUI) by enhancing the continence reflex. It has also been demonstrated that activation of spinal noradrenergic pathways enhances the sneeze-induced urethral continence reflex using a rat model that can examine the active urethral closure mechanism during the sneeze reflex[1, 2]. However, the major neurotransmitter that induces the continence reflex during sneezing have not been elucidated although spinal descending glutamatergic pathways are known to be the major excitatory system controlling activity of the lower urinary tract. We therefore investigated the effects of intrathecal (i.t.) administration of MK-801, a non-competitive NMDA receptor antagonist, on sneeze-induced urethral responses in rats in order to clarify the role of glutamatergic pathways in the active urethral closure mechanism during sneezing,.

Study design, materials and methods

Normal female rats 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 a 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 cumulative administration of MK-801, and changes in amplitude of urethral responses during sneezing (AURS) and urethral baseline pressure (UBP) were evaluated. MK-801 was administered at the L6-S1 spinal cord level and cumulatively given with each 0.25mol (10µl) injection at 10 to 15 minute intervals.

In addition, in order to estimate the magnitude of the effects of MK-801, we examined active urethral pressure responses during sneezing in rats with transection of hypogastric, pelvic and pudendal nerves. AURS and UBP in the nerve transacted rats were measured and compared with those after MK-801 treatment in normal rats.

Result

MK-801 (i.t.) dose-dependently inhibited urethral responses during sneezing. In eight rats, sneeze-induced urethral responses were gradually decreased with increasing doses of MK-801 (i.t.). The suppression of responses had reached to the plateau level at the dose of 0.75-1.0 µmol of MK-801 (i.t.). After the cumulative application of MK-801 (i.t.), AURS was significantly decreased from 49.6 ± 8.5 to 6.9 ± 2.1 cmH_2O (12.1 % of pre-treatment value). Administration of increasing doses of MK-801 (i.t.) also decreased urethral tone by reducing UBP from 29.3 ± 2.0 to 23.9 ± 2.1 cmH_2O.

After the transection of hypogastric, pelvic and pudendal nerves, the active urethral closure responses during sneezing were almost completely disappeared, and A-URS in nerve-transected rats was 4.16 ± 0.5 cmH_2O, which was comparable with the value after MK-801 administration in normal rats. Transection of these nerves also decreased urethral tone, and UBP after nerve transaction was 15.7 ± 3.5 cmH_2O, which was significantly lower than that after MK-801 treatment.

Interpretation of results

Because AURS was significantly decreased after i.t. administration of MK-801 to the same level as observed after transection of hypogastric, pelvic and pudendal nerves, it is assumed that glutamatergic transmission in the spinal cord is the major mechanism inducing the sneeze-induced continence reflex. On the other hand, i.t. administration of MK-801 at the L6-S1 spinal level decreased the urethral tone, however the decrease in UBP after MK-801 treatment was smaller compared with changes in UBP after nerves transection, indicating that UBP is controlled not only by spinal glutamatergic transmission at the sacral cord level, but also by sympathetic pathways that originate from the higher level (L1-L2) of spinal cord.

Concluding message

Since MK-801, a non-competitive NMDA receptor antagonist, almost completely suppressed the sneeze-induced continence reflex, glutamate seems to be the major neurotransmitter inducing the active continence reflex under stress conditions such as sneezing in the spinal cord. Thus the therapeutic effects of NE and/or serotonin reuptake inhibitors, such as duloxetine, on SUI could be mediated by enhancement of the excitatory spinal glutamate mechanism.

References

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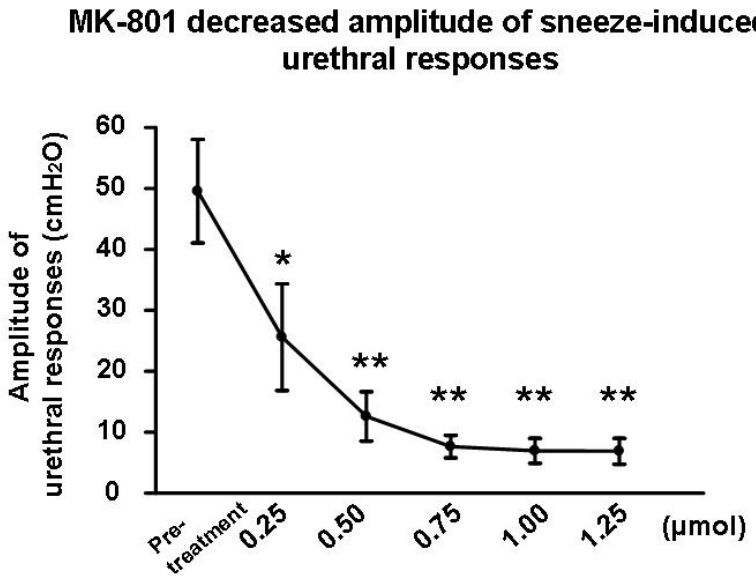

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