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α_2 -Adrenoceptors as a new target for stress urinary incontinence

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Introduction

There are few drugs to enhance the urinary continence function under stress conditions such as sneezing, coughing or lifting heavy objects because pharmacological targets for improving urethral closure mechanisms under stress conditions are not fully elucidated. Imipramine and duloxetine have been used clinically to treat stress urinary incontinence (SUI). The mechanisms of these drugs are thought to stimulate serotonin (5-hydroxytryptamine [5-HT]) and norepinephrine (NE) receptors by inhibiting reuptake of 5-HT and NE in the Onuf's nucleus, thereby increasing external urethral sphincter (EUS) activity.^{1–4} We have recently reported using rats that 5-HT and NE pathways are important to maintain sneeze-induced urethral continence reflexes and that duloxetine-induced enhancement of the reflexes is predominantly mediated by α_1 -ARs in the spinal cord.⁵

Previous studies that examined the pelvic-to-pudendal spinal reflex during urine storage^{6, 7} have demonstrated that pelvic nerve electrical stimulation or bladder distension induced by saline infusion can induce an increase in EUS activity, which is attenuated by intrathecal or intravenous (i.v.) administration of N-methyl-D-aspartate (NMDA) glutamate receptor antagonists. Glutamate is well known as an excitatory neurotransmitter in the central nervous system (CNS), and its release at nerve terminals is regulated by presynaptic α_2 -ARs in the dorsal horn^{8, 9} or sympathetic preganglionic neurons.¹⁰ However, the involvement of glutamate and α_2 -AR systems in the control of urethral closure reflexes induced in stress conditions remains to be explored.

Therefore, this review summarizes the results of our recent studies that examined the control of EUS responses in stress conditions by glutamate and/or α_2 -AR mechanisms.

Material and Methods

Animal preparation

The spinal cord in female Sprague-Dawley rats was transected at the T8-9 level to eliminate voiding reflex in spino-bulbo-spinal pathways under isoflurane anesthesia. The bladder neck was ligated with 4-0 silk threads through a middle abdominal incision to prevent urinary leakage when the lower abdominal wall was manually compressed. After the surgery, the abdominal wall was tightly closed, and then isoflurane anesthesia was replaced with urethane anesthesia (1.2 g/kg s.c.) to examine EUS-electromyogram activity. The bladder

was filled with 0.3 ml of saline, and then the activity of EUS-electromyogram during lower abdominal wall compression was recorded before and after drug application to examine the effects of test drugs on EUS activity.

Application of drugs

Cumulative doses of MK-801, an NMDA glutamate receptor antagonist (0.03, 0.3 and 3 mg/kg i.v.), or medetomidine, an α_2 -AR agonist (0.03, 0.3 and 3 mg/kg i.v.), were administered to examine the involvement of glutamate NMDA receptor and α_2 -AR in the control of EUS activity. Idazoxan, an α_2 -AR antagonist (0.3 mg/kg i.v.), was administered before or after administration of MK-801 (1 mg/kg i.v.) to investigate the relationship between α_2 -AR and NMDA receptor activation.

Results

Cumulative administration of MK-801 (0.03, 0.3 and 3 mg/kg i.v.) showed that the lowest dose (0.03 mg/kg) of MK-801 did not change the EUS activity. However, higher doses (0.3 and 3 mg/kg) of MK-801 significantly decreased the EUS activity by 70% ($P<0.05$) and 91% ($P<0.01$) compared with pre-drug control, respectively (Fig. 1A).

Cumulative administration of medetomidine (0.03, 0.3 and 3 mg/kg i.v.) significantly decreased the EUS activity by 27% ($P<0.05$), 54% ($P<0.01$) and 82% ($P<0.01$) compared with control, respectively (Fig. 1B).

Administration of idazoxan (0.3 mg/kg i.v.) significantly increased the EUS activity by 64% compared with control ($P<0.05$), and subsequent application of MK-801 (1 mg/kg i.v.) decreased the EUS activity to 33 % of the control value ($P<0.05$) (Fig. 2A). On the other hand, administration of MK-801 significantly decreased the EUS activity by 74% compared with control ($P<0.01$); however subsequent application of idazoxan did not further change the EUS activity (Fig. 2B).

Discussion

These results demonstrate that: 1) glutamatergic NMDA receptors are important to induce the urethral continence reflex in response to abdominal pressure increases as evidenced by MK801-induced suppression of EUS reflex activity, and 2) α_2 -ARs are tonically activated to inhibit the urethral continence reflex during abdominal pressure increases because the α_2 -AR agonist and antagonist respectively inhibit and enhance the EUS reflex.

Cumulative administration of MK-801 dose-dependently decreased EUS activity during abdominal compression by up to 91%. Glutamate is known to be the major neurotransmitter controlling lower urinary tract function in CNS,¹¹ and the inhibitory effects of MK-801 in the spinal cord on EUS activity increased during stimulation of the pelvic nerve have been reported in rats.^{6, 7} Thus, the pelvic-to-pudendal urethral continence reflex induced in Valsalva-like stress conditions is also likely to be dependent upon activation of glutamatergic NMDA receptors in the spinal cord.

We also found that cumulative administration of medetomidine, an α_2 -AR receptor agonist, dose-dependently decreased EUS activity during abdominal compression by 82% while inhibition of α_2 -ARs by idazoxan conversely increased EUS activity by 64%. These results indicate that α_2 -ARs are activated to suppress the spinal urethral continence reflex that increases EUS activity during abdominal pressure increases. Thus, we further examined the relationship between α_2 -ARs and glutamatergic mechanisms in the control of the urethral continence reflex. Administration of idazoxan increased EUS activity by 64%, and the

idazoxan-induced increase in EUS activity was abolished by subsequent application of MK-801. However, administration of idazoxan following MK-801 did not increase EUS activity decreased by MK-801. These results suggest that the α_2 -AR-mediated inhibitory effect may be mediated by suppression of glutamatergic mechanisms. Thus it seems reasonable to assume that α_2 -ARs also regulate the release of glutamate in the spinal cord to modulate the pelvic-to-pudendal spinal reflex induced in Valsalva-like stress conditions. Therefore, the use of α_2 -AR antagonists, which increase EUS activity during abdominal pressure increases, could be an alternative modality for the treatment of SUI. In addition, to the best of our knowledge, these results confirmed for the first time the interrelationship between α_2 -ARs and glutamate systems in the pelvic-to-pudendal spinal continence reflex.¹²

Duloxetine, a 5-HT and NE reuptake inhibitor, has demonstrated clinical efficacy in the treatment of SUI.¹³ Danuser et al.¹ previously demonstrated that modulation of somatic reflex pathways to the lower urinary tract in cats by NE reuptake inhibition caused activation of not only facilitatory α_1 -ARs, but also inhibitory α_2 -ARs in the spinal cord. We have also recently reported that the enhancing effects of duloxetine on the urethral continence reflex during sneezing were mainly mediated by activation of α_1 -ARs in the spinal cord although α_2 -AR-mediated inhibition by duloxetine was only observed when both α_1 -ARs and 5-HT receptors were suppressed in rats.⁵ Our recent study has also shown that the enhancing effects of duloxetine on the urethral continence reflex induced by abdominal wall compression can be increased by simultaneous application of idazoxan, an α_2 -AR antagonist.¹² Therefore, combined applications of 5-HT/NE reuptake inhibitors and α_2 -AR antagonists could be more effective for the treatment of SUI than the single drug therapy.

Conclusions

Our recent studies provide the evidence that glutamate is the major excitatory neurotransmitter in the pelvic-to-pudendal spinal reflex induced in Valsalva-like stress conditions. Since α_2 -ARs can inhibit the release of glutamate presynaptically in the spinal cord, α_2 -AR antagonists would be useful as an alternative treatment of SUI. In addition, α_2 -AR antagonists could enhance the therapeutic effects of 5-HT/NE reuptake inhibitors by blocking the inhibitory effects of duloxetine mediated via α_2 -AR activation.

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Fig. 1.

Effects of cumulative application of MK-801 (A), a NMDA glutamate receptor antagonist, and medetomidine (B), an α_2 -AR agonist, on EUS activity. A; higher doses (0.3 and 3 mg/kg) of MK-801 (MK) significantly decreased the EMG activity of EUS during abdominal wall compression by 70% (*P<0.05) and 91% (**P<0.01) compared with pre-drug control, respectively. B; Cumulative application of medetomidine (Med; 0.03, 0.3 and 3 mg/kg) significantly decreased the EUS activity dose-dependently by 27% (*P<0.05), 54% (**P<0.01) and 82% (**P<0.01) compared with pre-drug control, respectively.

Fig. 2.

Relationship between the effects of idazoxan, an α_2 -AR antagonist, and MK-801, a NMDA glutamate receptor antagonist, on EUS activity. A; Idazoxan (Ida; 0.3 mg/kg) significantly increased the EUS activity during abdominal wall compression by 64% compared with pre-drug control (* $P < 0.05$). The increased EMG activity after idazoxan was then eliminated and reduced to the level lower than control (* $P < 0.05$) after subsequent application of MK-801 (MK; 1 mg/kg). B; MK-801 significantly decreased the EUS activity by 74% compared with pre-drug control (** $P < 0.01$), but the decreased EUS activity by MK-801 was not changed by subsequent application of idazoxan.